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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ISMAEL PEDRO CALDERON RODRIGUEZ, ELEODORO CALIXTO RODRIGUEZ, OTONIEL RAMIREZ ESCOBAR, MARIO SANCHEZ CANO, and ROGEIRO TORRES, and on behalf of all others similarly situated,

Plaintiffs,

vs.

ARCHITECTURAL SURFACES GROUP, LLC, a Delaware limited liability company; ARIZONA TILE, L.L.C., an Arizona limited liability company; C & C NORTH AMERICA, INC., a Delaware corporation; CAESARSTONE USA, INC., a California corporation; CAMBRIA COMPANY LLC, a Minnesota limited liability company; DAL-TILE DISTRIBUTION, LLC, a Delaware limited liability company; DAL-TILE, LLC, a Delaware limited liability company; DAL-TILE TENNESSEE, LLC, is a Delaware limited liability company; ELITE QUARTZ MFG LLC, a Delaware limited liability company; HYUNDAI L&C USA, INC., a Delaware limited liability company; LX HAUSYS AMERICA, INC., a New Jersey corporation; M S INTERNATIONAL, INC., a Delaware corporation; PARAGON INDUSTRIES, INC., a California corporation; SURFACE WAREHOUSE, L.P., a Texas limited partnership.

Defendants.

CASE NO.

CLASS ACTION

COMPLAINT FOR MEDICAL MONITORING PREDICATED ON THE FOLLOWING LEGAL THEORIES:

(1) NEGLIGENCE;
(2) STRICT LIABILITY - WARNING DEFECT;
(3) STRICT LIABILITY - DESIGN DEFECT;
(4) FRAUDULENT CONCEALMENT

AND DEMAND FOR TRIAL BY JURY MADE PURSUANT TO RULE 38 OF THE FEDERAL RULES OF CIVIL PROCEDURE

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I. INTRODUCTION

1. This complaint is filed to secure essential healthcare for an especially vulnerable portion of the California population - young immigrant men from Latin America who came to the United States and found work in California fabricating countertops from artificial stone slabs and installing fabricated artificial stone countertops in kitchens and bathrooms throughout the state.

2. The Natural Stone Institute has estimated that approximately 3,000 fabricators in California and 12,000 to 20,000 fabricators in the U.S. have fabricated countertops from stone slabs.

3. Artificial stone is an inherently defective product primarily because it contains extraordinarily high concentrations of crystalline silica, an extremely toxic substance that is not only a known human carcinogen that causes lung and other human cancers, but also causes other chronic human diseases, especially silicosis, kidney disease, and a large variety of autoimmune diseases.

4. Silicosis is a fibrotic lung disease that is debilitating, progressive, irreversible, lethal and incurable, the only therapeutic option for advanced stage disease being lung transplantation.

5. California is the epicenter of a new silicosis epidemic, an occupational scourge of the past, the new epidemic occurring in Hispanic and Latino immigrant men who are now pulmonary cripples, tethered to oxygen tanks as they gasp for breath awaiting lung transplantation or death.

6. As of completion of the drafting of this Complaint, 466 cases and 25 deaths from artificial stone-induced silicosis have been documented in young Latino men on the Engineered Stone Silicosis Surveillance Dashboard of the California Department of Public Health (CDPH).

7. Thousands of young Hispanic immigrant men have fabricated deadly artificial stone in California over the last decade. They all have an extraordinarily high risk of developing silicosis, lung cancer and other silica-related diseases. Mostly undocumented workers, who lack medical insurance, workers' compensation, and medical care, these young men desperately need medical monitoring to detect the onset of silica-related disease and early medical treatment to prevent severe disease that would disable them from working to support their young wives and minor children.

8. The CDPH and employers lack the resources and personnel to medically monitor these workers. This complaint is filed to require those responsible for the epidemic to fund medical monitoring of workers exposed to artificial stone dust in California to detect silica-related disease.

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Plaintiffs, ISMAEL PEDRO CALDERON RODRIGUEZ, ELEODORO CALIXTO RODRIGUEZ, OTONIEL RAMIREZ ESCOBAR, MARIO SANCHEZ CANO, and ROGEIRO TORRES, on their own behalf and on behalf of all other persons similarly situated, hereby allege:

Jurisdiction

9. This Court has subject matter jurisdiction over this action pursuant to the Class Action Fairness Act of 2005 and 28 U.S.C. § 1332(d)(2), because this action arises under the laws of the United States, this action is brought on behalf of far more than 100 members of the class represented by the named Plaintiffs, and the amount in controversy exceeds $5,000,000.

Venue

10. Venue of this case is proper in the District Court for the Northern District of California, because named Plaintiffs and Class Members reside and worked in San Francisco where they were exposed to artificial stone dust and therefore have a significantly increased risk of developing silicosis and other chronic diseases caused by respirable crystalline silica and artificial stone dust.

Intradistrict Assignment

11. Assignment to the San Francisco Division is appropriate under Civil Local Rule 3-2© and (d), because named Plaintiffs reside and worked in San Francisco where they were exposed to artificial stone dust and therefore have a significantly increased risk of developing silicosis and other chronic diseases caused by respirable crystalline silica and artificial stone dust. Indeed, San Francisco is one of the two hot-spots in California where many stone countertop fabrication workers were exposed to artificial stone dust and have developed silicosis and other chronic diseases that are caused by respirable crystalline silica and artificial stone dust. Thus, a substantial part of the events or omissions giving risk to Plaintiffs' claim for medical monitoring occurred in San Francisco.

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II. THE PARTIES

A. Plaintiffs

12. At all material times hereto, Plaintiffs, ISMAEL PEDRO CALDERON RODRIGUEZ, ELEODORO CALIXTO RODRIGUEZ, OTONIEL RAMIREZ ESCOBAR, MARIO SANCHEZ CANO, and ROGEIRO TORRES, have resided in California and worked as countertop fabricators or installers in California.

13. Plaintiffs have all been occupationally exposed to respirable crystalline silica dust in the course of their work cutting, fabricating, and polishing artificial stone slabs and/or installing them as countertops in the State of California, but have not been diagnosed with any disease attributed to exposure to respirable crystalline silica. Plaintiffs bring this action against Defendants to require them to pay for medically necessary medical monitoring to detect silica-related disease.

B. Defendants

14. Plaintiffs are informed and believe and allege that Defendant, ARCHITECTURAL SURFACES GROUP, LLC (successor to PENTAL GRANITE AND MARBLE, LCC; PENTAL SURFACES, ARCHITECTURAL GRANITE AND MARBLE, LCC, CERAMIC MATRIX, MODUL MARBLE, and DA VINCI MARBLE, LLC), is a Delaware limited liability company, which, at all material times hereto, has had its principal place of business at19012 State Highway 71 West, Spicewood, Texas 78669, and was doing business in the County of Los Angeles.

15. Plaintiffs are informed and believe and allege that Defendant, ARIZONA TILE, L.L.C., is an Arizona limited liability company, which at all material times hereto, has had its principal place of business in California at 1620 S. Lewis Street, Anaheim, California 92805, and was doing business in the County of Los Angeles.

16. Plaintiffs are informed and believe and allege that Defendant, C & C NORTH AMERICA, INC., is a Delaware corporation, which at all material times hereto has had its principal place of business at 355 Alhambra Circle, Ste 1000, Coral Gables, Florida 33134, and was doing business at 8764 Beverly Blvd., West Hollywood, California 90048, in the County of Los Angeles.

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17. Plaintiffs are informed and believe and allege that Defendant, CAESARSTONE USA, INC., is a California corporation, which at all material times hereto, has had its principal office at 1401 West Morehead Street, Suite 100, Charlotte, North Carolina 28208, and was doing business at 11312 Penrose St., Sun Valley, California 91352, in the County of Los Angeles.

18. Plaintiffs are informed and believe and allege that Defendant, CAMBRIA COMPANY LLC, is a Minnesota limited liability company, which at all material times hereto, was doing business at 13102 Imperial Hwy, Santa Fe Springs, California 90670, in the County of Los Angeles.

19. Plaintiffs are informed and believe and allege that Defendant, DAL-TILE DISTRIBUTION, LLC, is a Delaware limited liability company, which at all material times hereto, was doing business at 7945 Orion Ave. Suite A, Van Nuys, California 91406, in the County of Los Angeles.

20. Plaintiffs are informed and believe and allege that Defendant, DAL-TILE, LLC, is a Delaware limited liability company, which at all material times hereto, was doing business in the County of Los Angeles, California.

21. Plaintiffs are informed and believe and allege that Defendant, DAL-TILE TENNESSEE, LLC, is a Delaware limited liability company, which at all material times hereto, was doing business in the County of Los Angeles, California.

22. Plaintiffs are informed and believe and allege that Defendant, ELITE QUARTZ MFG LLC, is a Delaware limited liability company, which at all material times hereto, has been a joint venture between Spectrum Quartz (Hirsch Glass Corporation) and M S International (MSI), and was doing business in the County of Los Angeles, California.

23. Plaintiffs are informed and believe and allege that Defendant, HYUNDAI L&C USA, LLC, is a Delaware limited liability company, which at all material times hereto, has had its principal place of business in the State of California at 16031 Carmenita Rd., Cerritos, California 90703, and was doing business in the County of Los Angeles, California.

24. Plaintiffs are informed and believe and allege that Defendant, LX HAUSYS AMERICA, INC., is a New Jersey corporation, which has had its principal place of business at 900 Circle 75

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Pkwy, Suite 150, Atlanta, Georgia 30339, its principal place of business in California at 711 S. Van Buren St., Placentia, California 92870, and was doing business in the County of Los Angeles, California.

25. Plaintiffs are informed and believe and allege that Defendant, M S INTERNATIONAL, INC., is a Delaware corporation, which at all material times hereto, has had its principal place of business in California at 2095 N. Batavia St., Orange, California 92865, and was doing business at 9111 Sunland Blvd., Sun Valley, California 91352, in the County of Los Angeles, California.

26. Plaintiffs are informed and believe and allege that Defendant, PARAGON INDUSTRIES, INC., is a California corporation doing business as Bedrosians Tile & Stone, which has had its principal place of business at 4285 N. Golden State Blvd., Fresno, California 92722, and was doing business at 16450 Foothill Blvd., Suite 100 Sylmar, California 91342 in the County of Los Angeles.

27. Plaintiffs are informed and believe and allege that Defendant, SURFACE WAREHOUSE, L.P., is a Texas limited partnership, which has done business since 2006 as U.S. SURFACE WAREHOUSE, and since 2017 as LIVINGSTONE, US SURFACES, SURFACE ENTERPRISES, L.L.C., and VADARA, and has done business as VADARA at 8969 Bradley Avenue, Sun Valley, California 91352, in the County of Los Angeles, California.

28. Defendants are all manufacturers, importers, distributors, suppliers, and/or sellers of slabs and blocks of artificial stone, also known as Agglomerate, Agglomerated Stone, Conglomerate, Engineered Stone, Manufactured Stone, Quartz, Reconstituted Stone, and Synthetic Stone.

29. Plaintiffs are informed and believe and based thereon allege that, at all times material hereto, each of the Defendants, was acting in an individual, corporate, partnership, associate, conspiratorial or other capacity or as the agent, employee, co-conspirator, and/or alter ego of its co-defendants, and in doing the acts herein alleged, was acting within the course and scope of its authority as such partner, associate, agent, employee, co-conspirator, or alter ego, and with the permission, consent, knowledge, authorization, ratification and direction of its co-defendants.

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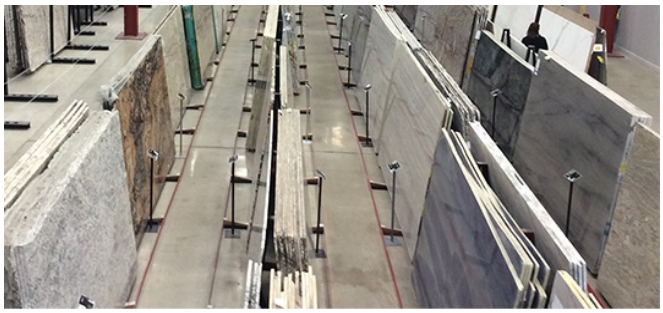
III. THE STONE SLAB AND COUNTERTOP INDUSTRIES

A. Stone Slabs and Countertops

30. Stone slabs are mineral products that were traditionally been made from natural stone but have increasingly been manufactured as artificial stone.



31. Prior to the 21st century, stone slabs were made from natural stone include basalt, dolomite, granite, limestone, marble, onyx, porcelain, quartzite, sandstone, serpentine and travertine.

32. In the past 25 years stone slabs have increasingly been manufactured from artificial stone, which is also called agglomerate, agglomerated stone, conglomerate, engineered stone, manufactured stone, quartz, reconstituted stone, and synthetic stone.

33. Until the last few years all stone slabs contained crystalline silica in concentrations ranging from as low as 3-5% in marble to as high as 93-95% in artificial stone.

34. Stone slabs are industrial products that require fabrication prior to installation as countertops for a consumer.

35. Natural stone slabs are cut from natural stone in quarries. Artificial stone slabs are manufactured in large industrial factories, most of which are located in foreign countries. Stone countertops are fabricated in many small fabrication shops located throughout the United States.

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B. Fabrication of Stone Countertops

36. The fabrication of stone countertops is typically done in small fabrication shops by a few workers. The workers who do this work have a few different job titles: "cutter," "fabricator," and "polisher." Workers who are called "installers" then transport and install countertops in homes and businesses, typically in kitchens and bathrooms.

37. Using a powered, large circular saw, the "cutter" cuts stone slabs to the size needed.

38. Using a smaller powered saw, the "fabricator" cuts holes for the sink, faucet, water return, and detergent dispenser. With a powered tool, the fabricator also grinds the edge of the slab.

39. Using another powered device, the "polisher" polishes the surface of the slab. In small fabrication shops that employ just a few workers, the fabricator also polishes the slab.

40. Lastly, using powered saws, grinding tools, drills, polishing machines, and various chemicals, the "installer" installs the countertop in the customer's kitchen or bathroom and does all necessary finishing work, including assembling and gluing stone pieces together, cutting holes for electrical outlets, edging, polishing, and sealing the finished countertops.

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C. Artificial Stone

41. Artificial stone is a composite material made of crushed stone that is bound together by an adhesive to create a solid surface. Artificial stone is also called Agglomerate, Agglomerated Stone, Conglomerate, Engineered Stone, Manufactured Stone, quartz, and/or Synthetic Stone.

42. Artificial stone was invented in the 1970s by Marcello Toncelli, who founded Breton SpA, an Italian company, at Castello di Godego in the province of Treviso, Italy. Breton obtained patents for vibro-compression under vacuum and a mixture of fragmented stone or silica dust with a polyester resin binder made of styrene monomer and anhydrides.

43. The basic raw material and major constituent of most artificial stone products is quartz, i.e., crystalline silica.

44. Artificial stone is usually sold as slabs, but is sometimes sold as blocks.

45. Artificial stone is primarily used to fabricate kitchen and bathroom countertops.

46. Artificial stone is manufactured in large factories, most of which have been located outside the United States, until quite recently.

47. In 1987 Caesarstone began manufacturing artificial stone at Kibbutz Sdot Yam near Haifa in Israel on the shore of the Mediterranean Sea; in 1990 Cosentino began manufacturing artificial stone in Almeria, Spain, in Andalusia in southeastern Iberia on the Mediterranean Sea.

48. Today artificial stone today is manufactured worldwide by Aro Granite Industries (India), Atlas Quartz (US), Baba Quartz (India), Baoliya (China), Belenco (Turkey), Bitto (China), Breton (Italy), Caesarstone (Israel), Cambria (US), Cimstone (Turkey), Compac (Spain), Cosentino (Spain), Dal-Tile (US), Diresco (Belgium), Dupont (Canada), Fortum (Finland), Gelandi (China), Guidoni Group (Brazil), Hanwha (South Korea), H&R Johnson (India), LX Hausys (South Korea), Lotte Chemical (South Korea), Meyate (China), M S International (India), Overland (China), Pokarna (India), Polystone (Germany), Quantra (India), Quarella (Spain), Quartzform (Germany), Qianyun (China), RMC (Portugal), Santa Margherita (Spain), Seieffe (Italy), Sinostone (China), Stone Italiana (Italy), Strasser Steine (Austria), Technistone (Czech Republic), Totem Quartz (Iran), USA Quartz (US), Uviistone (China), Vicostone (Vietnam), Wilsonart (South Korea), Zhongxun (China), et al.

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D. How Artificial Stone Is Manufactured

49. Artificial stone is manufactured in large factories, mostly in foreign countries.

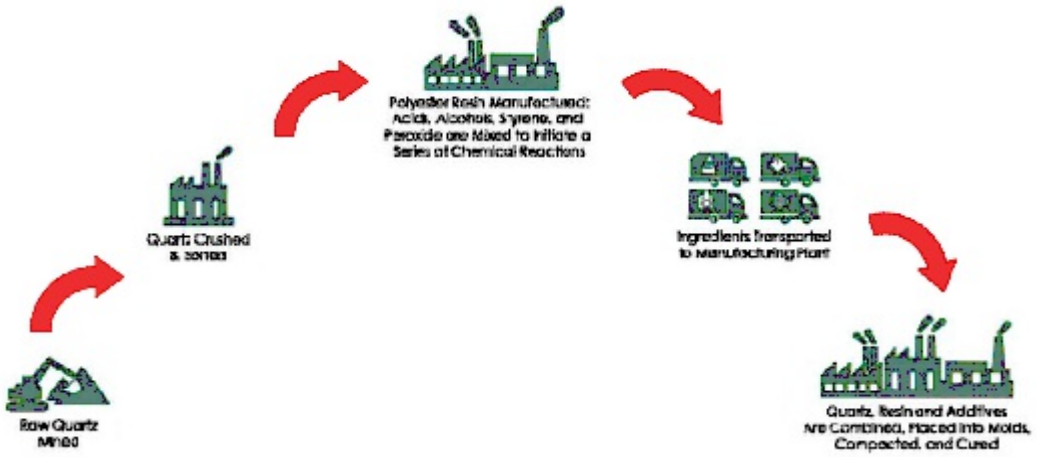
50. In 1987 Caesarstone began manufacturing artificial stone at Kibbutz Sdot Yam near Haifa in Israel on the shore of the Mediterranean Sea.

51. In 1990 Cosentino began manufacturing artificial stone in Almeria, Spain, located in Andalusia in southeastern Iberia on the Mediterranean Sea.

Caesarstone's artificial stone factory in Israel

Cosentino's artificial stone factory in Spain

52. Artificial stone is manufactured by mining quartz, transporting it to a factory where it is crushed and pulverized into a powder containing extremely small particles, mixing the powder with a polymeric resin, pigments, and other chemicals, heating the mixture, and curing it as slabs.



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E. Defendants' Artificial Stone Products

53. Pursuant to *Bockrath v. Aldrich Chemical Co.* (1999) 21 Cal.4th 71, Plaintiffs identify the following artificial stone products of the named defendants to which they were occupationally exposed in California in the course of their work as stone countertop fabricators and/or installers:

ARIZONA TILE, L.L.C.

Della Terra Quartz, Engineered Stone, Quartz

C & C NORTH AMERICA, INC. (dba Cosentino North America)

Cosentino, Dekton, Engineered Stone, Quartz, Sensa, Silestone

CAESARSTONE USA, INC.

Caesarstone Classico, Caesarstone Concetto, Caesarstone Metropolitan, Caesarstone Motivo, Caesarstone Supernatural, Engineered Stone, Quartz

CAMBRIA COMPANY LLC

Cambria Quartz Surfaces, Engineered Stone, Quartz

DAL-TILE DISTRIBUTION, LLC, DAL-TILE, LLC, and DAL-TILE TENNESSEE, LLC

Dal-Tile Quartz, Engineered Stone, One Quartz, One Quartz Surfaces, Quartz

ELITE QUARTZ MFG LLC

Elite Quartz, MSI Quartz, Quartz, Q Premium Natural Quartz, Spectrum Quartz

HYUNDAI L&C USA, LLC

Hanex Solid Surfaces, HanStone Quartz

LX HAUSYS AMERICA, INC.

Engineered stone, HIMACS, LX Hausys Quartz, LG Hausys Quartz, Quartz, Viatera

M S INTERNATIONAL, INC.

Engineered Stone, MSI Quartz, Quartz, Q Quartz (Premium Natural Quartz)

PARAGON INDUSTRIES, INC. (dba Bedrosians Tile & Stone)

Engineered Stone, Quartz, Revera Quartz, Sequel Quartz

SURFACE WAREHOUSE, L.P. (dba Vadara)

Engineered Stone, Living Stone, Quartz, Vadara

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IV. ADVERSE HEALTH EFFECTS OF ARTIFICIAL STONE PRODUCTS

A. Toxic Exposures of Artificial Stone Countertop Fabricators and Installers

54. Cutting, grinding, drilling, chipping, edging, and polishing artificial stone slabs produces large amounts of respirable crystalline silica dust which stone fabrication workers routinely inhale, causing silicosis and lung cancer, as well as other silica-related chronic diseases.

55. Fabrication workers who cut, grind, drill, chip, edge, and/or polish artificial stone products are not only exposed to high concentrations of respirable crystalline silica, but are also exposed to other toxic substances in artificial stone, including metals used as pigments and polymeric resins as binders.

56. In addition to crystalline silica, pulmonary fibrosis (scarring of the lung tissue) is caused by many metals that are constituents of artificial stone, including aluminum, antimony, arsenic, chromium, cobalt, copper, iron, manganese, nickel, titanium, tungsten, and vanadium. Some of these metals also cause an immunologic lung disease called hypersensitivity pneumonitis characterized by granulomas in lung tissue that also causes pulmonary fibrosis.

57. As a result of friction and heat generated by electric-powered tools that are used in fabricating artificial stone countertops, volatile organic compounds (VOCs) are produced, the predominant species being styrene, but also including phthalic anhydride, benzene, ethylbenzene, and toluene.

58. Styrene and phthalic anhydride are respiratory irritants that cause various adverse pulmonary effects including asthma, bronchiolitis obliterans, decreased lung function as well as sclerosis (destruction of lung tissue) and fibrosis (resultant scarring of lung tissue).

59. Artificial stone dust is especially toxic to the human lungs due to its extremely high respirable crystalline silica content, the ultrafine and nanosized particles that are released from artificial stone when it is fabricated, the fibrogenicity of the metals that are used as pigments in artificial stone, as well as the volatile organic compounds that are generated from heat and pressure by the electric-powered tools that are used by fabricators to fabricate artificial stone countertops.

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B. Diseases Caused by Crystalline Silica Exposure

60. Crystalline silica is one of the most toxic substances known to mankind, causing multiple chronic human diseases.[1]

61. One of the major hazards of crystalline silica is silicosis, a chronic, debilitating and incurable fibrotic lung disease has claimed the lives of more workers than any other chemical or substance, including asbestos. "Silicosis is the most prevalent pneumoconiosis worldwide."[2]

62. "If someone decided to compile a list of horrible and deadly occupational diseases, silicosis would surely lead it. Silicosis involves the chronic and massive destruction of the lungs and is caused by the long-term inhalation of silica (finely ground sand) dust. It initially causes terrible shortness of breath and ultimately slow suffocation and death."[3]

63. There are three types of silicosis - acute silicosis, accelerated silicosis, and chronic silicosis, which respectively manifest in less than 5 years, 5 to 10 years, and more than 10 years. Respirable crystalline silica can cause all three types of silicosis.[3]

64. Respirable crystalline silica has been classified by the International Agency for Research on Cancer as a known human carcinogen and is a major cause of industrial lung cancer.[4]

65. Other lung diseases that result from respirable crystalline silica exposure include usual interstitial pneumonia, asthma, chronic obstructive pulmonary disease, sarcoidosis, Caplan's syndrome, tuberculosis and other mycobacterial lung infections.[5]

66. Respirable crystalline silica is also a known cause of autoimmunity and many human

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[1] Hoy RF, et al., "Silica-related diseases in the modern world," *Allergy* 2020; 75:2805-2817.

[2] Fazio JC, et al., "A review of silicosis and other silica-related diseases in the engineered stone countertop processing industry," *J. Occup. Med. Toxicol.* 2025; 20:9.

[3] Markel H, et al., "Foreword," to Rosner D, et al., "Deadly Dust: Silicosis and the On-Going Struggle to Protect Workers' Health," (new and expanded ed., U. Michigan Press, 2006).

[4] International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 68: "Silica, Some Silicates, Coal Dust and *para*-Aramid Fibrils," (IARC 1997).

[5] Hoy RF, et al., "Silica-related diseases in the modern world," *Allergy* 2020; 75:2805-2817; Fazio JC, et al., "A review of silicosis and other silica-related diseases in the engineered stone countertop processing industry," *J. Occup. Med. Toxicol.* 2025; 20:9.

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autoimmune diseases including rheumatoid arthritis, systemic sclerosis, Sjögren's syndrome, systemic lupus erythematosus, mixed connective tissue disease, psoriatic arthritis, ankylosing spondylitis, dermatomyositis, polymyositis, antineutrophil cytoplasmic antibody-positive vasculitis.[6]

67. Exposure to crystalline silica can also cause systemic toxicity, resulting in injury and disease to multiple organ systems, including the kidneys, the heart, the liver, and other organs.[7]

68. Exposure to respirable crystalline silica is also a known cause of human kidney disease, including chronic kidney disease and end-stage kidney disease.[8]

69. Exposure to respirable crystalline silica is also a known cause of cardiovascular disease and heart disease.[9]

70. Exposure to respirable crystalline silica, especially silica nanoparticles, is also a known cause of liver disease, including fatty liver disease.[10]

71. Exposure to crystalline silica is also a known cause of mitochondrial dysfunction.[11]

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[6] Hoy RF, et al., "Silica-related diseases in the modern world," *Allergy* 2020; 75:2805-2817; Fazio JC, et al., "A review of silicosis and other silica-related diseases in the engineered stone countertop processing industry," *J. Occup. Med. Toxicol.* 2025; 20:9; Cocco P, "Occupational Exposure to Silica and Autoimmune Diseases: A Systematic Review," *Work Health* 2025; 1(1):2; Boudigaard SH, et al., "Occupational exposure to respirable crystalline silica and risk of autoimmune rheumatic diseases: a nationwide cohort study," *Int J. Epidemiol.* 2021; 50 (4):1213-1226; Cooper GS, et al., "Occupational exposures and autoimmune diseases," *Int. Immunopharmacol.* 2002; 2(2-3):303-313; Parks CG, et al., "Occupational Exposure to Crystalline Silica and Autoimmune Disease," *Environ. Health Perspect.* 1999; 107(Suppl. 5):793-802; Steenland K, et al., "Silica exposure and autoimmune diseases," *Am. J. Ind. Med.* 1995; 28(5):603-608.

[7] Hoy RF, et al., "Silica-related diseases in the modern world," *Allergy* 2020; 75:2805-2817; Fazio JC, et al., "A review of silicosis and other silica-related diseases in the engineered stone countertop processing industry," *J. Occup. Med. Toxicol.* 2025; 20:9.

[8] Rosenman KD, et al., "Kidney disease and silicosis," *Nephron* 2000; 85(1):14-19; Rapiti E, et al., "End stage renal disease among ceramic workers exposed to silica," *Occup. Environ. Med.* 1999; 56(8):5599-561; Möhner M, et al., "Occupational exposure to respirable crystalline silica and chronic non-malignant renal disease: systematic review and meta-analysis," *Int. Arch. Occup. Environ. Health* 2017; 90(7):555-574.

[9] Gurzu IL, et al., "Unveiling the threat of crystalline silica on the cardiovascular system: A comprehensive review of the current knowledge," *Front. Cardiovasc. Med.* 2025; 12:1506846.

[10] Carmichael, GP Jr, et al., "Hepatic silicosis," *Am. J. Clin. Pathol.* 1980; 73:720-722; Nishimori H, et al., "Silica nanoparticles as hepatotoxicants," *Eur. J. Pharm. Biopharm.* 2009; 72:496–501; Abulikemu A, et al., "Silica nanoparticles aggravated the metabolic associated fatty liver disease through disturbed amino acid and lipid metabolisms-mediated oxidative stress," *Redox Biol.* 2023; 59:102569.

[11] Zhao J-H, et al., "The role of mitochondrial dysfunction in macrophages on SiO_2-induced pulmonary fibrosis: A review," *J. Appl. Toxicol.* 2024; 44(1):86-95; Guo C, et al., "Mitochondrial dysfunction, perturbations of mitochondrial dynamics and biogenesis involved in endothelial injury induced by silica nanoparticles," *Environ. Pollution* 2018; 236:926-936.

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C. The New Artificial Stone Silicosis Epidemic

72. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation.[12]

73. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to artificial stone; all of the cases were diagnosed based on detailed occupational history. Histologic confirmation was obtained in all but 2 of the cases. Of these, 15 (60%) were determined to be lung transplant candidates. All of these patients worked with the same commercial brand of synthetic stone material, cutting it for kitchen and other countertops. The material was CaesarStone; it contained at least 85% crystalline silica. All 25 patients reported that more than 90% of their typical work duties involved handling Caesarstone. Less than 10% included exposure to other potential sources of silica, primarily natural granite.[13]

74. The first cases of silicosis in Spanish artificial stone workers were published in 2010 by researchers at the National Institute of Silicosis at the University Hospital in Asturias, Spain. They reported 3 cases in workers who had been employed for 17 years by a small ornamental stone company that fabricated and installed in homes and buildings. The workers were all young: 32, 34, and 37 years old. Chest x-rays of all 3 workers showed nodular opacities with diffuse bilateral distribution and more profuse localization in the upper lobes, with a slight increase in mediastinal and/or hilar nodes. In case 1, a cluster of nodules was observed with progressive massive fibrosis; this worker was diagnosed with complicated silicosis.[14]

75. In 2011, researchers at Galdakao Hospital in Bizkaia, Spain published a study of 11 workers who were exposed to different types of quartz surfaces since 1995. Four of the subjects

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[12] Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424.

[13] Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424.

[14] Martínez C, et al., "Silicosis, a Disease With an Active Present," *Arch. Bronconeumol.* 2010; 46(2):97-100 [in Spanish with English abstract].

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worked in the cutting workshop; the rest of the workers worked in assembly (i.e. fabrication), without any specific respiratory protection apparatus. They diagnosed 6 of the 11 workers with silicosis, which equated to a disease prevalence in this work environment of 54.5%. Of the 6 workers affected, 5 (83.3%) were assembles (fabricators). The investigators attributed silicosis in these workers to quartz conglomerates (artificial stone).[15]

76. The next series of cases were reported in 2012 by Italian researchers who identified 7 silicosis cases in a group of 29 fabrication workers.[16]

77. "In May 2014, the Texas Department of State Health Services was notified of a case of silicosis with progressive massive fibrosis in a Hispanic male aged 37 years who worked for an engineered stone countertop company as a polisher, laminator, and fabricator. He was exposed to dust for 10 years from working with conglomerate or quartz surfacing materials containing 70% - 90% crystalline silica. This is the first reported case of silicosis associated with exposure to quartz surfacing materials in North America."[17]

78. "In January 2019, the California Department of Public Health identified, through review of hospital discharge data for silicosis diagnoses (*International Classification of Diseases, Tenth Revision* [ICD-10] code J62.8), a Hispanic man aged 37 years who was hospitalized in 2017 (CA-1) (Table). He worked at a stone countertop fabrication company during 2004–2013, mainly with engineered stone. His work tasks included polishing slabs and dry-cutting and grinding stone edges. Workplace measurements during a California Division of Occupational Safety and Health inspection in 2009 showed respirable crystalline silica levels up to 22 times higher than the permissible exposure limit (PEL) of 0.1 mg/m3 in effect in California at that time. After developing respiratory symptoms in 2012, he had a chest CT scan, which revealed findings of silicosis.

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[15] Pascual S, et al., "Prevalence of silicosis in a marble factory after exposure to quartz conglomerates," *Arch. Bronconeumol.* 2011; 47(1):50-51 [in Spanish with English abstract].

[16] Bartoli D, et al., "Silicosis in employees in the processing of kitchen, bar and shop countertops made from quartz resin composite. Provisional results of the environmental and health survey conducted within the territory of USL 11 of Empoli in Tuscany among employees in the processing of quartz resin composite materials and review of the literature," *Ital. J. Occup. Environ. Hyg.* 2012; 3(3):138-143.

[17] Friedman GK, et al., "Silicosis in a Countertop Fabricator – Texas, 2014," *Morbidity and Mortality Weekly Report*, Feb. 13, 2015; 64(5):129-130.

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Pulmonary function testing showed restrictive defects with reduced diffusion capacity; surgical lung biopsy showed mixed dust pneumoconiosis with polarizable particles consistent with silica. He concurrently received a diagnosis of scleroderma, with positive anti-Scl-70 and antinuclear antibodies. He died from silicosis in 2018 at age 38 years. Further investigation of patient CA-1's place of employment, in collaboration with the California Division of Occupational Safety and Health, identified two additional silicosis cases among stone fabricators."[18]

79. "This report describes 18 cases of silicosis, including the first two fatalities reported in the United States, among workers in the stone fabrication industry in California, Colorado, Texas, and Washington. Several patients had severe progressive disease, and some had associated autoimmune diseases and latent tuberculosis infection. Cases were identified through independent investigations in each state and confirmed based on computed tomography (CT) scan of the chest or lung biopsy findings. Silica dust exposure reduction and effective regulatory enforcement, along with enhanced workplace medical and public health surveillance, are urgently needed to address the emerging public health threat of silicosis in the stone fabrication industry."[19]

80. By 2020 the epidemic was international in scope, with more than 300 cases (including 22 lung transplant cases) in Israel, more than 300 cases in Spain, more than 100 cases in China, 98 cases in Australia, 34 cases in Italy, and 18 cases in the United States.

81. In 2022 Australian researchers reported identifying 579 cases of silicosis among workers in the stone benchtop industry in Australia - 238 cases in Queensland, 175 in Victoria, 121 in New South Wales, 24 in Western Australia, 18 in South Australia and 3 cases in Tasmania.[20]

82. By the end of 2022 the Social Security agency in Spain had registered 4,906 reports of silicosis due to an occupational disease.[21]

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[18] Rose C, et al., "Severe Silicosis in Engineered Stone Fabrication Workers – California, Colorado, Texas, and Washington, 2017-2019," *Morbidity and Mortality Weekly Report*, Sept. 27, 2019; 68(38):813-818.

[19] Rose C, et al., "Severe Silicosis in Engineered Stone Fabrication Workers – California, Colorado, Texas, and Washington, 2017-2019," *Morbidity and Mortality Weekly Report*, Sept. 27, 2019; 68(38):813-818.

[20] Hoy RF, et al., "Correspondence on 'Demographic, exposure and clinical characteristics in a multinational registry of engineered stone workers with silicosis,' by Hua et al.," *Occup. Environ. Med.* 2022; 79(9):647-648.

[21] Inma Muro, "Silicosis: After the 1st prison sentence, Cosentino sits on the bench again," *Crónica Libre*, July 5, 2023.

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83. In 2022 researchers from Curtin University in Australia published a study in which they modeled the future course of the artificial stone silicosis epidemic. One of the investigators of this study, Dr. Renee Carey, concluded: "Our modelling predicts more than 10,000 Australians will develop lung cancer and up to 103,000 workers will be diagnosed with silicosis as the result of their current exposure to silica dust at work."[22]

84. In 2023, researchers from California published a study in which they described clinical, socioeconomic, and occupational characteristics of patients diagnosed with silicosis associated with engineered stone in California. This case series included reported cases of silicosis associated with fabrication of engineered stone countertops, as identified by statewide surveillance by the California Department of Public Health (2019-2022). Data analysis was performed from October 2022 to March 2023. Patient interviews and medical record abstractions were used to assess occupational exposure to respirable crystalline silica, including duration of work tenure and preventive measures undertaken. Demographics, clinical characteristics, health care utilization, and clinical outcomes were obtained, including vital status, hypoxia, and lung transplant. This case series identified 52 male patients meeting inclusion criteria; median (IQR) age was 45 (40-49) years, and 51 were Latino immigrants. Ten (19%) were uninsured, and 20 (39%) had restricted-scope Medi-Cal; 25 (48%) presented initially to an emergency department. A delay in diagnosis occurred in 30 (58%) patients, most commonly due to alternative initial diagnoses of bacterial pneumonia (9 [30%]) or tuberculosis (8 [27%]). At diagnosis, 20 (38%) patients had advanced disease (progressive massive fibrosis) with severely or very severely reduced forced expiratory volume in 1 second in 8 (18%) and 5 (11%), respectively. Of the cases, 10 (19%) were fatal; median age at death was 46 years, and 6 patients (12%) were alive with chronic resting hypoxia. Eleven were referred for lung transplant: 3 underwent transplant with 1 fatality; 7 were declined transplant with 6 fatalities; and 1 died prior to listing. Median work tenure was 15 years; 23 (45%) reported use of water suppression for dust mitigation, and 25 (48%) continued to fabricate stone after being diagnosed with silicosis. The researchers concluded silicosis associated with occupational exposure to dust from engineered

[22] Curtin University Press Release: "10,000 Aussie workers set to develop lung cancer from silica dust: study," *News at Curtin,* July 12, 2022.

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stone primarily occurred among young Latino immigrant men; many patients presented with severe disease, and some cases were fatal.[23]

85. Updating data regarding silicosis in Victoria, Australia in 2023 Australian researchers published a stud reporting a silicosis prevalence of 28.3% (117 of 414 participants who met prespecified criteria for secondary screening) among stone benchtop workers in Victoria, Australia.[24]

86. On May 29, 2024, the *Los Angeles Times*, reported that Cal/OSHA recently estimated that out of nearly 5,000 such workers statewide, as many as 200 could die of the disease [silicosis]."[25]

87. On September 4, 2025, researchers from the California Department of Public Health published a study regarding the silicosis epidemic in California. Of 1,817 reports of possible silicosis for 648 individuals that the department received from 2019 to 2024, silicosis was confirmed in 296 (46%) of cases, including 243 (82%) associated with engineered stone exposures. Engineered stone cases were more likely to be younger, men, Latino, and from Los Angeles County than were non–engineered stone cases. Of engineered stone cases, at least 15 (6%) were known to have died, and 60 (25%) were referred for lung transplant, including 30 (12%) who received transplants. The investigators from the California Department of Public Health concluded: "This is 1 of the largest case series of engineered stone silicosis reported worldwide and is especially noteworthy because nearly all cases were found through ongoing passive data collection, as opposed to active screening of engineered stone workers."[26]

88. As of completion of drafting of this Complaint at year's end in 2025, 466 cases and 25 deaths from artificial stone-induced silicosis have been documented in young Hispanic and Latino men on the Engineered Stone Silicosis Surveillance Dashboard of the California Department of Public Health.

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[23] Fazio JC, et al., "Silicosis Among Immigrant Engineered Stone (Quartz) Countertop Fabrication Workers in California," *JAMA Intern. Med.* 2023; 183(9):991-998.

[24] Hoy RF, et al., "Prevalence and risk factors for silicosis among a large cohort of stone benchtop industry workers," *Occup. Environ. Med.* 2023; 80(8):439-446.

[25] Emily Alpert Reyes, "California could require licenses for stonecutting shops amid deaths of young workers," *Los Angeles Times* (May 29, 2024).

[26] Flattery J, et al., "Silicosis Surveillance in California, 2019-2024: Tracking an Epidemic," *Am. J. Public Health* 2025; 115(11):1913-1921.

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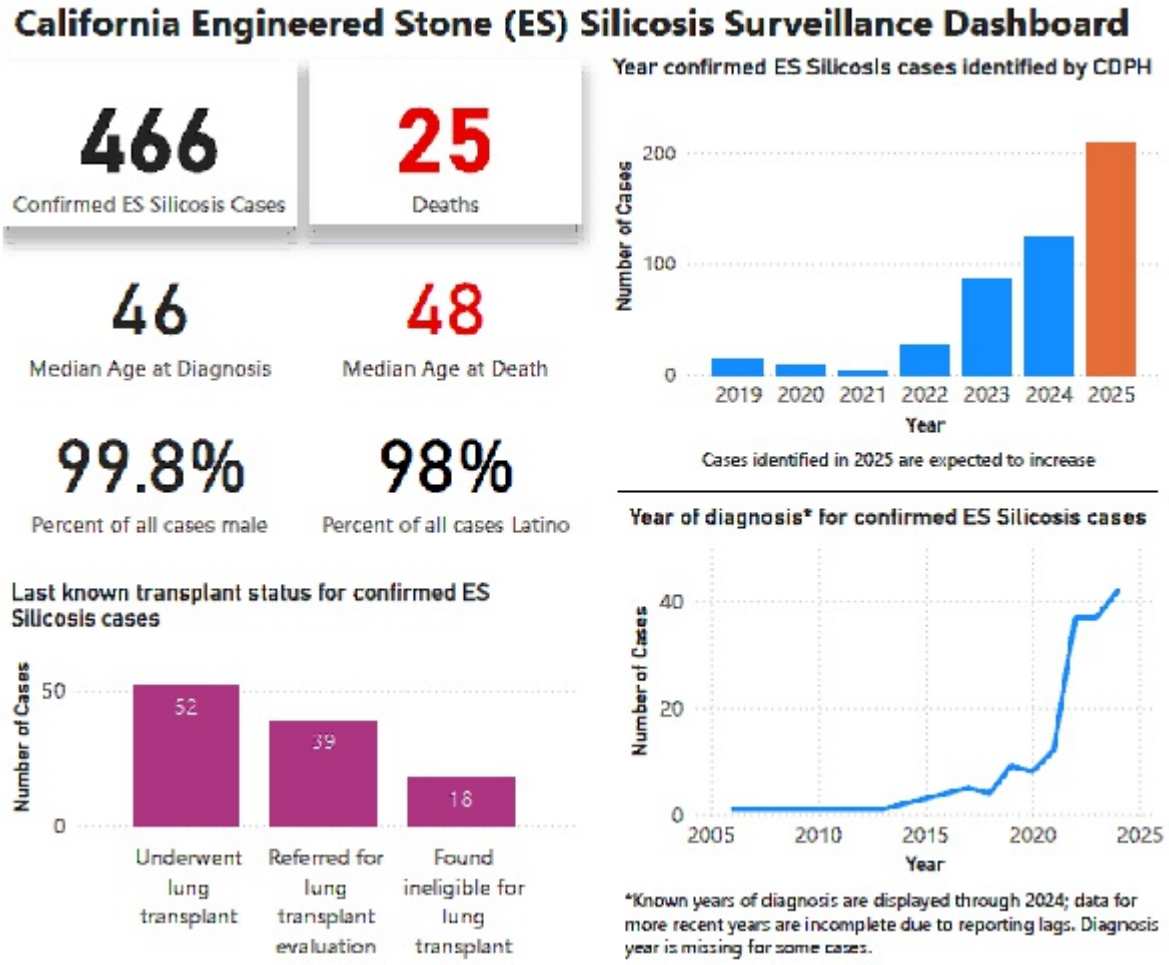
89. Following is a screenshot of the webpage of the California Engineered Stone (ES) Silicosis Surveillance Dashboard as of December 31, 2025:



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D. Australia's Ban of the Importation and Use of Artificial Stone

90. Since at least as early as 2019, Australian silicosis victims, their families, workers, unions, physicians, regulators, and public health officials and others have called for a ban on the importation, sale, and use of artificial stone due to its extreme dangers to worker health and safety.

91. In 2019 Laura Kewley of ABC (Australian Broadcasting Corporation) News reported that "a man who developed silicosis after working with engineered stone products has called for the products to be banned to prevent more people developing the disease." She reported: "Renee and Braden Barnes' life has changed dramatically since Braden was diagnosed with silicosis." He said: "There's no way you can produce a kitchen purely, without having some sort of dust come off the manufacturing process. Even when it is used wet (and) turns to sludge, the sludge dries, gets on your boots and turns back to powder." She reported that "new figures . . . show a surge in new cases." At the time she reported that "[t]here are now 260 cases across Australia."

92. "When Cal/OSHA took a closer look at the industry in 2019 and 2020, it found that 72% of shops where it conducted air sampling were in violation of silica rules. It recently estimated that out of nearly 5,000 such workers statewide, as many as 200 could die of the disease [silicosis]."[27]

93. In 2020, Alison Reid, Associate Professor in Epidemiology and Biostatistics at the School of Public Health of Curtin University in Perth, Australia, called for a ban of artificial stone. She prepared a PowerPoint presentation titled "Engineered Stone: Why a Ban Is The Only Answer."[28]

94. In her PowerPoint presentation, Dr. Reid noted that artificial stone has a much higher silica content than natural stone (95% v 10-45% in granite) and that fabrication processes with power tools product high levels of silica dust -- more than 300 times the occupational standard. She noted

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[27] State of California, Department of Industrial Relations, Occupational Safety and Health Standards Board, *Finding of Emergency, Government Code Section 11346.1, Occupational Safety and Health Standards Board, Proposed Emergency Regulation, Title 8, California Code of Regulations, General Industry Safety Orders, Chapter 4, Subchapter 7, Revised Section 5204: Occupational Exposures to Respirable Crystalline Silica* (December 14, 2023).

[28] Available online at https://research.curtin.edu.au/businesslaw/wp-content/uploads/sites/5/2020/09/Curtin-Corner-Engineered-Stone-A-Reid-11-Sep-2020-.pdf

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that a study from the UK showed that 61% of respirable crystalline silica exposures where water suppression was present exceeded the respirable crystalline silica workplace exposure limit and that high levels of exposure were reported even when wet cutting.[29]

95. Dr. Reid compared the situation to the asbestos disease epidemic of the last century, when Australian regulators aimed to control exposure rather than eliminate it, resulting in high rates of unnecessary morbidity and mortality from asbestosis, lung cancer and mesothelioma. Dr. Reid noted that efforts to control asbestos exposure rather than ban it resulted in an estimated 18,000 cases of mesothelioma, 108,000 cases of lung cancer, and a substantial, but unknown number of cases of asbestosis, and that Australia had one of the highest rates of asbestos-related diseases globally.

96. Dr. Reid argued that engineered stone should be banned because it is a known cause of a preventable disease, silicosis is an incurable disease with limited treatment options, artificial stone dust is difficult to control, and there are safer product alternatives. Pointedly, Dr. Reid wrote: "LET'S LEARN FROM OUR ASBESTOS EXPERIENCE RATHER THAN REPEAT IT!"

97. In 2022, Professor Lin Fritschi, a co-author of the 2021 Curtin University Study, said that banning engineered stone would prevent almost hundreds of lung cancers and thousands of silicosis cases. Brett Lackey and Peter Vincent, *Daily Mail Australia* (November 22, 2022).

98. The same day Mary Lloyd of ABC News quoted Zach Smith, incoming national secretary of the union saying: "This product is killing workers and the reality is Australian workers will keep dying unless we ban engineered stone." Mary Lloyd further reported that Kate Cole, president of the Australian Institute of Occupational Hygienists, likened the risk of exposure to silica to that of asbestos and said that high-silica stone products should be banned as soon as possible."

99. The next day, November 23, 2022, Claire Siracuse and Najma Sambul of The Sydney Morning Herald reported that the Construction, Forestry, Maritime, Mining and Energy Union (CFMMEU) sought to "stop this killer stone" by banning artificial stone, and that the union "has announced it will ban the use of engineered stone if the federal government fails to do so by 2024."

[29] Alison Reid, "Engineered Stone: Why a Ban Is The Only Answer," citing PEJ Baldein et al, "Exposure to RCS in the BG brick manufacturing and stone working industries," *Ann. Work Exp Health* 2019; 63(2):184-196; Office of Industrial Relations Workplace Health and Safety Queensland. Findings report: phase one audits of engineered stone benchtop fabricators in South East Queensland. (2019)

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100. By February of 2023, medical and health organizations Lung Foundation Australia, the Thoracic Society of Australia, the Australian and New Zealand Society of Occupational Medicine, the Australian Institute of Health & Safety, Public Health Association Australia, and the Australian Institute of Occupational Hygienists had all called for a ban of engineered stone.[30]

101. On February 22, 2023, Adele Ferguson and Angus Thompson of WAtoday, reported that even Cosentino, "one of the world's largest stone benchtop companies . . . called for a ban on products blamed for a deadly silicosis epidemic." They reported: "Manufacturer Cosentino produces more than one in every five domestic kitchen benchtops sold in Australia and is facing international scrutiny over its safety record. It is not pushing for a national coordinated approach to reduce risks associated with products containing high levels of silica, ahead of a meeting of workplace safety ministers next week." They quoted a Cosentino spokesperson as saying: "We have an immediate solution without disrupting the construction and building market, and prices won't increase. The immediate solution is everyone buys products that are less than 40 per cent silica."

102. On February 28, 2023, *The Guardian* reported that federal workplace relations minister, Tony Burke, said that the work, health and safety ministers of all Australian states and territories had unanimously agreed to ask Safe Work Australia to prepare a plan to ban artificial stone products.[31]

103. In August 2023, Safe Work Australia presented its report to federal, state and territory Work Health and Safety ministers with recommendations on options to ban engineered stone.

104. On October 27, 2023, Safe Work Australia released its report recommending a ban on the importation and use of all artificial stone in Australia, which concluded: "A complete prohibition on the use of engineered stone is recommended." It reached this conclusion upon finding that "[t]he risks posed by working with engineered stone are serious and the possible consequences of being exposed to RCS [respirable crystalline silica] generated by engineered stone are severe and sometimes fatal. To date, we – PCBUs [persons conducting a business or undertaking], workers,

[30] Available at https://www.aumanufacturing.com.au/medical-bodies-call-for-ban-on-engineered-stone.

[31] Paul Karp, "Australia moves to fast-track ban on silica stone benchtops that cause fatal lung disease," *The Guardian* (February 28, 2023), available online at https://www.theguardian.com/australia-news/2023/feb/28/australia-moves-to-ban-silica-engineered-stone-benchtops-silicosis-fatal-lung-disease.

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regulators and policy agencies – have failed to ensure the health and safety of all workers working with engineered stone."[32]

105. Safe Work Australia rejected proposals to allow the use of engineered stone containing lower crystalline silica concentrations because upon finding that "[a] lower silica content engineered stone is not expected to result in improvements in compliance," because "[t]he features of the sector that have contributed to the current levels of non-compliance remain" and "permitting work with lower silica engineered stone may encourage even greater non-compliance with WHS [worker health and safety] laws as there may be an incorrect perception that these products are 'safer'."

106. Safe Work Australia found "[t]here is also no evidence that lower silica engineered stone poses less risk to worker health and safety. Manufacturers have not yet established (through independent scientific evidence) that these products are without risks to the health and safety of workers and others in the workplace. There is no toxicological evidence of a 'safe' threshold of crystalline silica content, or that the other components of lower silica engineered stone products (e.g. amorphous silica including recycled glass, feldspar) do not pose additional risks to worker health." The agency concluded: "The only way to ensure that another generation of Australian workers do not contract silicosis from such work is to prohibit its use, regardless of its silica content. The cost to industry, while real and relevant, cannot outweigh the significant costs to Australian workers, their families and the broader community that result from exposure to RCS from engineered stone."

107. On December 13, 2023, ABC News reported Australian ministers met that day and voted unanimously to ban the importation and use of engineered stone in all states and territories throughout Australia - the first nationwide ban of artificial stone in the world. The report stated that the ban would start on July 1, 2024 in most Australian states and territories, with people being advised not to order any artificial stone after January 1, 2024.[33]

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[32] Safe Work Australia, *Decision Regulation Impact Statement: Prohibition on the use of engineered stone*, https://www.safeworkaustralia.gov.au/sites/default/files/2023-10/decision_ris_-_prohibition_on_the_use_of engineered_stone_-_27_october_2023.pdf.

[33] Michael Atkin, "Australia makes world-first decision to ban engineered stone following surge in silicosis cases," *ABC News* (Dec. 13, 2023). https://www.msn.com/en-au/health/other/australia-makes-world-first- decision-to-ban-engineered-stone-following-surge-in-silicosis-cases/ar-AA1lqbWZ.

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E. Cal-OSHA'S Emergency Temporary Standard

108. On December 14, 2023, the California Occupational Safety and Health Standards Board issued a report, *Finding of Emergency, Government Code Section 11346.1, Occupational Safety and Health Standards Board, Proposed Emergency Regulation, Title 8, California Code of Regulations, General Industry Safety Orders, Chapter 4, Subchapter 7, Revised Section 5204:* ***Occupational Exposures to Respirable Crystalline Silica.*** This report identified 15 "Key Points":

- The Board is proposing an Emergency Temporary Standard (ETS) to protect workers in the stone fabrication industry from exposure to respirable crystalline silica (RCS).
- When inhaled, RCS can result in silicosis, an incurable, progressive lung disease that causes pulmonary fibrosis, respiratory failure, and in many cases, death.
- RCS exposure from working with artificial stone produces an aggressive form of silicosis, with rapid disease progression, accelerated decline in lung function, and high mortality, typically at a young age.
- There is a growing number of silicosis cases in the artificial stone fabrication industry that began in 2019 and has since been described by the California Department of Health (CDPH) Occupational Health Branch (OHB) as an epidemic.
- In July 2023, OHB investigators reported a total of 52 workers with silicosis who were exposed to RCS while fabricating countertops from artificial stone.
- The median age of these workers was 45 years at diagnosis; 51 (98%) were Latino men. Ten of these patients (19%) died by the time investigators reported their findings. The median age at death was 46 years, with a median work tenure of 15 years. Three individuals underwent lung transplantation, which has a five-year survival rate of 59%.
- In November 2023, OHB reported that the total number of silicosis cases in the artificial stone industry had increased 79%, from the 52 workers reported in July of 2023, to a total of 93. One worker with severe silicosis is 27 years of age, is on continual oxygen, and worked for a period of 10 years in the industry.

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- About 4,040 workers are employed in California's stone fabrication shops. Based on a silicosis prevalence rate of 12% to 21% and a fatality rate of 19%, Cal/OSHA estimates that between 500 and 850 cases of silicosis will occur among these workers, and between 90 and 160 will likely die of silicosis.
- Cal/OSHA's existing silica standard, California Code of Regulations (CCR) title 8, section 5204, was promulgated based on the experience of silicosis in traditional industries such as mining, quarrying and sandblasting; it is not well calibrated to the small businesses and working conditions of the stone fabrication industry. In 2019, Cal/OSHA found that 72% of shops in this industry were out of compliance with section 5204.
- Section 5204 also contains three key loopholes that allow employers to easily exempt themselves from the requirements of the regulation and put workers in grave danger.
- In light of these factors, an ETS is needed that will require far safer conditions for workers who handle both artificial stone (containing >0.1% silica) and natural stone (containing >10% silica). An ETS is needed that will be clearer for employers to implement and more efficient for Cal/OSHA to enforce.
- The proposed ETS meets these objectives with new requirements pertaining to engineering controls, safe work practices, respiratory protection, signage, housekeeping, training and reporting.
- The proposed ETS also provides a means for Cal/OSHA to quickly identify RCS hazards and efficiently stop certain operations in a shop, or shut-down the shop itself, pending abatement of those hazards.
- With these immediate improvements, the proposed ETS is expected to substantially reduce the number of silicosis cases and deaths in California.
- Over 10 years, the expected costs of the proposed ETS to businesses are $66 million; benefits over the same period are estimated at $603 million, not including indirect costs associated with lost wages and benefits, lost lifetime productivity, and pain and suffering.

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109. The report explained the objective of the proposed emergency regulation as follows:

> The objective of the proposed emergency regulation is to reduce occupational RCS exposure and silicosis occupational disease cases by responding as efficiently as possible to an epidemic of silicosis that has emerged among workers in the artificial stone fabrication industry. To date, all of the affected workers have been exposed occupationally to RCS while fabricating countertops from artificial stone. Many of these workers have since died of their disease. Relative to the typical experience with silicosis, these workers' cases of silicosis have been particularly aggressive, characterized by rapid disease progression, accelerated decline in lung function, and high mortality, typically at a young age.
>
> The proposed emergency regulation will require employers in the artificial stone fabrication industry to implement safeguards that will prevent RCS exposures among their employees. The proposal will also apply to other industries where workers cut, grind or polish natural stone materials with a silica content of 10% or greater.

110. The report concluded that issuance of the proposed standard was necessary to address an occupational health emergency:

> The Occupational Safety and Health Standards Board (Board) finds that the adoption of this proposed emergency standard is necessary to address an emergency pursuant to GC section 11346.1(b)(1). The Board finds that immediate action must be taken to avoid serious harm to the public peace, health, safety or general welfare, for the reasons stated below.

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111. The Board identified 15 facts as the basis for its finding of emergency:

1) Exposure to RCS can result in silicosis.

2) Silicosis is an incurable disease.

3) Silicosis primarily affects workers.

4) Artificial stone contains more than 93% crystalline silica.

5) Artificial stone now dominates the U.S. market for stone countertops.

6) There is an epidemic of silicosis occurring in California's artificial stone fabrication industry.

7) The silicosis cases occurring in this industry are particularly aggressive and deadly.

8) Similar cases of silicosis in this industry are occurring worldwide.

9) Workers in this industry are uniquely vulnerable.

10) The dust from artificial stone is uniquely hazardous, compared to natural stone.

11) There is evidence of widespread non-compliance with title 8 standards in the artificial stone fabrication industry.

12) Individual workers in this industry report high levels of employer non-compliance with title 8 requirements.

13) The existing silica standard is not well suited to the artificial stone fabrication industry.

14) On the current trajectory, many workers in this industry will develop silicosis and die.

15) An emergency regulation is necessary to protect workers in this industry.[34]

[34] *Finding of Emergency, Government Code Section 11346.1, Occupational Safety and Health Standards Board, Proposed Emergency Regulation, Title 8, California Code of Regulations, General Industry Safety Orders, Chapter 4, Subchapter 7, Revised Section 5204: Occupational Exposures to Respirable Crystalline Silica*. Available online at https://www.dir.ca.gov/OSHSB/documents/Respirable-Crystalline-Silica-Emergency-FOE.pdf.

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112. The Emergency Temporary Standard requires employers to use the following engineering controls and work practices to reduce occupational exposure to artificial stone dust:

Engineering controls: "effective wet methods"

Housekeeping and Hygiene:

1. Prompt and proper cleanup of wastes, dusts, residues, debris, etc.
2. Wet methods or vacuum cleaners equipped with HEPA filters to collect all wastes, dusts, residues, debris, etc. from high-exposure tasks.
3. Respiratory protection for workers engaged in housekeeping tasks.
4. Washing Facilities.

113. The Emergency Temporary Standard prohibits the following practices for high-exposure tasks:

1. Any use of compressed air wherever silica dust may be present.
2. Any dry sweeping, shoveling, disturbing, or other dry clean-up of wastes ....
3. Use of employee rotation as a means of reducing employee exposure to RCS.
4. Walking or moving equipment on or through dry dust, debris, residue, etc.

114. The Emergency Temporary Standard also requires employers to establish and implement a written exposure control plan that includes description of tasks, engineering controls, and housekeeping measures and to review and evaluate the effectiveness of the plan at least annually.

115. In workplaces where high-exposure trigger tasks occur, the Emergency Temporary Standard also requires employers to include the following in their written exposure control plan:

1. Air monitoring records that demonstrate engineering controls are effective and continuously maintain exposure levels below the action level.
2. Procedures for the proper donning and doffing of personal protective equipment, including work clothing and respiratory protection to effectively prevent exposures to respirable crystalline silica and prevent take-home exposures;
3. Documentation of proper reporting to the Division; and
4. Procedures ensuring employees are properly trained to prevent RCS exposure

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116. The Emergency Temporary Standard requires employers to ensure that employees properly use the following respiratory protection when employees perform high-exposure trigger tasks or work within a regulated area where high-risk exposure tasks occur:

1. A full face tight-fitting powered-air purifying respirator (PAPR) or a respirator providing equal or greater protection equipped with a HEPA, N100, R100, or P100 filter and organic vapor cartridge shall be used.

2. A full face, tight-fitting supplied-air respirator in pressure-demand or other positive pressure mode for any employees known to the employer to be diagnosed with confirmed silicosis, or who meet the definition of suspected silicosis, or whenever the PLHCP or specialist recommends use of a supplied-air respirator. The air source for the supplied-air respirator shall be located outside the regulated area and in an area that is free of respirable crystalline silica and other airborne contaminants.

117. The Emergency Temporary Standard also mandates that "the employer shall make medical surveillance available at no cost to the employee, and at a reasonable time and place, for each employee who will be occupationally exposed to respirable crystalline silica at or above the action level for 30 or more days per year."

118. The medical surveillance includes an initial examination consisting of

1. a medical and work history, with emphasis on he respiratory system;

2. a physical examination with special emphasis on the respiratory system;

3. a chest x-ray interpreted and classified according to the International Labour Office (ILO) International Classification of radiographs of Pneumoconioses by a NIOSH-certified B Reader;

4. A pulmonary function test to include forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) and FEV_1 / FVC ratio,

5. Testing for latent tuberculosis infection; and

119. The initial examination is to be followed with periodic examinations at least every three years, or more frequently if recommended by the PLHCP.

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F. Prevalence Studies of Silicosis Among Artificial Stone Fabricators

120. In 2011, researchers at Galdakao Hospital in Bizkaia, Spain published a study of 11 workers who were exposed to different types of quartz surfaces for between 7 and 14 years. Four of the subjects worked in the cutting workshop; the rest of the workers worked in assembly (i.e. fabrication), without any specific respiratory protection apparatus. They diagnosed 6 of the 11 workers with silicosis, which equated to a disease prevalence in this work environment of 54.5%. Of the 6 workers affected, 5 (83.3%) were assembles (fabricators). The investigators attributed silicosis in these workers to quartz conglomerates (artificial stone).[35]

121. In 2019, Israeli researchers published a study of 68 workers with up to 20 years of artificial stone dust exposure at small enterprises throughout Israel. CT scans of the workers were evaluated for features indicative of silicosis in three zones of each lung. Thirty-four patients had CT scores between 0 and 42; 29 of them were diagnosed with silicosis, yielding a prevalence of 42.6%.[36]

122. In 2021, researchers from the California Department of Public Health published a study in which they sought to determine the prevalence of silicosis among current employees of an engineered stone countertop fabrication company. All 43 currently employed fabrication workers were screened for silicosis by chest x-rays. Five employees whose average duration of exposure was 14.9 years, had silicosis, yielding a prevalence rate of 11.6%.[37]

123. In 2021, Australian researchers screened all current and former workers from the stone benchtop industry in the State of Victoria. Primary evaluations included a standardised questionnaire, physical examination, spirometry and gas transfer assessment and International Labour Organisation-categorised chest X-ray. Secondary evaluations include high-resolution CT chest, blood tests, and a respiratory physician evaluation. At the end of the first 12 months, 86 of

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[35] Pascual S, et al., "Prevalence of silicosis in a marble factory after exposure to quartz conglomerates," *Arch. Bronconeumol.* 2011; 47(1):50-51 [in Spanish with English abstract].

[36] Ophir N, et al., "Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure," *Occup. Envrion. Med.* 2019; 76:875-879.

[37] Heinzerling A., et al., "Radiographic Screening Reveals High Burden of Silicosis among Workers at an Engineered Stone Countertop Fabrication Facility in California," *Am. J. Respir. Crit. Care Med.* 2021; 203(6):764-766.

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239 workers who had completed secondary evaluation were diagnosed with silicosis (65 simple silicosis and 21 complicated silicosis), yielding a prevalence rate of 36.0%. The duration of exposure was less than 10 years in 22 of the workers and greater than 10 years in 64 of the workers.[38]

124. In 2022, American researchers described an outbreak of work-related asthma and silicosis at a facility that manufactures and fabricates chemical resistant countertops comprised of sand, epoxy resin, and phthalic anhydride, a known respiratory sensitizer. Clinical and epidemiologic investigations identified 16 workers with confirmed or suspected work-related asthma. Two years later, after OSHA began to enforce its new silica standards, 12 workers received medical surveillance for silicosis. Of these 12 workers, four were diagnosed with silicosis based on abnormal chest computed tomography examinations, yielding a prevalence rate of 33.3%. In this study the duration of exposure was not stated.[39]

125. In 2023, Spanish researchers published an observational study in which artificial stone silicosis patients were evaluated between January 2006 and June 2021. Once the diagnosis of the first patient (index case) was completed, the other workers who handled artificial stone from the same company were also evaluated. Diagnosis was based on occupational exposure to artificial stone, radiological findings, and the exclusion of other entities. The chest X-ray was assessed according to the International Labour Office criteria and high-resolution computed tomography (HRCT) as described by Kusaka, et al. When the diagnosis was not considered certain, a compatible histological sample was required. Twenty-seven out of 61 workers who handled artificial stone were diagnosed with silicosis, yielding a prevalence rate of 44.3%. The mean duration of exposure of the workers diagnosed with silicosis was 112.2 years.[40]

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[38] Hoy RF, et al., "Identification of early-stage silicosis through health screening of stone benchtop industry workers in Victoria, Australia," *Occup. Environ. Med.* 2021; 78:296-302.

[39] Tustin AW, et al., "An outbreak of work-related asthma and silicosis at a US countertop manufacturing and fabrication facility," *Am. J. Ind. Med.* 2022; 65:12-19.

[40] Orriols R., et al., "Artificial Stone Silicosis. Progression and Laboral Impact After 3-years Follow-up, *Arch. Bronconeumol.* 2023; 59:267-269.

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126. In 2023, Australian researchers published a study in which 544 stone benchtop industry workers, 95% of whom worked with artificial stone, underwent screening for silicosis. Workers undertook primary screening, including an International Labour Office (ILO) classified chest x-ray and, subject to prespecified criteria, also underwent secondary screening including high-resolution CT of the chest and respiratory physician assessment. 117 were diagnosed with silicosis, yielding a prevalence rate of 28.2%. In this study the mean duration of exposure was just 8 years, which may explain the lower prevalence rate than other prevalence screening studies.[41]

127. It is now well-recognized that chest x-rays are inadequate to detect silicosis among artificial stone fabricators.[42]

128. Considering only those screening studies utilizing high resolution CT scans (HRCT), the prevalence rates of silicosis in the studies ranged from 28.2% to 44.3%, yielding an overall prevalence rate of about 34%, a very high silicosis prevalence among stone countertop fabricators.

129. Overall, the prevalence studies show that artificial stone countertop fabricators have an unacceptably high risk of developing silicosis young in life. Since silicosis remains in incurable, progressive, and ultimately fatal lung disease, all artificial stone countertop fabricators who have worked in this industry have a high risk of developing silicosis and other silica-related diseases.

G. The Risk of Lung Cancer Among Artificial Stone Fabricators

130. Crystalline silica was classified as a known human carcinogen by the International Agency for Research on Cancer in 1997 - before artificial stone was used in the United States. IARC's classification of crystalline silica as a human carcinogen was based on epidemiological studies showing significantly increased rates of lung cancer in workers exposed to crystalline silica.

131. In 2022, researchers from Curtin University in Perth, Australia issued a preliminary report, "The future burden of lung cancer in silicosis from occupational silica exposure in Australia."

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[41] Hoy RF, et al., "Prevalence and risk factors for silicosis among a large cohort of stone benchtop industry workers," *Occup. Environ. Med.* 2023; 80(8):493-446.

[42] See, Hoy RF, et al., "Chest x-ray has low sensitivity to detected silicosis in artificial stone benchtop industry workers," *Respirology* 2024; 29(9):785-794.

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They used the Future Excess Fraction (FEF) method to estimate the future number of lung cancer cases arising from occupational RCS exposure. This method, based on the lifetime risk approach, estimates the excess future burden of disease among those exposed to a risk factor (i.e., respirable crystalline silica)in a specific year. From a cohort of 18,770,982 adult Australians in 2016, They estimated that 5.4% (n≈1,022,150) will develop lung cancer over their lifetime, of which 1.0% (n≈10,390) are attributable to occupational exposure to respirable crystalline silica. They estimated that 100 lung cancers and 770-960 silicosis cases would be avoided by banning artificial stone, which is exactly what the Australian government did to prevent silica-related disease in fabricators.[43]

132. In 2024 Nordic and Dutch authorities issued a consensus report regarding the risk of lung cancer from crystalline silica exposure. They noted that recent epidemiological studies have shown excess lung cancer risk among workers exposed to respirable crystalline silica even in the absence of silicosis. They used lung cancer as the critical effect in calculating the risk of cancer from occupational exposure to respirable crystalline silica among workers who fabricate artificial stone countertops. Their study showed a risk of death from lung cancer among artificial stone countertop fabricators of 4 additional deaths per 1,000 workers exposed to crystalline silica at a concentration of 0.0363 mg/m^3, which is lower than OSHA's Permissible Exposure Limit. One extra cancer is generally considered acceptable in a working population of 100,000. The results of this study reveal a risk of lung cancer 400 times greater than the generally accepted risk among artificial stone countertop fabricators exposed to respirable crystalline silica below the Permissible Exposure Limit. Since most artificial stone countertop fabricators are exposed to crystalline silica in excess of the Permissible Exposure Limit and since the respiratory toxicity of artificial stone dust is likely greater due to particle size and other respiratory toxins released from artificial stone, the risk of lung may well be even greater than the high excess lung cancer risk estimated in this study.[44]

[43] Carey R, et al., "The future burden of lung cancer in silicosis from occupational silica exposure in Australia: A preliminary analysis," Report commissioned by the Australian Council of Trade Unions (ACTU), April 2022, available at https://www.curtin.edu.au/about/wp-content/uploads/sites/5/2022/07/FEFreport_formatted.pdf.

[44] Daisy Boers, Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety, Report No. 156: *Respirable crystalline silica* (October 9, 2024).

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H. Autoimmune Disease Among Artificial Stone Fabricators

133. In 2015, Israeli researchers published a study in which they systematically reviewed data from all cases of silicosis due to synthetic stone dust who were referred to the lung transplant center in Israel for lung transplantation assessment. Of 40 patients they identified nine (23%) with Of 40 patients in our advanced silicosis national data, we identified nine (23%) with findings consistent with various autoimmune diseases. Based on an expected autoimmune disease prevalence of 3% (based on the upper-end estimate for this group of diseases in European international data), the proportion of disease in their group represents a greater than 7-fold excess (prevalence ratio 7.5; 99% confidence interval 2.6–16.7). The researchers concluded that these cases underscore the strong link between silicosis and multiple distinct syndromes of autoimmune diseases.[45]

134. In 2021, Spanish researchers published a study of 489 silicosis cases and 95 cases of silica exposure without silicosis to examine prevalence and the clinical impact of systemic autoimmune rheumatic diseases. Fifty-four (11.0%) patients with silicosis had systemic autoimmune rheumatic disease (SARD); 12 (2.4%) had rheumatoid arthritis; 10 (2.0%) had systemic lupus erythematosus, 10 (2.0%) had systemic sclerosis, 3 (0.6%) had Sjögren syndrome, 2 (0.4%) had vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), 6 (1.2%) had psoriatic arthritis, 3 (0.6%) had ankylosing spondylitis, and 8 (1.6%) had other autoimmune diseases with no special features. Of the 54 patients, 9 (1.8%) had been exposed to artificial quartz conglomerates, 2 of whom had systemic autoimmune rheumatic diseases.[46]

135. In 2024 Spanish researchers published a multicentre prospective study in 105 patients diagnosed with silicosis, of whom 18 worked with artificial quartz conglomerate. Autoantibodies analysed were antinuclear antibodies, isotypes IgA, IgM and IgG, rheumatoid factor, anticyclic citrullinated peptide, anti-Scl70, anti-Ro, and anti-LA. Pulmonary function tests were performed. Autoimmunity was assessed in 105 patients. Autoimmune findings were recorded in 29 (27%)

[45] Shtraichman O, et al., "Outbreak of autoimmune disease in silicosis linked to artificial stone," *Occup. Med.* 2015; 65:444-450.

[46] Blanco-Perez JJ, et al, "Prevalence and clinical impact of systemic autoimmune rheumatic disease in patients with silicosis," *Arch. Broncopneumol.* 2021; 57:571-576.

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patients, including antinuclear antibodies (*n*=21), anti-Ro (*n*=7), rheumatoid factor (*n*=5) and anti-Scl70 (*n*=3). Autoimmune disease was diagnosed in 16 (15%) patients, mainly rheumatoid arthritis (*n*=7) and systemic lupus erythematosus (*n*=4). Patients with silicosis and autoimmune findings had a lower mean time of exposure to silica and showed a trend toward lower values in pulmonary function tests. Exposure to artificial quartz conglomerate was more common in the Barcelona and Murcia hospitals. The researchers concluded that autoimmune findings and diagnosis of autoimmune diseases were frequent in patients with silicosis in Spain.[47]

136. In 2024 Australian researchers published a study of autoimmune disease among stone benchtop industry workers in Victoria, Australia who were offered free medical screening for silicosis and related disorders. Symptoms or diagnoses of autoimmune disease were evaluated by questionnaire and blood tests taken for rheumatoid factor (RF), antinuclear antibodies (ANAs) and extractable nuclear antigens (ENAs). Among 1238 workers screened from 2019 to 2021, 0.9% were confirmed with autoimmune disease. Among those without clinical disease, 24.6% had detectable ANAs (93.5% male), 4.6% detectable ENAs and 2.6% were positive for RF. Silicosis was diagnosed in 253 workers (24.3% of those with diagnostic information available). Of those with ANA readings, 54 (6.6%) had ANA titre >1:320. The likelihood of positive autoantibodies increased with age, smoking, higher exposure to RCS and silicosis diagnosis. The researchers concluded that the proportion of stone benchtop workers with detectable ANAs or ENAs was considerably higher than the 5%–9% expected in the general population and that some of the antibodies detected (e.g., Scl-70, CENPB) have high sensitivity and specificity for systemic sclerosis. Finally, the researchers concluded that screening for autoimmune disease is indicated in workers exposed to respirable crystalline silica in the artificial stone fabrication industry because these individuals needs specialized management and may be entitled to compensation.[48]

[47] González Fernández C, et al., "Autoimmune findings in patients with silicosis in Spain," *Drugs Context* 2024; 13:2023-11-1.

[48] Tomic D, et al., "Autoimmune diseases, autoantibody status and silicosis in a cohort of 1238 workers from the artificial stone benchtop industry," *Occup. Environ. Med.* 2024; 81(8):388-394.

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V. THE NEED FOR MEDICAL MONITORING

A. Clinical Value of Early Detection and Diagnosis of Silicosis

137. "Early diagnosis is crucial for preventing and treating silicosis."[49] "Early detection of silicosis is vital to identify the disease at a pre-clinical stage to allow interventions that improve outcomes for workers."[50] "Since silicosis is an incurable, irreversible, and progressive disease with high morbidity and premature mortality, early detection appears to be the only way for secondary prevention."[51]

138. "Occupational health surveillance aims to prevent occupational disease and serious harm by monitoring the health of workers exposed to hazardous substances. The goals are to detect early change before adverse health effects or disease develops, and to assist workers to avoid or minimise further exposures. These goals reflect one of the primary roles of occupational medicine in working environments."[52]

139. "Early identification of silicosis in exposed workers is critical to detecting disease in a pre-clinical stage."[53] "The importance of early detection of silicosis is highlighted by León-Jiménez et al.'s study, which found that artificial stone workers, initially diagnosed with ILO category 0 silicosis, exhibited progression to categories 1 (42%) and 2 (21%), and some even to PMF (5%), within four years of ceasing exposure."[54]

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[49] Wang Z, et al., "The value of single biomarkers in the diagnosis of silicosis: A meta-analysis," *iScience* 2024; 27:109948.

[50] Austin EK, et al., "Early Detection Methods for Silicosis in Australia and Internationally," *Int. J. Environ. Res. Public Health* 2021; 18:8123.

[51] Sarkar K, et al., "Secondary prevention of silicosis and silico-tuberculosis by periodic screening of silica dust exposed workers using serum club cell protein 16 as a proxy marker," *Health Sci. Rep.* 2021; 4:e373.

[52] Lee E, et al., "Silica health surveillance: a new approach," *Occup. Med.* 2022; 72(6):357-359.

[53] Gandhi SA, et al., "Active Surveillance of Engineered Stone Workers Facilitates Early Identification of Silicosis: A Discussion of Surveillance of Occupational Lung Diseases," *New Solut.* 2023; 33(2-3):119-129.

[54] Chen C-H, et al., "Dose-response relationship between lung function and chest imaging response to silica exposures in artificial stone manufacturing workers," *Environ. Health* 2024; 23:25, citing León-Jiménez A., et al., "Artificial stone silicosis: rapid progression following exposure cessation," *Chest* 2020; 158(3):1060-1068.

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140. In their recently published article regarding the engineered stone silicosis epidemic in California, investigators from the California Department of Public Health wrote:

> Since 2019, the California multisource silicosis surveillance system has processed 1817 reports for 648 individuals, of whom 243 were confirmed with engineered stone–associated silicosis. This is 1 of the largest case series of engineered stone silicosis reported worldwide and is especially noteworthy because nearly all cases were found through ongoing passive data collection, as opposed to active screening of engineered stone workers. Although the addition of case-finding mechanisms in the past 3 years has nearly tripled the number of all reported silicosis cases regardless of exposure, the number of confirmed engineered stone cases has increased 9-fold. This result illustrates the value of multisource surveillance and that without it, many cases may be unidentified; the burden of disease is likely underestimated because of reliance on physician reporting and can be better estimated by enhancing surveillance methods.[55]

141. The investigators from the California Department of Public Health discussed the overwhelming predominance of young male Latino immigrants in Los Angeles County as victims of the engineered stone silicosis epidemic and then wrote: "These findings emphasize the importance of screening workers for disease and controlling workplace hazards." The public health investigators then discussed the lack of medical insurance and consequent lack of access to medical care among engineered stone workers, and concluded that "[e]arly diagnosis is critical," noting that "[p]revious studies have demonstrated that delays in identification can result in more severe disease and poorer outcomes."[56]

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[55] Flattery J, et al., "Silicosis Surveillance in California, 2019-2024: Tracking an Epidemic," *Am. J. Public Health* 2025; 115(11):1913-1921.

[56] Flattery J, et al., "Silicosis Surveillance in California, 2019-2024: Tracking an Epidemic," *Am. J. Public Health* 2025; 115(11):1913-1921.

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142. A large study from Guangdong Province, China published in May 2025 demonstrates both the survival benefit of early diagnosis and mortality of delayed diagnosis in silicosis patents. The study noted that early diagnosis is hypothesized to improve survival outcomes, but that evidence linking diagnostic stage to mortality remained scarce. The investigators their aimed to evaluate the association between early diagnosis and survival in silicosis patients and assess the impact of delayed diagnosis on mortality. A retrospective cohort study analyzed 11,809 silicosis patients diagnosed between 1956 and 2020 in Guangdong Province, China. Data were extracted from occupational disease registries, multi-sectoral databases, and provincial monitoring systems. Exclusion criteria included ambiguous diagnosis dates, pre-adolescent exposure, and missing variables. Cox proportional hazards models adjusted for covariates (sex, age, region, industry, exposure duration) were used to assess mortality risks across stages I–III. Survival curves, temporal trends, and subgroup analyses were performed. Most patients (77.8%) were diagnosed at stage I, with median survival times declining sharply across stages: 27 years (stage I), 20 years (stage II), and 11 years (stage III) ($p < 0.001$). Adjusted mortality risks increased progressively: stage II (*HR* = 1.42, 95%, *CI*: 1.33–1.51) and stage III (*HR* = 2.42, 95%, *CI*: 2.17–2.70) compared to stage I. Temporal analysis revealed peak diagnoses in 1963 and the early 1980s, stabilizing post-2006. Subgroup analyses confirmed staging as an independent prognostic factor across industries and exposure durations ($p < 0.001$). The investigators concluded that their study demonstrates that early diagnosis significantly prolongs survival in silicosis patients, with advanced stages correlating with exponentially higher mortality, and that their findings underscore the urgent need for systematic early screening, such as high-resolution CT and stricter occupational health policies to reduce silica exposure. Despite limitations of the study, including unmeasured confounders like smoking status, the investigators concluded that their study provides critical evidence to inform global strategies for mitigating silicosis through timely detection and workplace safety reforms. This large, well designed and conducted epidemiological study, clearly establishes a survival benefit of early silicosis detection and increased mortality for delayed diagnosis of silicosis.[57]

[57] Fan C, et al., "Early diagnosis and survival outcomes in silicosis: a retrospective cohort study of 11,809 patients in Guangdong Province, China (1956-2020)," *Front. Public Health* 2025; 13:1587161.

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B. Stone Countertop Fabricators Need Medical Monitoring for Silica-Related Diseases

143. In 2024, researchers from National Jewish Health in Denver published an abstract of a young artificial stone fabricator who developed three silica-related diseases. They described a young artificial stone worker who developed severe, progressive and disabling silicosis with pleural effusions, ANCA-positive vasculitis, and glomerulonephritis requiring respirable crystalline silica exposure removal and immunosuppressive therapy. A 28-year-old former smoker developed acute fever, chills, night sweats, weight loss, dyspnea, cough and chest tightness. Pulmonary function testing showed restrictive lung disease (FVC 56%) with reduced DLCO (60%). Chest CT imaging showed profuse pulmonary nodules, mediastinal/hilar lymphadenopathy, and pleural effusions. Surgical lung biopsy to rule out lymphoma showed fibrohistiocytic nodules containing birefringent particles indicating silicosis. An occupational history showed that the patient had worked part-time at his family's countertop fabrication/installation company from childhood through adolescence, then full-time from age 22 to 28. His job duties included polishing, grinding, cutting, and installing engineered stone countertops. He was medically removed from workplace RCS exposure and awarded worker's compensation benefits. Despite exposure removal, the patient suffered worsening chest and systemic symptoms and a decline in lung function. One year after diagnosis, he developed a recurrent lower extremity pruritic, erythematous rash that resolved temporarily with short-course prednisone. Autoimmune serologies showed markedly positive ANA (titer 1:2560) and P-ANCA/MPO (1:5120) indicating vasculitis. The patient also developed worsening renal function (creatinine 2.0 mg/dL, eGFR 45.8 mL/min/1.73 m2). Kidney biopsy showed necrotizing and crescentic glomerulonephritis. The researchers noted that along with silicosis, the case underscored the risk for other severe and life-threatening sequelae including autoimmune vasculitis and inflammatory kidney disease. They observed that the case illustrated the importance of medical surveillance for all known complications of RCS. Kraus R, et al., "Severe Progressive Silicosis, Autoimmune Vasculitis and Glomerulonephritis in a Young Engineered Stone Fabricator," *Am. J. Respir. Crit. Care Med.* 2024; 209:A5988.

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144. In September 2025, researchers from Yale University published an industry-sponsored study in which they surveyed 257 stone countertop fabrication shops for respirable crystalline silica monitoring reports, engineering controls, and medical surveillance. They noted that "information on workplace health and safety practices in the stone countertop industry, such as monitoring for RCS [Respirable Crystalline Silica], silica medical surveillance, and respirator use and fit testing, is . . . limited, especially in the United States" and that "an OSHA-administered questionnaire survey of ES [Engineered Stone] workers in California found that only 20% workers reported respirator fit testing and only 5% reported having a silica medical examination." The authors reported that only 19.5% of the stone countertop fabrication shops that they surveyed had performed medical surveillance of their workers. They reported that "despite recent increased attention regarding the hazards of RCS exposure in this industry and OSHA silica regulations, real world practices regarding sampling for RCS, medical surveillance, and respiratory protection were highly variable and frequently not in compliance with the OSHA silica standard." They also reported that "over 1/3 of shops surveyed noted that they wanted assistance with OSHA compliance (45.1%), medical surveillance (36.6%), RCS air monitoring (43.6%), and respiratory protection (38.5%)." The authors reported: "Also notable in our findings is that medical surveillance was frequently found to be missing key components, including chest X-rays or spirometry . . . ." They concluded: "The findings underscore the extensive use of ES and the opportunity for overexposure to RCS in this industry. They highlight the need to eliminate dry processing methods, enhance respiratory protection, and perform repeated RCS sampling to monitor the effectiveness of controls. Additionally, more widespread medical surveillance is urgently needed to assess the extent of silicosis in this industry.[58]

145. In 2025, Australian researchers published a study of an artificial stone worker with multisystem autoimmune disease, concluding: "Proactive autoimmune screening in this population [artificial stone workers] is essential, as early ANA detection may indicate underlying autoimmune disease or serve as a predictor of future onset, providing an opportunity for early intervention."[59]

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[58] McGowan CM, et al., "Work Practices and Respirable Crystalline Silica Exposures in Stone Countertop Fabrication Shops," *Am. J. Ind. Med.* 2025; 68(11):973-987.

[59] Lin T, et al., "The Case for Autoantibody Screening in Stone Benchtop Workers," *Respirology Case Reports* 2025; 13: e70363

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C. Stone Fabricators Need Medical Monitoring Even Years After Exposure Ceases

146. A recent study by Spanish investigators demonstrated high metabolic activity and systemic inflammation years after cessation of exposure to artificial stone dust, establishing the necessity of lifetime medical monitoring of former artificial stone workers for silica-related disease. Seventeen patients with complicated silicosis were enrolled, all of whom had worked for at least 5 years in "finishing" and installing engineered stone and had ceased exposure for at least 7 years. Clinical data, positron emission tomography/computed tomography using 18F-fluorodeoxyglucose (18F-FDG PET/CT), respiratory function tests and blood samples were collected. The patients' mean age was 44 years. Their average exposure duration was 11 years and more than 11 years had passed from cessation of exposure. The average maximum standardized uptake value (SUVmax) of large opacities was 6.32. All patients presented with hypermetabolic mediastinal lymphadenopathies and 88.2% also had extrathoracic lymphadenopathies. SUV max of large opacities was correlated with fibrinogen ($\rho = 0.717$, $P = 0.001$), lymphocyte-to-monocyte ratio ($\rho = -0.506$, $P = 0.038$), systemic inflammatory response index ($\rho = 0.559$, $P = 0.02$) and CD4 + NKT cells. Large lung opacities and lymphadenopathies showed high metabolic activity even years after silica exposure ended. The investigators observed that one of the characteristics detected in their series was intense metabolic activity, despite an average of more than 11 years since exposure had ceased, not only in lung lesions but also in mediastinal and even extrathoracic lymphadenopathy. Indeed, 70% of the patients had hypermetabolic lymphadenopathy in the supraclavicular and abdominal regions, in contrast to the series of 6 patients described by Reichert with classical silicosis, where only one patient had mediastinal lymphadenopathy and none had hypermetabolic extrathoracic lymphadenopathy. The investigators commented that the greater aggressiveness of this type of silicosis and differences in composition and morphology between natural and artificial compounds could explain the findings. This impressive study convincingly showed the need of medical monitoring of artificial stone fabricators for silica-related diseases long after cessation of exposure. Léon-Jiménez A, et al., "Complicated silicosis due to engineered stone: High metabolic activity in positron emission tomography and systemic inflammation years after exposure cessation," *Res. Square*, Feb. 3, 2025.

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D. Statement of the American College of Occupational and Environmental Medicine

147. In 2006, the American College of Occupational and Environmental Medicine (ACOEM) published a position statement whose purpose was "to recommend objectives, key elements, and implementation strategies for a medical surveillance program for workers exposed to silica." whose goal was "to prevent and eventually eliminate silicosis at both the national and international an evidence-based statement titled "Medical Surveillance of Workers Exposed to Crystalline Silica." Raymond LW, et al., "Medical Surveillance of Workers Exposed to Crystalline Silica," *J. Occup. Environ. Med.* 2006; 48(1):95-101.

148. *Target Population.* In its consensus statement, ACOEM identified the "Target Population" for medical surveillance, writing: " The pool of workers to be included consists of those individuals exposed to levels of crystalline silica that place them at risk for silicosis. Because the exact exposure–response relationship remains unclear, it is appropriate to make the inclusion criteria for this program conservative. Thus, inclusion of any workers exposed to a crystalline silica concentration $\geq$ 0.05 mg/m^3 is recommended. This level is both the National Institute for Occupational Safety and Health's (NIOSH's) recommended exposure limit (REL) and essentially one half of the current OSHA PEL for pure crystalline silica." [0.05 mg/m^3 is now also the OSHA PEL for respirable crystalline silica.]

149. *Components of the Evaluation.* In its consensus statement, ACOEM identified "Components of the Evaluation," writing: "As specified in the OSHA Special Emphasis Program, components of the surveillance evaluation should include the following:

1. Occupational and medical history (questionnaire);
2. Physical examination;
3. Purified protein derivative (PPD) tuberculin skin test;
4. Chest radiography; and
5. Spirometry.

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E. Medical Surveillance Requirements of the Silica Standard

150. OSHA's Silica Standard includes the following provisions for medical surveillance:

1910.1053(i)(1) General.

1910.1053(i)(1)(I) The employer shall make medical surveillance available at no cost to the employee, and at a reasonable time and place, for each employee who will be occupationally exposed to respirable crystalline silica at or above the action level for 30 or more days per year.

1910.1053(i)(1)(ii) The employer shall ensure that all medical examinations and procedures required by this section are performed by a PLHCP [Physician or other Licensed Health Care Professional] as defined in paragraph (b) of this section.

1910.1053(i)(2) Initial examination. The employer shall make available an initial (baseline) medical examination within 30 days after initial assignment, unless the employee has received a medical examination that meets the requirements of this section within the last three years. The examination shall consist of:

1910.1053(i)(2)(I) A medical and work history, with emphasis on: Past, present, and anticipated exposure to respirable crystalline silica, dust, and other agents affecting the respiratory system; any history of respiratory system dysfunction, including signs and symptoms of respiratory disease (e.g., shortness of breath, cough, wheezing); history of tuberculosis; and smoking status and history;

1910.1053(i)(2)(ii) A physical examination with special emphasis on the respiratory system;

1910.1053(i)(2)(iii) A chest X-ray (a single posteroanterior radiographic projection or radiograph of the chest at full inspiration recorded on either film (no less than 14 x 17 inches and no more than 16 x 17 inches) or digital radiography systems), interpreted and classified according to the International Labour Office (ILO) International Classification of Radiographs of Pneumoconioses by a NIOSH-certified B Reader;

1910.1053(i)(2)(iv) A pulmonary function test to include forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) and FEV1/FVC ratio, administered by a spirometry technician with a current certificate from a NIOSH-approved spirometry course;

1910.1053(i)(2)(v) Testing for latent tuberculosis infection; and

1910.1053(i)(2)(vi) Any other tests deemed appropriate by the PLHCP.

1910.1053(i)(3) Periodic examinations. The employer shall make available medical examinations that include the procedures described in paragraph (i)(2) of this section (except paragraph (i)(2)(v)) at least every three years, or more frequently if recommended by the PLHCP.

Additional tests that PLHCPs may order based on findings of medical examinations include chest computerized tomography (CT) scan for lung cancer or COPD, testing for immunologic diseases, and cardiac testing for pulmonary-related heart disease, such as cor pulmonale. (Appendix B, § 2.6)

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F. Medical Surveillance Requirements of the New Cal-OSHA Silica Standard

151. In February 2025, the California Occupational Safety and Health Administration (Cal-OSHA) amended Labor Code § 5204 to address the new silicosis epidemic among artificial stone countertop fabricators in California. Subsection (j) of this new regulation requires medical surveillance, including low-dose high-resolution computerized tomography (HRCT):

> Medical surveillance.
>
> (1) General.
>
> (A) The employer shall make the initial and periodic medical examinations that are required by this subsection available at no cost to the employee, and at a reasonable time and place.
>
> (B) The employer shall ensure that all initial and periodic medical examinations and procedures required by this section are performed by a PLHCP.
>
> (2) Initial medical examination.
>
> (A) For each employee exposed to a high-exposure trigger task for at least 30 days each year regardless of exposure assessments or objective data, the employer shall make available and shall inform employees of their right to, an initial (baseline) medical examination within 30 days after initial assignment, unless the employee has received a medical examination that meets the requirements of section (j)(4) within the last year.

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(B) For each employee who is occupationally exposed to respirable crystalline silica at or above the action level for 30 or more days per year, and who is not covered by subsection (j)(2)(A), the employer shall make available, and shall inform employees of their right to, an initial (baseline) medical examination within 30 days after initial assignment, unless the employee has received a medical examination that meets the requirements of this section within the last three years.

(3) Periodic medical examinations.

(A) For each employee covered by subsection (j)(2)(A) or (j)(2)(B), the employer shall make available, and shall inform employees of their right to, a medical examination once every three years, or more frequently if recommended by the PLHCP, that meets the requirements of subsection (j)(4).

(4) Medical examination procedures.

(A) Except as noted in (j)(4)(A)5, the initial and periodic medical examinations required by this subsection shall consist of the following:

1. A medical and work history that includes past, present, and anticipated exposure to respirable crystalline silica, dust, and other agents affecting the respiratory system, including as a result of performing high-exposure trigger tasks; the approximate percentage of time the employee performed high-exposure trigger tasks, if any, over their working lifetime; the type of respiratory protection used by the employee for protection against respirable crystalline silica, if any, over their working lifetime, and the approximate percentage of time the employee used the respiratory protection; current or preexisting respiratory system health conditions or impairment, including signs and symptoms of respiratory disease (e.g., shortness of breath, cough, wheezing); history of tuberculosis; and smoking status and history;

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2. A physical examination with special emphasis on the respiratory system;

3. A chest X-ray (a single posteroanterior radiographic projection or radiograph of the chest at full inspiration recorded on either film (no less than 14 x 17 inches and no more than 16 x 17 inches) or digital radiography systems), interpreted and classified according to the International Labour Organization (ILO) International Classification of Radiographs of Pneumoconioses by a NIOSH-certified B Reader. A chest computed tomography (CT) scan at the lowest possible dose may be substituted for the chest X-ray when deemed appropriate by the PLHCP or specialist;

4. A pulmonary function test to include forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) and FEV1/FVC ratio, administered by a spirometry technician with a current certificate from a NIOSH-approved spirometry course;

5. Testing for latent tuberculosis infection as part of the initial medical examination only; and

6. Any other tests deemed appropriate by the PLHCP or specialist.

(B) A chest CT scan performed at the lowest dose possible shall be substituted for the chest X-ray required in subsection (j)(4)(A)(3) as part of initial and periodic examinations for all the following:

1. For any employee when deemed appropriate by the PLHCP.

2. For any employee with suspected silicosis.

3. For any employee covered by subsection (j)(2)(A).

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G. Requirements of Senate Bill 20

152. On October 13, 2025, Governor Newsom signed Senate Bill 20, which amends Sections 6302 and 6432 of the Labor Code and adds Chapter 2.2 (Section 5369.1 et seq.) thereto.

153. This new legislation seeks to solve the current silicosis epidemic among artificial stone countertop fabricators in California *inter alia* by:

(1) imposing criminal penalties on fabricators of artificial stone countertops for doing certain tasks that must be done in fabricating and installing artificial stone countertops (i.e., the countertops cannot be fabricated or installed without doing the tasks that will constitute crimes);

(2) imposing enforcement requirements on the Division of Occupational Safety and Health (Cal-OSHA) which cannot be performed because Cal-OSHA lacks both the funding and the highly skilled technical personnel necessary to enforce these requirements;

(3) placing the onus of preventing silicosis on small minority-owned businesses that lack the technical and financial resources to comply with the requirements, and subjects them to criminal liability for failure to comply with requirements that are impossible of performance, while imposing no obligations on the multi-billion dollar manufacturers and distributors of lethal artificial stone products that have caused the new silicosis epidemic in California and worldwide.

154. Although well-intentioned, the essential flaw with this legislation is that it erroneously assumes that artificial stone countertops can be safely fabricated, contrary to the report of the Australian Institute of Occupational Hygienists which concluded that artificial stone cannot be safely fabricated, which prompted Australian regulators banned the importation and use of all artificial stone products to prevent another epidemic like the asbestos epidemic of the last century.

155. SB 20 prohibits all dry-cutting by fabricators and criminalizes such activity. However, artificial stone countertops cannot be installed without dry-cutting. Most countertops are too long to fabricate without laminating pieces of artificial stone together. The lamination process cannot be done using wet methods, because water prevents lamination. Further, while wet methods could theoretically be used for all processing of artificial stone in fabrication shops, they cannot be used in customers' kitchens and bathrooms during installation, because doing so would flood and damage homes. The proper installation of artificial stone countertops requires cutting at consumers'

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homes and businesses (e.g. to make holes for electrical outlets and other obstructions), grinding the edges of the countertops, and polishing the countertops. Performing all of these activities on artificial stone countertops (which contain approximately 95% crystalline silica) create levels of respirable crystalline silica that exceed OSHA permissible exposure limits. Indeed, a study published two weeks ago reported that the daily (8 hour) occupational exposure limit installing artificial stone "is likely to be exceeded."[60] Moreover, multiple studies have shown that the use of wet methods does not prevent silicosis.[61]

156. Cal-OSHA has not been able to enforce its Emergency Standard for Respirable Crystalline Silica for lack of sufficient OSHA inspectors and financial resources to hire inspectors.[62] Cal-OSHA most certainly cannot do so now that funding to OSHA, the National Institute of Occupational Safety and Health, and Cal-OSHA has been decimated by the Department of Governmental Efficiency, which has also terminated the majority of those agencies' employees. To enforce the requirements, Cal-OSHA would have to hire a veritable army of industrial hygienists specially trained to monitor workplaces for exposure to respirable crystalline silica. Cal-OSHA lacks funding to hire such specialists and there is a dearth of trained specialists available in California to perform inspections at hundreds of stone countertop fabrication facilities throughout the state.

157. Even State Senator Menjivar, who sponsored SB 20, acknowledged in a Press Release dated October 14, 2025 that "this bill alone will not end silicosis from fabrication activities."

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[60] Borghi F, et al., "Evaluation of occupational exposure to airborne quartz in the cutting and grinding of ceramic tiles," *Ann. Work Exp. Health* (advance access 9-16-2025) available at https://academic.oup.com/annweh/advance-article/doi/10.1093/annweh/wxaf044/8254991.

[61] Soo J-C, Houlroyd J, Warren H, Philpot BJ, Castillo S, "Respirable dust and respirable crystalline silica exposures among workers at stone countertop fabrication shops in Georgia from 2017 through 2023," *Annals Work Exposure Health* 2025; 69(5):473-485, available at https://academic.oup.com/annweh/article/69/5/473/8116008; DeVaughn A, et al., "Investigation of occupational exposure to respirable crystalline silica (RCS) among engineered stone fabricators in Chicago – A pilot study," *J Occup Environ Med.* 2025; 22(2):101-109; Qi L, et al., "Engineering Control of Silica Dust from Stone Countertop Fabrication and Installation," Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health Report No. 375-11a (March 2016), efaidnbmnnnibpcajpcglclefindmkaj/https://www.cdc.gov/niosh/surveyreports/pdfs/375-11a.pdf; Qi L, et al., "Engineering Control of Silica Dust from Stone Countertop Fabrication and Installation," Dept Health & Human Services, Centers for Disease Control & Prevention, Nat. Inst. Occupational Safety and Health Report 375-12a (Sept. 2016), efaidnbmnnnibpcajpcglclefindmkaj/https://www.cdc.gov/niosh/surveyreports/pdfs/375-12a.pdf.

[62] See, California State Auditor, Report No. 2024-115,*The Division of Occupational Safety and Health: Process Deficiencies and Staffing Shortages Limit Its Ability to Protect Workers* (July 17, 2025).

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H. Silicosis Center of Excellence Ideal Medical Monitoring Program

158. On December 17, 2025, the Silicosis Center of Excellence of University of California San Francisco published its Ideal Medical Monitoring Program for engineered stone workers at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence:

Executive Summary

Background. Engineered stone workers face some of the highest risks for developing silicosis, a severe and irreversible lung disease caused by exposure to respirable crystalline silica dust. Unlike traditional industries, engineered stone contains over 90% crystalline silica, and fabrication tasks release extremely hazardous levels of dust. Workers are developing silicosis at younger ages, after shorter exposure durations, and with more aggressive disease progression than seen in other industries.

Problem. Despite legal requirements, many workers are not being screened or medically monitored. A recent study by Surasi et al. (2022) found that over one-third of employers failed to provide required medical surveillance. Self-employed workers, those in small shops, and employees in financially strained workplaces are especially vulnerable. Cal/OSHA lacks the staffing and resources to ensure compliance. As a result, the current system is failing to detect disease early, leaving workers at risk of severe disability and premature death.

Our Recommendation. We propose a comprehensive, independent medical surveillance program for all workers exposed to engineered stone dust for at least 30 days, including both current and former workers. The program is specifically designed for individuals without established parenchymal silicosis, though those with only lymph node calcifications are eligible.

Key Testing Components

A. Medical History and Physical Exam: Annual history and physical exam focusing on heart, lungs, skin, joints, ENT (ear, nose, mouth, and throat), and extremities with medical and exposure history including exposure questionnaire. Performed by an occupational medicine or pulmonary physician.

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B. Symptom and quality of life screening: Annual standardized questionnaires (KBILD, MMRC, PROMIS-29).

C. Chest CT scans: Annually during employment; annually for 15 years after leaving the industry; then every 3 years thereafter, with the option to stop at age 75 following joint decision with physician.

D. Pulmonary function testing: Full annual testing (spirometry, lung volumes, DLCO, 6-minute walk) on the same schedule as CT scans.

E. Cardiopulmonary exercise test (CPET): At baseline, then every 3–5 years, or sooner if clinically indicated.

F. Infectious disease screening: Annual tuberculosis (Quantiferon Gold + sputum cultures) and nontuberculous mycobacterial screening.

G. Systemic disease markers: Routine labs including basic metabolic panel, liver panel, complete blood count with differential, IgE, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and angiotensin-converting enzyme (ACE). These tests provide critical information about systemic inflammation, immune dysregulation, and organ function.

H. Autoimmune testing: Comprehensive laboratory panel at baseline, then every 5 years, with earlier repeat if symptoms arise.

I. Emerging tools: Biomarkers, breath biopsy, and forced oscillometry may be used at physician discretion.

Oversight

The protocol will be developed by experienced occupational medicine physicians and pulmonologists who specialize in silicosis and pneumoconiosis. It will be reviewed and updated every two years to reflect new clinical evidence and diagnostic tools.

Why This Matters

Silicosis is preventable but irreversible once established. Early detection allows for removal from exposure, closer monitoring, and better long-term outcomes. Independent, expert-led surveillance is necessary to close the gaps left by employer-based systems and ensure that all exposed workers—past and present—receive the medical care they need.

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159. The Silicosis Center of Excellence of University of California San Francisco Ideal Medical Monitoring Program for engineered stone workers includes the following Table:

Table 1: Recommended Testing and Frequency for Artificial Stone Workers:

Category	Test/Tool	Frequency
Medical History and Physical Exam	Exposure history (validated questionnaire) + physical exam (heart, lung, skin, joints, ENT, extremities)	Annually during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician)
Respiratory Symptoms & Quality of Life	KBILD, MMRC, PROMIS-29 questionnaires	
Imaging	HRCT Chest	
Pulmonary Function Testing (PFTs)	Spirometry, lung volumes, DLCO, post-bronchodilator spirometry, 6-minute walk test	
Cardiopulmonary Exercise Testing (CPET)	Performed using bicycle or treadmill	Baseline, then every 5 years (shorter if recommended by physician)
Infectious Disease Screening	Tuberculosis: Quantiferon Gold + 3 sputum cultures; NTM screening	Annually during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician)
Systemic Disease Testing	Basic metabolic panel, Liver panel, Complete blood count with white blood cell differential, Immunoglobulin-E, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)	
Autoimmune Testing	Rheumatoid Factor (RF); Anti-Cyclic Citrullinated Peptide (anti-CCP); Antinuclear Antibody (ANA); Anti-dsDNA; Anti-Sm; Anti-Ro/SSA; Anti-La/SSB; Complement levels; Anti-centromere; Anti-Scl-70; Anti-RNA polymerase III; p-ANCA (MPO); c-ANCA (PR3); Anti-Mi-2; Anti-Jo-1; Anti-SRP; Anti-MDA5; Anti-TIF1-γ, Anti-NXP2, Creatine Kinase (CK); Angiotensin-Converting Enzyme (ACE)	Baseline, then every 5 years (or more frequently if indicated by examining physician)

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160. The Silicosis Center of Excellence of University of California San Francisco Ideal Medical Monitoring Program for engineered stone workers includes: **Screening recommendations for exposed artificial stone workers without evidence of parenchymal silicosis.**

Introduction

Disease surveillance for silicosis involves the systematic and ongoing monitoring of workers at risk of developing lung disease due to exposure to respirable crystalline silica. This process typically includes periodic health evaluations such as symptom screening, imaging, and pulmonary function testing, with the goal of detecting disease at an early, potentially asymptomatic stage to enable timely intervention and prevent progression. Surveillance is especially critical for workers involved in engineered stone countertop fabrication, a sector associated with exceptionally high-intensity silica exposure. Engineered stone contains over 90% crystalline silica, which far exceeds that of natural stone, and fabrication tasks such as cutting, grinding, and polishing generate hazardous levels of respirable dust. As a result, engineered stone workers are developing silicosis at younger ages, after shorter exposure durations, and with more aggressive progression than historically observed in other industries. Given this severe clinical course and the potential for preventable morbidity, comprehensive and frequent disease surveillance is essential to protect the health of this high-risk workforce.

Despite the importance of medical surveillance, current strategies often fall short, especially in the engineered stone industry. A key limitation is the overreliance on air monitoring, which, while valuable, is expensive and often infeasible in many workplace settings. Recognizing the high baseline risk in this sector, jurisdictions such as California and Australia have revised their surveillance protocols to include universal screening of engineered stone workers, rather than relying solely on

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exposure measurements. Furthermore, effective surveillance must extend beyond imaging alone. A comprehensive approach should incorporate standardized symptom questionnaires, complete pulmonary function testing with diffusion capacity, and emerging biomarkers that may signal early, subclinical silica-related inflammation. While healthcare systems and regulatory frameworks differ across regions, occupational medicine providers and public health officials should adopt and tailor these strategies to their local contexts, ensuring that the core goals of early detection, accurate exposure assessment, and prompt clinical intervention are maintained.

Early identification of silicosis is particularly critical for workers with ongoing exposure to respirable crystalline silica, as continued exposure significantly accelerates disease progression. Historical data show that between one-third and nearly 90 percent of individuals with silicosis experience worsening disease over time. Engineered stone workers are especially vulnerable due to the intensity of exposure, even after relatively short periods of work. Evidence from Swedish registries and studies in South African and Brazilian miners consistently demonstrates that ongoing silica exposure after diagnosis leads to more rapid progression, including to severe forms like progressive massive fibrosis (PMF). Although disease can continue to progress even after exposure ceases, the rate of deterioration tends to slow. However, among engineered stone workers, progression may occur with alarming speed. For example, one Spanish study found that over half of workers with simple silicosis progressed within four years, and more than one-third developed PMF. Because PMF has a poor prognosis and often culminates in cardiopulmonary failure requiring lung transplantation, detecting disease early, ideally before or at the time of diagnosis, offers a vital opportunity to reduce exposure and potentially alter the trajectory of this otherwise devastating condition.

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Medical Necessity of Non-employer-based Screening Programs

Medical surveillance and diagnostic testing for workers exposed to respirable crystalline silica, particularly in the engineered stone industry, is medically necessary due to the high risk of early, aggressive, and irreversible lung disease. Many affected workers are not covered by employer-sponsored surveillance programs because they are self-employed, work in very small shops, or are employed in workplaces with limited financial resources and no capacity to provide such monitoring. As a result, there is a critical gap in access to appropriate medical evaluation and ongoing surveillance.

Furthermore, while Cal/OSHA has adopted emergency standards, the agency does not have adequate staffing or resources to ensure that mandated testing is consistently implemented across workplaces. This lack of enforcement and oversight has left a large segment of high-risk workers without the protections necessary to detect disease early and prevent progression.

The current system is therefore failing to protect this workforce. Independent medical testing and surveillance programs are required to fill this gap and ensure that at-risk individuals receive timely and comprehensive evaluation. As documented by Surasi et al., significant shortcomings in existing surveillance infrastructure underscore the urgent need for accessible, standardized, and medically directed testing for silica-exposed workers.

Eligibility

Workers are eligible for participation in this screening program if they have a history of occupational exposure to artificial stone dust for a cumulative lifetime

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duration of at least 30 days. The program is designed for individuals who do not have established evidence of parenchymal silicosis. Eligible participants therefore include those without any radiographic abnormalities suggestive of silicosis, as well as those whose only radiographic findings are isolated lymph node calcifications, which may reflect exposure but do not constitute parenchymal disease. Importantly, eligibility extends to both current and former workers, recognizing that individuals who are no longer employed in the industry remain at risk for disease development and progression.

Protocol Development and Oversight

This protocol will be developed by a multidisciplinary team of occupational medicine physicians and pulmonologists with extensive experience caring for patients with silicosis and other pneumoconioses. Their expertise ensures that the recommended evaluations reflect both best clinical practices and the unique needs of silica-exposed workers. To maintain relevance and scientific rigor, the protocol will undergo systematic review every two years. During each review cycle, the team will evaluate the most current clinical recommendations, incorporate advances in diagnostic testing, and assess the feasibility of integrating novel tools that may not yet exist at the time of this documentation.

Medical History and Physical Exam

Given the complexity of diagnosing and managing silicosis, particularly in workers exposed to high concentrations of respirable crystalline silica from engineered stone, it is essential that affected individuals be evaluated by specialists in occupational and pulmonary medicine with specific expertise in silica-related lung disease. These clinicians are uniquely trained to interpret the interplay between work

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history, radiographic findings, pulmonary function data, laboratory results, and symptom progression. Accurate diagnosis is especially challenging in early or atypical cases, where imaging and pulmonary function testing may be equivocal. Misclassification can lead to under-recognition of at-risk individuals or, conversely, to unnecessary anxiety and over-treatment. Evaluation by experienced specialists ensures accurate interpretation, timely removal from exposure when needed, and the initiation of interventions that may slow disease progression. Ideally, these assessments should occur within dedicated Silicosis Centers of Excellence, where multidisciplinary teams can deliver standardized, high-quality care, facilitate early detection through advanced diagnostics, and contribute to broader surveillance and research efforts.

Occupational questionnaires are a critical component of the medical assessment for engineered stone workers. These tools systematically capture information about work history, job tasks, exposure duration and intensity, use of personal protective equipment, and the presence or absence of dust-control measures. In the context of engineered stone fabrication—an industry associated with exceptionally high levels of respirable crystalline silica—questionnaires provide essential context that imaging and pulmonary function testing alone cannot offer. They help identify high-risk workers who may require more frequent medical surveillance or earlier diagnostic evaluation, even in the absence of symptoms. Furthermore, standardized occupational questionnaires strengthen epidemiologic research, guide exposure mitigation strategies, and inform regulatory responses by highlighting patterns of unsafe practices.

The medical assessment itself will include a detailed exposure history obtained through these standardized questionnaires and a full physical examination, with emphasis on the heart, lungs, skin, joints, ears, nose, throat, and extremities.

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Physicians will also integrate results from symptom and quality-of-life questionnaires, imaging studies, pulmonary function testing, infectious disease screening, autoimmune and systemic laboratory markers, and other relevant diagnostics. Together, these elements provide a holistic understanding of both respiratory and systemic health, ensuring early detection, guiding individualized treatment, and supporting evidence-based policy and workplace protections.

Symptoms-based Questionnaires

Respiratory symptom questionnaires provide essential clinical information that complements imaging and physiologic testing. Many early manifestations of silicosis, such as cough, sputum production, or exertional breathlessness, may not be captured by CT scans or pulmonary function tests. Standardized questionnaires allow clinicians to systematically track changes in symptoms over time and ensure that subtle but clinically important declines are not overlooked.

Quality of life assessments extend beyond respiratory symptoms to capture the broader impact of silica-related disease on daily functioning. Workers with silicosis or early lung impairment frequently experience fatigue, anxiety, sleep disturbance, musculoskeletal pain, and reduced participation in work or social activities. By using validated instruments such as the King's Brief Interstitial Lung Disease (KBILD) questionnaire, the Modified Medical Research Council (MMRC) dyspnea scale, and the PROMIS-29, clinicians can quantify how disease affects physical, emotional, and social well-being. This information not only guides individualized treatment decisions but also highlights the real-world burden of disease for policymakers, insurers, and employers.

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Imaging testing

Traditional chest X-rays are inadequate for detecting early-stage silicosis, especially when compared to the significantly greater sensitivity and diagnostic clarity offered by high-resolution computed tomography (HRCT). HRCT is now widely recognized as the superior imaging tool for surveillance, given its ability to detect subtle abnormalities that are not visible on standard radiographs. Despite some emerging interest in low-dose CT as a potential alternative, no studies have directly compared it to chest X-rays for this purpose, and current evidence is insufficient to conclude that it offers a reliable replacement.

In cases of simple silicosis, HRCT allows for much more precise identification of characteristic features, such as centrilobular and subpleural nodules with a perilymphatic distribution, and provides improved visualization of hilar lymph-adenopathy. It can also differentiate silicotic nodules from other causes of nodularity. In complicated silicosis, HRCT is particularly useful for clearly defining mass borders, internal architecture, and associated paracicatricial emphysema. Additional pathologic findings—including lymph node calcification, pleural plaques, or superimposed infections such as tuberculosis—are also better visualized on HRCT.

Data from Australian and Italian studies underscore this superiority: 35–43% of engineered stone workers with CT-confirmed silicosis had normal chest X-rays, and only 42% of Italian workers diagnosed with silicosis via CT had abnormal chest radiographs. These findings have led regulatory bodies in Australia and California to transition from chest X-rays to mandatory chest CT scans for surveillance, underscoring the critical need to adopt more sensitive imaging to enable earlier diagnosis and intervention.

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We recommend that all eligible people undergo chest CT imaging as part of medical surveillance. For individuals who remain actively employed in the industry, CT scans should be performed annually during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician) throughout the duration of their work tenure, reflecting their continued risk of exposure and disease progression. For those who have left the industry, annual CT scans are advised for the first 15 years following cessation of exposure, given the ongoing risk of delayed disease development. After this period, the interval may be extended to every three years with the option to stop testing at age 75 following a joint decision between the patient and the examining physician. Shorter-interval follow-up scans (e.g., every 3–6 months) may be warranted at the discretion of the treating physician if concerning radiographic findings such as isolated lymph node calcifications or pulmonary nodules are identified.

This approach aligns with practices adopted in Australia and reflects the high-intensity silica exposure associated with engineered stone fabrication, as well as the increased risk of disease progression in this population. After evaluation by a specialist in occupational and pulmonary medicine, the surveillance interval may be extended to every two years in cases where there is compelling evidence of clinical and radiographic stability. Such decisions should be individualized and based on specialist judgment.

Pulmonary function testing

Pulmonary function testing (PFT) refers to a group of non-invasive tests that assess how well the lungs are working, including measurements of lung volume, airflow, and gas exchange capacity. These tests, such as spirometry and diffusing

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capacity for carbon monoxide (DLCO), are essential tools in the early detection of respiratory impairment. For workers exposed to respirable crystalline silica, particularly in the engineered stone industry, regular PFTs can help identify early signs of lung damage before symptoms appear or radiographic abnormalities develop.

In Australia, it is recommended that workers in high-risk industries such as engineered stone fabrication undergo baseline pulmonary function tests (PFTs) at the start of employment, followed by annual testing to monitor for any decline in lung function over time. This approach is more rigorous than current U.S. OSHA requirements, which do not mandate routine pulmonary function surveillance for silica-exposed workers. The increased frequency of testing in Australia reflects the recognized rapid progression of silicosis in engineered stone workers and the need for more intensive monitoring. Both Safe Work Australia and the [Australian] National Dust Disease Taskforce emphasize that repeated PFTs allow for the identification of meaningful changes by establishing trends and distinguishing true physiological decline from normal variability. When significant changes are detected or clinical concerns arise, more frequent testing and referral to a respiratory specialist are warranted. As with imaging surveillance, this proactive approach to lung function monitoring is a critical strategy for early detection, prevention of disease progression, and protection of workers' respiratory health in this high-risk population.

Pulmonary function testing in engineered stone workers can reveal a variety of abnormalities, with restrictive patterns being the most frequently observed. However, many individuals with CT evidence of silicosis may still have normal pulmonary function tests, particularly at the time of diagnosis. In an Italian case series, only 33% of workers with CT-confirmed silicosis had abnormal spirometry, whereas 50% had a reduced diffusing capacity for carbon monoxide (DLCO), highlighting the greater sensitivity of diffusion measurements. Similarly, in an

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Australian study, more than half of the individuals with progressive massive fibrosis showed normal spirometry results. These findings underscore the limited sensitivity of spirometry alone for early disease detection. Including DLCO in routine testing provides a more comprehensive assessment and improves the likelihood of detecting physiologic impairment. While pulmonary function testing is less sensitive than chest CT for diagnosing silicosis, it remains an important tool for monitoring disease progression and assessing functional disability—particularly when full testing, including DLCO, is performed.

We recommend full pulmonary function testing which includes spirometry, lung volumes, diffusion capacity, and 6-minute walk test to be completed annually during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician) during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician).

Cardiopulmonary Exercise Testing (CPET) offers a valuable diagnostic advantage in dust-exposed workers by assessing the combined performance of the respiratory, cardiovascular, and muscular systems during exertion. Unlike resting spirometry or DLCO alone, CPET can detect ventilatory inefficiency and reduced aerobic capacity even in individuals who appear normal at rest. For instance, in coal miners with small airway dysfunction, CPET revealed that at modest exercise workloads they used a significantly higher fraction of their maximal voluntary ventilation, had elevated ventilatory equivalents (VE/VO and VE/VCO), and exhibited a 27% lower peak oxygen consumption—despite normal resting spirometry and DLCO . Similarly, in a cohort of former U.S. coal miners, resting DLCO strongly

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predicted abnormalities in CPET gas exchange measures such as elevated A-a gradient and reduced VO max, while FEV was less predictive. These studies highlight CPET's ability to unmask early functional limitation, even when resting pulmonary tests and imaging are relatively preserved. Incorporating CPET into surveillance of silica-exposed workers—such as those in engineered stone fabrication—can therefore provide critical insights into subclinical impairment, guide targeted evaluations, and enhance early detection of disease progression and disability risk. Cardiopulmonary exercise testing (CPET) has been used to evaluate veterans exposed to burn pit smoke, providing a detailed assessment of exercise intolerance and revealing abnormalities in gas exchange, ventilatory efficiency, and cardiovascular response that may not be apparent on resting pulmonary function tests.

Cardiopulmonary exercise testing is currently being used as part of expansive clinical protocols in the diagnosis of early lung disease in exposed workers, including the Department of Labor's Black Lung Program and the Veterans' Administration's Post-Deployment Cardiopulmonary Evaluation Network. Cardiopulmonary exercise testing (CPET) should be performed at baseline and then repeated every 3–5 years, with shorter intervals if recommended by the examining physician based on clinical findings.

Infectious diseases

A well-established link exists between silicosis and tuberculosis, with a recent meta-analysis reporting a pooled relative risk of 4.01 for developing TB in individuals with silicosis. For example, among 2,758 former South African miners, the prevalence of silicotuberculosis was 25.7%. In California, among engineered stone countertop workers, 2 out of 45 individuals (4%) were diagnosed with active tuberculosis. However, due to overlapping clinical and radiographic features,

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particularly the micronodular pattern in the upper lung zones, 10 of the 45 workers (22%) were initially misdiagnosed with active pulmonary TB rather than silicosis. Many of these individuals underwent prolonged multidrug TB treatment before silicosis was correctly identified. Thus, while tuberculosis is an important comorbidity in engineered stone-associated silicosis, it is also a potential source of diagnostic confusion due to similar imaging patterns.

Nontuberculous mycobacterial (NTM) infection is linked to underlying lung diseases like cystic fibrosis, COPD, and silicosis. Once thought to be harmless colonizers, NTMs were defined as true pathogens in 2007, with diagnosis requiring symptoms, positive cultures (two sputum or one BAL), and characteristic imaging. In engineered stone (ES) silicosis, studies from Israel, California, and Brazil show a 9% NTM disease prevalence, often with cavitary lesions. Common species include *M. kansasii*, *M. abscessus*, *M. intracellulare*, *M. fortuitum*, and *M. xenopi*. NTM is more frequent in progressive massive fibrosis and may worsen outcomes. Species distribution varies by region; in the U.S., NTM surpasses TB prevalence, which may explain its prominence in ES silicosis despite many patients being Latin American immigrants. Further research is needed to clarify biological and epidemiologic risk factors.

For this reason, all those exposed to silica dust, especially those with engineered stone dust exposure must be screened for tuberculosis and other mycobacterial lung diseases. The recommended screening test would be a Quantiferon Gold blood test along with 3 expectorated sputum cultures to be completed annually during work tenure and for 15 years after cessation of work, and then every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician) during work tenure and for 15 years after cessation of work, and then

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every 3 years thereafter (aligned with CT chest intervals, with the option to stop testing at age 75 following a joint decision between the patient and the examining physician).

Markers of Systemic Disease

In addition to imaging and pulmonary function testing, baseline and periodic laboratory evaluation provides essential information about systemic health in silica-exposed workers. A basic metabolic panel and liver panel help assess kidney and liver function, which may be impaired either by silica-associated autoimmune disease or by medications used to treat related conditions. A complete blood count with white blood cell differential can identify anemia, cytopenias, or elevated inflammatory markers that may indicate systemic involvement of silica-related disease, infections such as tuberculosis or nontuberculous mycobacteria, or autoimmune processes. Measurement of IgE levels is important for evaluating allergic or atopic disease and may provide clues to immune dysregulation associated with silica exposure, including vasculitis. In addition, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) serve as nonspecific but sensitive markers of systemic inflammation, useful in tracking autoimmune activity or identifying occult infection. Though often elevated in sarcoidosis, angiotensin-converting enzyme (ACE) levels can also be abnormal in silicosis and may serve as a marker of granulomatous inflammation.

Autoimmune biomarkers

The connection between silicosis and autoimmune diseases has been recognized since the early-to-mid 20th century. Notably, scleroderma was reported in stone masons, systemic sclerosis (SSc) in South African gold miners (known as

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Erasmus Syndrome), and rheumatoid arthritis (RA) in coal miners (Caplan's Syndrome). In addition to these, silica exposure has been associated with conditions such as systemic lupus erythematosus (SLE), dermatomyositis, polymyositis, and ANCA-associated vasculitis, among other autoimmune diseases.

Recent studies of engineered stone (ES) countertop workers have shown continued links between silicosis and autoimmune conditions, with approximately 20% affected—about seven times higher than in the general population. The most commonly reported conditions are RA, SSc, and SLE, but cases of ANCA vasculitis and others have also been observed. Furthermore, the presence of autoimmune and inflammatory markers increases with disease severity. Among ES workers, the prevalence of positive antinuclear antibodies (ANA) and elevated angiotensin-converting enzyme (ACE) levels rose from 24.2% and 10.3% in exposed individuals without silicosis to 34.0% and 34.8% in those with simple silicosis, and to 47.1% and 55.6% in those with complex silicosis, respectively. The likelihood of detecting autoantibodies in silicosis is also linked to older age, smoking history, and higher levels of respirable crystalline silica (RCS) exposure. In a large group of over 1,000 exposed workers, confirmed autoimmune disease was identified in about 1%.

To evaluate, for autoimmune diseases, these biomarkers are recommended:

Systemic disease testing

- Complete blood count with white blood cell differential
- Complete metabolic panel (evaluate kidney and liver function)
- IgE (immunoglobulin in asthma and some rheumatologic diseases such as vasculitis)

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Rheumatoid Arthritis (RA)

- RF (Rheumatoid Factor)
- Anti-CCP (Cyclic Citrullinated Peptide)

Systemic Lupus Erythematosus (SLE)

- ANA
- Anti-dsDNA (Double-Stranded DNA)
- Anti-Smith (Sm)
- Anti-Ro/SSA and Anti-La/SSB (also seen in Sjögren's, may overlap with lupus)
- Low complement levels (C3, C4)

Systemic Sclerosis (Scleroderma)

- ANA
- Anti-centromere antibodies (limited cutaneous Ssc)
- Anti-Scl-70 / Anti-topoisomerase I (diffuse cutaneous Ssc)
- Anti-RNA polymerase III

ANCA-Associated Vasculitis

- p-ANCA (MPO – Myeloperoxidase)
- c-ANCA (PR3 – Proteinase 3)

Dermatomyositis / Polymyositis

- ANA
- Anti-Mi-2 (more specific to dermatomyositis)
- Anti-Jo-1 (associated with antisynthetase syndrome)
- Anti-SRP (Signal Recognition Particle)
- Anti-MDA5, Anti-TIF1-γ, Anti-NXP2 (subtypes, associated with different clinical features)

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- CK (Creatine Kinase): Elevated in myositis (dermatomyositis, polymyositis)

Sarcoidosis

- Angiotensin-Converting Enzyme (ACE): May be elevated in sarcoidosis but can also rise in chronic inflammation like silicosis

Additional biomarkers

Several biomarkers have been investigated for their potential to distinguish early silicosis from simple occupational exposure to crystalline silica. Among these, **CC16 (Clara cell protein 16)** has shown the most consistent ability to differentiate silicosis, even at early stages, from silica exposure, with significantly lower serum levels in affected individuals. **KL-6 (Krebs von den Lungen 6)** also appears elevated in silicosis patients relative to exposed controls and correlates with fibrotic disease severity, although further silica-specific validation is needed. In contrast, pro- and anti-inflammatory cytokines such as **TNF-α**, **IL-1**, **IL-6**, and **IL-10**, along with **neopterin**, tend to be elevated in both exposed individuals and those with silicosis, limiting their standalone diagnostic specificity. The **MUC5B gene**, while associated with fibrotic susceptibility, does not clearly distinguish exposure from disease. However, it is important to emphasize that this body of research is still in its early stages. While some markers currently lack specificity, they may ultimately contribute valuable predictive power as part of a **multi-biomarker model** for early disease detection. Future work should avoid prematurely excluding any candidates and instead focus on validating their combined utility across diverse cohorts and exposure profiles.

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Other early surveillance techniques

Breath Biopsy

There is emerging research exploring the use of **breath biopsy**, a noninvasive method analyzing volatile organic compounds (VOCs) in exhaled breath, as a potential tool for early detection and exposure surveillance in silicosis. Recent studies have profiled VOCs in the breath of workers exposed to crystalline silica dust and individuals with confirmed silicosis. In a case–control study of silica-exposed workers and silicosis patients, investigators identified significantly elevated levels of VOCs such as acetaldehyde, hexanal, nonanal, decane, pentadecane, 2-propanol, and 3-hydroxy-2-butanone compared with healthy controls. These findings suggest oxidative stress and inflammatory responses as underlying mechanisms. A larger study combining VOC analysis with machine learning models achieved nearly 90% accuracy in distinguishing silicosis cases from healthy individuals by identifying nine breath biomarkers, including 2,3-butanedione, ethyl acetate, chlorobenzene, and phthalic anhydride. A corporate research effort (Owlstone Medical) also used a VOC atlas to cross-reference compounds produced in silicosis patients, reinforcing that specific exhaled VOC patterns could serve as candidate biomarkers of disease and silica exposure.

Despite promising findings, there are currently no validated or clinically approved breath-biopsy–based tests for silicosis surveillance. Further research is needed to replicate these VOC signatures in broader populations, establish standardized sampling protocols, and determine clinical utility. Nonetheless, breath biopsy offers a compelling future avenue for noninvasive early detection of silica-related lung injury, particularly in high-risk groups such as engineered stone workers.

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Forced Oscillation Technique

The **forced oscillation technique (FOT)** is an emerging pulmonary function tool that offers distinct advantages in the early detection of silicosis, particularly in engineered stone workers at high risk for rapid disease progression. Unlike spirometry, which often remains normal until moderate or advanced disease, FOT can detect subtle changes in airway resistance and reactance during tidal breathing, making it highly suitable for screening and surveillance. In a study of never-smoking silicosis patients, FOT parameters—including total respiratory resistance and indicators of ventilation heterogeneity—were found to worsen progressively even in the early stages of disease, providing sensitivity to physiologic abnormalities not captured by traditional tests. Further evidence showed that FOT metrics such as resistance at 4 Hz (Rrs) and zero-intercept resistance ®) were significantly elevated even in patients with mild spirometric obstruction, while reactance and dynamic compliance declined with increasing disease severity. Importantly, these metrics demonstrated high diagnostic accuracy, with area under the curve (AUC) values exceeding 0.80 for mild disease and 0.90 for moderate to severe disease. Additionally, these functional changes have been shown to correlate with radiographic findings of parenchymal damage. Given its ability to detect early small airway and parenchymal abnormalities during normal breathing, FOT may be particularly valuable for identifying subclinical or early silicosis in high-risk workers, facilitating earlier intervention and removal from exposure before irreversible lung damage occurs.

I. Why Defendants Should Have to Fund Medical Monitoring of Exposed Workers

161. Defendants should have to fund medical monitoring of workers for many reasons.

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162. First, Defendants manufactured and distributed their inherently defective and lethal products to workplaces throughout California, causing the new artificial stone silicosis epidemic.

163. Second, Defendants knew that their artificial stone products contained extremely high levels of crystalline silica, that workers would be exposed to respirable crystalline silica dust from their products, and that countertop fabrication workers would therefore develop silicosis.

164. Third, Defendants profited greatly from their sales of artificial stone products (a multi-billion dollar industry) and have the financial resources to fund medical monitoring of workers.

165. Fourth, for these reasons, Defendants bear primary responsibility for the new silicosis epidemic in California and, in justice and equity, should have to bear the cost of medical monitoring.

166. Plaintiffs are vulnerable workers who lack access to medical care and diagnostic medical services, and who lack financial resources to themselves obtain medical monitoring services.

167. Although the Cal-OSHA Standard and SB 20 impose obligations on employers to medically monitor employees, it cannot secure adequate monitoring for exposed workers because:

(1) Most countertop fabricators and installers work independently as independent contractors, so they have no employers required by the new Cal-OSHA standard to provide medical monitoring for them, because OSHA standards do not apply to hirers of independent contractors.[63]

(2) Employers of the small percentage of employed workers are small businesses that lack financial resources to comply with the Cal-OSHA standard and SB 20, because the cost of compliance entails initial capital expenditures of about $3.5 million to purchase and install equipment and would require annual expenditures of about $600,000 to maintain compliance with the Standard, even though most employers operating stone countertop fabrication shops are small minority-owned businesses whose annual gross revenues are less than $500,000.[64]

(3) Faced with exorbitant costs of complying with the Cal-OSHA Standard and

[63] See, Occupational Safety and Health Administration, Standard 1975.3(d) and the Interpretative Opinion of OSHA dated May 23, 2001, regarding CPL 2-0.124 ("Multi-Employer Citation Policy"); self-employed contractors by Russell B. Swanson, Director, Directorate of Construction ["If a construction worker is truly self-employed – is not an employee – and has no employees working for him or her, OSHA has no authority to require that individual to abide by OSHA construction requirements."].

[64] See, Jenny Leigh Houlroyd, "Economic Feasibility of Complying with the OSHA Silica Standard in the Cut Stone Industry," (Houlroyd Health and Safety Consulting, 2024).

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SB 20, stone fabrication businesses in California have found it economically impossible to comply with these new requirements; about 95% violate the Standard, including the requirement to provide employees medical monitoring.[65]

(4) The small number of stone countertop fabrication businesses in California, if any, that may have sufficient resources to comply with the new Cal-OSHA Standard and SB 20, have begun implementing alternative solutions to complying with the Standard including its medical monitoring requirements, such as ceasing to do business, closing their fabrication shops, ceasing to fabricate artificial stone countertops so as not to incur medical monitoring costs to monitor their employees for exposure to artificial stone dust, closing their fabrication shops and opening new fabrication shops in order to avoid detection by Cal-OSHA, and simply not complying with the Cal-OSHA Standard.

(5) Stone countertop fabrication businesses will not comply with Cal-OSHA Standard and SB 20 absent constant, rigorous enforcement by Cal-OSHA, which Cal-OSHA has not been able to do for lack of sufficient OSHA inspectors and financial resources to hire OSHA inspectors,[66] and most certainly cannot do now that funding to OSHA, the National Institute of Occupational Safety and Health, and Cal-OSHA has been decimated by the Department of Governmental Efficiency, which has also terminated the majority of those agencies' employees.

(6) funding of the CDPH has also been decimated by federal funding reductions.

(7) A recent report prepared for the stone industry recognizes that "OSHA-mandated medical surveillance (chest X-ray and spirometry) can miss early stage silicosis."[67] Thus, monitoring beyond that which is mandated by OSHA is necessary to protect artificial stone workers.

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[65] Cal. Dept. of Industrial Relations, Finding of Emergency, Gov't Code § 11346.1 Occupational Safety and Health Standards Board, Proposed Emergency Regulation, Title 8, California Code of Regulations, General Industry Safety Orders, Chapter 4, Subchapter 7, Revised Section 5204: Occupational Exposures to Respirable Crystalline Silica at p. 13 [only 5% of workers reported their employers sent them for required silica medical examinations.]

[66] See, California State Auditor, Report No. 2024-115, *The Division of Occupational Safety and Health: Process Deficiencies and Staffing Shortages Limit Its Ability to Protect Workers* (July 17, 2025).

[67] Yale University, "Review of Selected Literature Relevant to the Production of Natural and Engineered Stone Countertops and Adverse Health Effects," study sponsored by the Natural Stone Institute (NSI) and International Surface Fabricators Association (ISFA), April 1, 2025.

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VI. MEDICAL MONITORING TECHNIQUES

168. Traditional radiographic and pathology techniques have been used to detect silicosis in workers exposed to artificial stone dust; noninvasive and minimally invasive technologies are increasingly being used to detect silicosis early in the disease process, to deter disease progression.

169. Historically, radiographic imaging technologies have been the primary technologies used to detect and diagnose silicosis and other pneumoconioses. These techniques include high-kV (HKV) X-ray imaging, computed radiography, direct digital radiography (DR), computed tomography (CT), and positron emission tomography (PET).

170. Imaging techniques that entail minimal or no radiation exposure can be used to detect silicosis, to differentiate silicosis from lung cancer and other lung diseases, and to assist surgeons in obtaining tissue specimens for pathological analysis. These techniques include ultrasound, magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT).

171. In recent years computer-aided diagnosis (CAD) including artificial intelligence (AI) and deep learning (DL), which minimize potential interpreter bias, have been used to detect silicosis.

172. Pulmonary function tests (PFTs) including spirometry with diffusing capacity (DLCo) have been used to determine extent of pulmonary function loss and disease progression in silicosis.

173. Tissue-invasive techniques have been used to obtain samples for pathological analysis. The surgical techniques to obtain tissue samples include surgical lung biopsy (SLB), transbronchial lung biopsy (TBLB), percutaneous lung biopsy (PCLB), and transbronchial cryobiopsy (TBCB). The major pathological technique used to make a definitive diagnosis of silicosis is scanning electron microscopy with energy-dispersive x-ray spectroscopy (SEM-EDS).

174. In recent years various biomarkers have been used to detect silicosis in early stages of the disease, before silicosis is detectable with chest radiographs and even computed tomography. Multiple biomarkers that can be obtained from blood, serum, and urine have been identified, which permit pre-clinical detection of silicosis, allowing early interventions to prevent disease progression. Non-invasive breath tests and electronic nose technologies can now be used to detect early silicosis.

175. All of these silicosis detection techniques will be discussed in detail.

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A. Imaging Techniques

1. Chest X-rays

176. Chest x-rays have traditionally been used for silicosis surveillance and diagnosis because they chest radiography is a non-invasive technique that entails relatively low radiation exposure, they are often done at diagnosis and treatment centers, and they are relatively inexpensive. However, chest x-rays lack sufficient sensitivity to detect early silicosis and therefore have minimal utility for screening silicosis in populations occupationally exposed to respirable crystalline silica.

177. The inadequacy of chest x-rays to detect pneumoconiosis has been known for at least 20 years. In 2004, Turkish researchers compared chest x-ray (CXR) and high-resolution computer tomography (HRCT) findings of 67 coal workers. Discordance between CXR and HRCT was high, especially for CXR negative and early pneumoconiosis cases. The investigators concluded that the role of CXR in screening coal workers to detect early pneumoconiosis findings should be questioned. They recommended using HRCT as a standard screening method instead of CXR to distinguish between normal and early pneumoconiosis.[68]

178. In 2019, researchers from Brisbane, Australia used chest x-rays to quantify the severity of disease of 659 artificial stone stonemasons in Queensland. They found it interesting that 43% of reviewed International Labour Office (ILO) reports reviewed were described as normal, suggesting chest radiographs may have a low sensitivity for silicosis in these workers. In these cases, the treating respiratory physician relied on high-resolution computed tomography for diagnosis.[69]

179. In 2024, researchers from Victoria, Australia sought to assess the sensitivity of chest x-rays to detect silicosis in artificial stone benchtop industry workers. Paired CXR and high-resolution computed tomography (HRCT) images were acquired from 110 artificial stone benchtop industry workers. Blinded to the clinical diagnosis, each CXR and HRCT was independently read by two thoracic radiologists from a panel of seven, in accordance with International Labour Office

[68] Savranlar A, et al., "Comparison of chest radiography and high-resolution computed tomography findings in early and low-grade coal worker's pneumoconiosis," *Eur. J. Radiol.* 2004; 51:175-180.

[69] Newbigin K, et al., "Stonemasons with silicosis: Preliminary findings and a warning message from Australia," *Respirology* 2019; 24:1220-1221.

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(ILO) methodology for CXR and International Classification of HRCT for Occupational and Environmental Respiratory Diseases. Accuracy of screening positive (ILO major category 1, 2 or 3) and negative (ILO major category 0) CXRs were compared with identification of radiological features of silicosis on HRCT. CXR was positive for silicosis in 27/110 (24.5%) workers and HRCT in 40/110 (36.4%). Of the 83 with a negative CXR (ILO category 0), 15 (18.1%) had silicosis on HRCT. All 11 workers with ILO category 2 or 3 CXRs had silicosis on HRCT. In 99 workers ILO category 0 or 1 CXRs, the sensitivity of screening positive CXR compared to silicosis identified by HRCT was 48% (95% CI 29–68) and specificity 97% (90–100). The investigators concluded that compared to HRCT, sensitivity of CXR was low and that reliance on chest x-rays for health monitoring would provide false reassurance for many workers, delay management and underestimate the prevalence of silicosis in the artificial stone benchtop industry.[70]

180. In 2025, British researchers investigated the diagnostic accuracy of CXR for silicosis screening compared to computed tomography (CT), high-resolution CT (HRCT) and autopsy. They also modeled the relationship between CXR sensitivity and disease severity. Using meta-analytical methods, they estimated missed silicosis cases and the number needed to screen (NNS) in hypothetical populations of low (5%), medium (15%) and high (30%) silicosis prevalence. Twenty studies included 2156 participants and 1105 silicosis cases. CXR had moderate sensitivity (0.76; 95% CI 0.63-0.86, I2=84%) and high specificity (0.89, 95% CI 0.77-0.95, I2=57%) compared to HRCT in 12 studies, and low sensitivity (0.50, 95% CI 0.45-0.55, I2=0%) and high specificity (0.91, 95% CI 0.87 - 0.93, I2 = 20%) compared to autopsy in two studies. CXR sensitivity increased with higher reference test severity cut-offs. Clinically relevant numbers of cases were missed in fixed and relative sensitivity scenarios; increased prevalence and less severe disease resulted in more missed cases and a lower NNS. The researchers noted that silicosis severity and reference test type plausibly influence CXR sensitivity and that assuming either fixed or relative sensitivity results in missed silicosis cases. They concluded that judicious HRCT screening is likely to improve case detection.[71]

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[70] Hoy RF, et al., "Chest x-ray has low sensitivity to detect silicosis in artificial stone benchtop industry workers," *Respirology* 2024; 29:785-794.

[71] Howlett P, et al., "The diagnostic accuracy of chest xray screening for silicosis: A systematic review, meta-analysis and modelling study," *MedRxiv preprint* May 28, 2025.

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181. Based on their meta-analysis the same research group re-estimated a previously published dose-response relationship between cumulative respirable crystalline silica (RCS) exposure and silicosis risk, under the assumptions that sensitivity was either fixed or relative to the population proportion of severe silicosis. They combined unpublished logistic regression models from Scottish coal miners with meta-analysis results to model how CXR sensitivity changed according to cumulative RCS exposure. Among mining cohorts, they calculated the difference in the cumulative risk of silicosis between the unadjusted, and fixed and relative scenarios. Finally, they re-estimated the dose-response meta-analysis and related absolute risk reductions (ARR). In all mining cohorts the cumulative risk of silicosis was substantially higher in both the fixed and relative sensitivity scenarios compared to the unadjusted estimate. This was most pronounced in the relative scenario and when cumulative RCS exposures were below approximately 6 mg/m^3-years. A reduction from 4 to 2..mg/m^3-years in cumulative RCS exposure corresponded to larger ARRs in the fixed and relative scenario than the unadjusted scenario; 409 (374, 434) and 557 (451, 620) cases per 1000 miners compared to 323 (298, 344) cases per 1000 miners, respectively. The investigators concluded that currently reported estimates of silicosis risk according to cumulative silica exposure are likely significant underestimates due to the low sensitivity of chest x-rays for silicosis.[72]

182. The California Department of Public Health has noted that data from Australian and Italian studies showed that 35-43% of engineered stone workers with CT-confirmed silicosis had normal chest X-rays, and only 42% of Italian workers diagnosed with silicosis via CT had abnormal chest radiographs, and that these findings have led regulatory bodies in Australia and California to transition from chest X-rays to mandatory chest CT scans for surveillance. In issuing its medical monitoring recommendations, the CDPH therefore concluded: "Traditional chest X-rays are inadequate for detecting early-stage silicosis, especially when compared to the significantly greater sensitivity and diagnostic clarity offered by high-resolution computed tomography (HRT)."[73]

[72] Howlett P, et al., "Adjusting for the reduced sensitivity of CXR in the dose-response relationship between cumulative silica exposure and silicosis in miners," *MedRxiv preprint* May 29, 2025.

[73] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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2. Computed Tomography

183. Computed Tomography creates cross-section images by projecting a beam of emitted photons through one plane of an object from defined angle positions performing one revolution. As the X-rays (emitted photons) pass through the object, some of them are absorbed, some are scattered, and some are transmitted.[74]

184. High Resolution Computed Tomography (HRCT) of the lungs has developed into a mature technique for the evaluation of diffuse pulmonary parenchymal abnormality. At its simplest, high-resolution CT is a sampling tool that combines 1- to 2-mm thin-collimation CT images with a high-spatial-frequency reconstruction algorithm to generate images showing exquisite lung detail.[75]

185. HRCT is now widely recognized as the superior imaging tool for silicosis surveillance, given its ability to detect subtle abnormalities that are not visible on standard radiographs.[76]

186. In cases of simple silicosis, HRCT allows for much more precise identification of characteristic features, such as centrilobular and subpleural nodules with a perilymphatic distribution, and provides improved visualization of hilar lymphadenopathy. It can also differentiate silicotic nodules from other causes of nodularity. In complicated silicosis, HRCT is particularly useful for clearly defining mass borders, internal architecture, and associated paracicatricial emphysema. Additional pathologic findings—including lymph node calcification, pleural plaques, or superimposed infections such as tuberculosis—are also better visualized on HRCT.[77]

187. In 2019, Chinese researchers explored the CT imaging features of artificial stone-agglomerated quartz associated silicosis. A total of 37 cases confirmed with artificial stone-agglomerated quartz associated silicosis from December 2016 to August 2018 and 38 cases

[74] Cantatore A, et al., "Introduction to computed tomography," DTU Mechanical Engineering (2011).

[75] Kazerooni EA, "High-Resolution CT of the Lungs," *Am. J. Roentgenology* 2001; 177:501-519.2

[76] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[77] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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confirmed with traditional classical silicosis during the same period were retrospectively reviewed. The clinical characteristics (including gender, age and working age) and the imaging features (including nodule features, ground glass opacity, merging features, consolidation, secondary changes, etc.) of the two groups were recorded. The variables including the imaging findings between the two groups were analyzed by Fisher exact test. Of all the cases, there were bilateral diffuse small nodules which distributed with upper-zone predominance. Small nodules can merge together and form mass shadow. The complications such as lymphadenopathy, calcification, emphysema/pneumatocele, and pulmonary interstitial fibrosis could also be found. Among the various imaging features, the presence of ground glass opacity, small nodules merging together in the subpleural zones, consolidation, pulmonary interstitial fibrosis, and pneumothorax were found in 28, 16, 18, 17, and 5 cases, respectively in the artificial stone-agglomerated quartz associated silicosis group, and 2, 4, 4, 4, and 0 cases, respectively in the traditional classical silicosis group. The percentages of these signs were significantly higher in the artificial stone-agglomerated quartz associated silicosis group than the traditional classical silicosis group (P<0.01). The artificial stone-agglomerated quartz associated silicosis group had 3 cases with mediastinal lymph node enlargement with calcification, while the traditional classical silicosis group had 12 cases. This difference was also statistically significant. The investigators concluded that the characteristic changes of CT imaging features in artificial stone-agglomerated quartz associated silicosis are small nodules with the background of ground glass opacity, the nodules merging together under subpleural zones, consolidation, mediastinal lymph node enlargement with less calcification, complicated with interstitial lung fibrosis and pneumothorax.[78]

188. Similar findings were published the following year by Australian investigators.[79]

189. In 2024, Taiwanese researchers performed low dose chest CT examination on 19 workers engaged in the manufacture of artificial stone. Among these individuals, 12 exhibited abnormal CT opacities, and four displayed subpleural curvilinear lines in their upper lobes. The

[78] Xie J, et al., "CT imaging analysis of artificial stone-agglomerated quartz associated silicosis," *Chinese J. Radiol.* 2019; 53(10):882-885 [in Chinese, with English abstract].

[79] Jones CM, et al., "Silicosis in artificial workers: Spectrum of radiological high-resolution CT chest findings," *J. Med. Imaging Radiation Oncol.* 2020; 64(2):241-249.

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estimated exposure levels to respirable crystalline silica for these four individuals were 0.27, 0.77 4.44, and 4.44 mg/m^3, respectively, resulting in cumulative exposures of 1.35, 2.30, 13.32, and 26.64 mg/m^3-years. Three of the four subjects were raw material operators who blended quartz sand, resin, curing agents, and additives, and then molded these materials into the desired form. The other worker operated a water-suppressed grinding or polishing machine to customize and process artificial stone slabs. All four cases exhibited ground-glass opacities and scattered nodules. The researchers noted that subpleural curvilinear lines had previously been founded to be a distinguishing characteristic on chest CT, which was used to differentiate lung parenchyma affected by asbestos, but that this specific radiographic finding had not previously been reported in cases of silicosis.[80]

190. For individuals exposed to engineered stone dust, the California Department of Public Health (CDPH) recommends annual chest CT scans for disease surveillance. This approach aligns with practices adopted in Australia and reflects the high-intensity silica exposure associated with engineered stone fabrication, as well as the increased risk of disease progression in this population. After evaluation by a specialist in occupational and pulmonary medicine, the surveillance interval may be extended to every two years in cases where there is compelling evidence of clinical and radiographic stability. Such decisions should be individualized and based on specialist judgment.[81]

191. If initial CT imaging demonstrates radiologic markers of significant exposure or increased risk of silicosis, such as calcified lymphadenopathy (also called "lymph node silicosis"), pleural thickening or plaques, or a solitary pulmonary nodule, the CDPH recommends more frequent follow-up with CT scans every 3 to 6 months. Ongoing evaluation by a pulmonary specialist is also recommended to monitor for disease development or progression. The CDPH has not recommended low-dose CT as a diagnostic alternative because no studies have directly compared it to chest X-rays for this purpose and current evidence is insufficient to conclude it offers a reliable replacement.[82]

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[80] Chen CH, et al., "Subpleural curvilinear lines as an early indicator of silicosis in artificial stone workers," *Pulmonology* 2024; 30:174-176.

[81] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[82] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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3. Positron Emission Tomography (PET)

192. "Nuclear imaging uses radioisotope-labeled, small-molecule compounds, known as tracers, to detect *in vivo* biological processes at the molecular level. PET and SPECT [Single Photon Emission Computed Tomography] systems are common instruments that record gamma rays emitted by radiotracers. Most current nuclear imaging devices integrate PET and SPECT with high-resolution CT. These bimodal systems coregister molecular imaging data with fine structural data obtained by CT, enabling the precise anatomical localization of nuclear imaging signals."[83]

193. "[18F]-fluoro-2-deoxy-D-glucose (18F-FDG), a 18F-labeled glucose analog, is the most widely used PET tracer. It competes with glucose for uptake into metabolically active cells through glucose transporter-1. In the cytoplasm, 18F-FDG is phosphorylated by hexokinase to deoxyglucose-6-phosphate. Radiolabeled deoxyglucose-6-phosphate does not undergo further metabolism and accumulates in cells. Metabolically (specifically, glycolysis) active cells have a higher rate of 18F-FDG uptake and therefore have a higher accumulation of 18F-FDG, which distinguishes them from quiescent normal cells on PET scans."[84]

194. "18F-FDG PET is a sensitive imaging modality for the detection of cellular glucose uptake in rabbit models of lung inflammation and fibrosis as well as in human IPF."[85]

195. "PET scans have shown that lung uptake of 18F-FDG after intravenous injection was increased in microcrystalline silica- or BLM-treated rabbits compared with control rabbits, and the 18F-FDG signals persisted for several weeks in the lung."[86]

196. In 2009, Turkish researchers published a case report of a 21-year-old male smoker

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[83] Zhou Y, et al., "Noninvasive Imaging of Experimental Lung Fibrosis," *Am. J. Respir. Cell Mol. Biol.* 2015; 53(1):8-13.

[84] Zhou Y, et al., "Noninvasive Imaging of Experimental Lung Fibrosis," *Am. J. Respir. Cell Mol. Biol.* 2015; 53(1):8-13.

[85] Zhou Y, et al., "Noninvasive Imaging of Experimental Lung Fibrosis," *Am. J. Respir. Cell Mol. Biol.* 2015; 53(1):8-13, citing Jones HA, et al., "Pulmonary fibrosis correlates with duration of tissue neutrophil activation," *Am. J. Respir. Crit. Care Med.* 1998; 158:620-628; Win T, et al., "18F-Fluorodeoxyglucose positron emission tomography pulmonary imaging in idiopathic pulmonary fibrosis is reproducible: implications for future clinical trials," *Eur. J. Nucl. Med. Mol. Imaging* 2012; 39:521-528.

[86] Zhou Y, et al., "Noninvasive Imaging of Experimental Lung Fibrosis," *Am. J. Respir. Cell Mol. Biol.* 2015; 53(1):8-13, citing Jones HA, et al., "Positron emission tomography in the quantification of cellular and biochemical responses to intrapulmonary particulates," *Toxicol. Appl. Pharmacol.* 2005; 207(Suppl):230-236.

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who developed silicosis after working as a sandblaster at a denim factory for four years. They injected 10 mCi FDG intravenously and did PET scanning from forehead to proximal thigh one hour later. FDG PET showed peripherally diffuse uptake in both lungs, especially in apical and posterior regions, indicating active inflammation in lung regions. The researchers concluded that FDG uptake in inflammatory regions of the lung in silicosis can be used to evaluate the efficacy of future possible treatment modalities and recommended in situ measurement of metabolic activity of the neutrophil with PET to provide an indication of disease activity and to monitor efficacy of directed therapies.[87]

197. FDG PET/CT has been used to differentially diagnose silicosis from other chronic lung diseases and to diagnose silicosis in the presence of lung and other cancers, with confirmation by histopathology.[88]

198. In 2017, Chinese researchers explored the feasibility of dynamic observation and measurement of a living silicosis rat model by using small animal positron emission tomography (PET)-computed tomography (CT). They determined that early inflammation and terminal fibrosis of the living silicosis rat model could be observed effectively by small animal PET-CT, and that this technique could be used as a new approach for dynamic tracing silicosis in rat models.[89]

199. In the last few years Positron Emission Tomography has been used to diagnose workers who developed silicosis as a result of their occupational exposure to artificial stone dust.[90]

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[87] Özkan M, et al., "FDG PET findings in a cause with acute pulmonary silicosis," *Ann. Nucl. Med.* 2009; 23:883-886.

[88] Sasikumar A, et al., "Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in a rare case of carcinoma stomach with concomitant silicosis," *Indian J. Nucl. Med.* 2016; 31:307-308; Yadav M, et al., "Potential Clinical Utility of FDG-PET in Non-malignant Pulmonary Disorders," *Indian J. Chest Dis. Allied Sci.* 2016; 58:165-172; Sen F, et al., "Sarcoid-Like Reaction Mimicking Nodal Spread of Lung Cancer in a Silica-Exposed Patient on Positron Emission Tomography/Computed Tomography," *Respir. Case Rep.* 2018; 7(1): 13-16; Galvis DC et al., [Hypermetabolic lesions with 18F-FDG PET/CT in a case of rectal cancer concomitant with conglomerate silicosis], *Alasbimn J.* 2019; Choi EK, et al, "The clinical value of F-18 FDG PET/ CT in differentiating malignant from benign lesions in pneumoconiosis patients," *Eur. Radiol.* 2020; 30:442-451; Mochizuka Y, et al., "Sarcoid-like Granulomatous Lung Disease with Subacute Progression in Silicosis," *Intern. Med.* 2022; 61:395-400.

[89] Huang M, et al., "Observation and measurement of silicosis animal model by PET-CT," *China Occup. Med.* 2017; 44(3):245-252.

[90] del Castillo-Otero D, et al., "Positron emission tomography in artificial stone silicosis," *J. Lung, Pulmonary Respir. Res.* 2024; 11(2):37-39 [4 cases of artificial stone silicosis]; León-Jiménez A, et al., "Complicated silicosis due to engineered stone: High metabolic activity in positron emission tomography and systemic inflammation years after exposure cessation," *Research Square* 2025 [preprint in advance of publication].

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4. Magnetic Resonance Imaging

200. Magnetic resonance imaging is a form of medical imaging that measures the response of the atomic nuclei of body tissues to high-frequency radio waves when placed in a strong magnetic field, and produces images of the internal organs. "The development of magnetic resonance imaging (MRI) for use in medical investigation has provided a huge forward leap in the field of diagnosis, particularly with avoidance of exposure to potentially dangerous ionizing radiation. With decreasing costs and better availability, the use of MRI is becoming ... pervasive throughout clinical practice."[91]

201. The primary benefits of Magnetic Resonance Imaging in silicosis are the detection of Progressive Massive Fibrosis (PMF)[92] and distinguishing between PMF and lung cancer.[93]

202. Magnetic resonance imaging may also be useful in monitoring the initiation and progression of silicosis and in obtaining needle aspirate and tissue biopsies of silicosis patients.[94]

203. "DWI [Diffusion-weighted magnetic resonance imaging] is a reproducible technique and has demonstrated high accuracy for differentiating between malignant and benign states in thoracic lymph nodes."[95] DWI therefore provides clinical utility in distinguishing lymph node silicosis (lymph node inflammation caused by inhalation of silica) from cancer of the lymph nodes.

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[91] Grover VPB, et al., "Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians," *J. Clin. Exp. Hepatol.* 2015; 5:246-255.

[92] Matsumoto S, et al., "MRI signal characteristics of progressive massive fibrosis in silicosis," *Clin. Radiology* 1998; 53(7):510-514.

[93] Chong S, et al., "Pneumoconiosis: Comparison of Imaging and Pathologic Findings," *Radiographics* 2006; 26:59-77; Jun JS, et al., "Complications of pneumoconiosis: Radiologic overview," *Eur. J. Radiology.* 2013; 82: 1819-1830; Zhang L, et al., "Diagnostic and clinical application value of magnetic resonance imaging (MRI) for progressive massive fibrosis of coal worker pneumoconiosis: Case reports," *Medicine* 2017; 96:20; Du P, et al., "Added Value of Thoracic Magnetic Resonance Imaging in the Differential Diagnosis Between Peripheral Lung Cancer and Progressive Massive Fibrosis of Coal Silicosis," *J. Med. Imaging Health Informatics* 2020; 10(4):974-977; Guneyli S, et al., "Spin-echo and diffusion-weighted MRI in differentiation between progressive massive fibrosis and lung cancer," *Diagn. Interv. Radiol.* 2021; 27:469-475. Deivasigamani M, et al., "Silicosis presenting as progressive massive fibrosis: A case series," *J. Assoc. Chest Physicians* 2024; 12:124-127.

[94] Hammond E, et al., "Computed Tomography and Magnetic Resonance Imaging for Longitudinal Characterization of Lung Structure Changes in a Yucatan Miniature Pig Silicosis Model," *Toxicol. Pathology* 2016; 44(3):373-381.

[95] Santos FS, et al., "Diffusion-weighted magnetic resonance imaging for differentiating between benign and malignant thoracic lymph nodes: a meta-analysis," *Radiol. Bras.* 2021; 54(4):225-231.

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5. Computer-Aided Diagnosis (CAD)

204. Computer-aided diagnosis (CAD) including Artificial Intelligence (AI) and especially deep learning (DL) is increasingly being utilized to screen industrial workers for silicosis.

205. In 2022, a team of international researchers published a systematic review of studies that assessed computer-aided diagnosis of coal workers' pneumoconiosis in chest X-rays using machine learning. They categorized and summarized the feature extraction and detection approaches of computer-based analysis in coal workers' pneumoconiosis using chest X-ray radiographs. They systematically reviewed 11 databases that focused on science, engineering, medicine, health, and clinical studies. They identified and compared 40 articles from the previous 5 decades, covering 3 main categories of computer-based coal workers' pneumoconiosis detection: classical handcrafted features-based image analysis, traditional machine learning, and deep learning-based methods.[96]

206. In 2022, South African researchers sought to determine whether CAD systems developed to date primarily for Tuberculosis (TB) were able to identify TB (without distinction between prior and active disease) and silicosis (or "other abnormality") among former South African Gold miners. A total of 501 chest X-rays (CXRs) from a screening program were submitted to two commercial CAD systems for detection of "any abnormality," TB (any) and silicosis. The outcomes were tested against the readings of occupational medicine specialists with experience in reading miners' CXRs. Accuracy of CAD against the readers was calculated as the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Sensitivity and specificity were derived using a threshold requiring at least 90% sensitivity. One system was able to detect silicosis and/or TB with high AUCs (>0.85) against both readers, with specificity > 70% in most of the comparisons. The investigators concluded that CAD systems have the potential to come close to expert readers in the identification of TB and silicosis among former gold miners.[97]

207. In 2022, Chinese researchers published a study seeking to develop a successful deep

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[96] Devnath L, et al., "Computer-Aided Diagnosis of Coal Workers' Pneumoconiosis in Chest X-ray Radiographs Using Machine Learning: A Systematic Literature Review," *Int. J. Environ. Res. Pub. Health* 2022; 19:6439.

[97] Ehrlich R, et al., "Accuracy of Computer-Aided Detection of Occupational Lung Disease: Silicosis and Pulmonary Tuberculosis in Ex-Miners from the South African Gold Mines," *Int. J. Environ. Res. Pub. Health* 2022; 19:12402.

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learning model with data augmentation technique to discover the clinical uniqueness of chest X-ray imaging features of coal workers' pneumoconiosis (CWP). They enrolled 149 CWP patients and 68 dust-exposed workers for a prospective cohort study between August and December 2021 at First Hospital of Shanxi Medical University. A total of 217 chest X-ray images were collected obtaining reliable diagnostic results through the radiologists' team, and confirming clinical imaging features. They segmented regions of interest with diagnosis reports, classifying them in three categories. To identify clinical features, they developed a deep learning model (ShuffleNet V2-ECA Net) with data augmentation through performance of different deep learning models by assessing Receiver Operation Characteristics (ROC) curve, area under the curve (AUC), accuracy (ACC), and Loss curves. The ShuffleNet V2-ECA was the optimal model with an average AUC of 0.98 and all classifications of clinical imaging features having an AUC above 0.95. The deep learning model of ShuffleNet V2 and ECA-Net were successfully constructed using data augmentation, achieving accuracy of 98%.[98]

208. In 2023, researchers from India generated 9 deep learning models to predict silicosis using computed tomography images from case reports. A total of 1320 images of healthy-normal lung and 129 images of silicosis were collected. The model generated with Visual Geometry Group (VGG) network produced 99.4% accuracy in detecting silicosis.[99]

209. In 2024, Chinese researchers evaluated models of Multi-scale Lesion Perception Attention Networks (MLANet) screening and staging pneumoconiosis using digital radiographic images. A series of indicators including area under the receiver operating characteristic curve, accuracy, recall, precision, and F1 score were used to comprehensively evaluate the performance of the model. The results showed that the MLANet model can effectively improve the consistency and efficiency of pneumoconiosis diagnosis. The accuracy of the MLANet model for pneumoconiosis diagnosis on the internal test set, external validation set, and prospective test set reached 97.87%, 98.03%, and 95.40%, respectively, which was close to the level of qualified radiologists. The model effectively screened stage I pneumoconiosis with an accuracy of 97.16%, a recall of 98.25, a

[98] Dong H, et al., "Use data augmentation for a deep learning classification model with chest X-ray clinical imaging featuring coal workers' pneumoconiosis," *BMC Pulmonary Med.* 2022; 22:271.

[99] Shivaanivarsha N, et al., "Identification of Silicosis using Deep Learning Model on Computed Tomography Images," 2023 IEEE 3rd Mysore Sub Section International Conference Abstract.

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precision of 93.42%, and an F1 score of 95.59%. The built model performed better than the other four classification models. The investigators concluded that the model could be applied in clinical work to realize the automated diagnosis of pneumoconiosis using digital chest radiographs.[100]

210. In 2024, Chinese researchers assessed three models (Resnet50, Resnet101, and DenseNet) for pneumoconiosis classification based on 1250 chest X-ray images. Three experienced, highly qualified physicians read the collected digital radiography images and classified them from category 0 to category III in a double-blinded manner. The results of the 3 physicians in agreement were considered the relative gold standards. Three models were used to train and test these images and their performance was evaluated using multi-class classification metrics. Kappa values and accuracy were used to evaluate the consistency and reliability of the optimal model with clinical typing. The results showed that ResNet101 was the optimal model among the 3 convolutional neural networks. The AUC of ResNet101 was 1.0, 0.9, 0.89, and 0.94 for detecting pneumoconiosis categories 0, I, II, and III, respectively. The micro-average and macro-average mean AUC values were 0.93 and 0.94, respectively. The accuracy and Kappa values of ResNet101 were 0.72 and 0.7111 for quadruple classification and 0.98 and 0.955 for dichotomous classification, respectively, compared with the relative standard classification of the clinic. The researchers concluded that their study developed a deep learning based model for screening and staging of pneumoconiosis using chest radiographs and that the ResNet101 model performed relatively better in classifying pneumoconiosis than radiologists. The dichotomous classification displayed outstanding performance, indicating the feasibility of deep learning techniques in pneumoconiosis screening.[101]

211. In 2025, Chilean researchers developed and evaluated "eTóraxLaboral," an intelligent platform for detecting signs of pneumoconiosis in chest radiographs and assessed its predictive capacity. A retrospective analysis of 2300 randomly selected chest radiographs was performed. Sensitivity, specificity, false positive/negative rates, predictive values, likelihood ratios, efficiency,

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[100] Wang Y, et al., "Deep Learning Models of Multi-Scale Lesion Perception Attention Networks for Diagnosis and Staging of Pneumoconiosis: A Comparative Study with Radiologists," *J. Imaging Informatics Med.* 2024; 37:3025-3033.

[101] Zhang Y, et al., "Potential of digital chest radiography-based deep learning in screening and diagnosing pneumoconiosis: An observational study," *Medicine* 2024; 103:25(e38478).

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error rate, and area under the receiver operating characteristic curve (AUC) were evaluated. A Fagan nomogram and ROC curve analysis were included. "eTóraxLaboral" demonstrated high sensitivity to signs of pneumoconiosis (LR+ 23, LR- 0.2). A slight tendency toward a higher number of false positives was observed, possibly due to the superposition of anatomical elements and increased lung markings. False negatives were less common, often misinterpreting pneumoconiotic opacities as consolidation-type findings. The researchers concluded that "eTóraxLaboral" facilitates early pneumoconiosis detection, providing crucial diagnostic support for healthcare workers.[102]

212. In 2025, Chinese researchers published results of a case-control study in which they screened biomarkers for the diagnosis of silicosis using LASSO regression, SVM and RF. A sample of 612 subjects (half cases and half controls) were randomly divided into training and test groups in a 2:1 ratio. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to construct a multiple biomarker-based model for the diagnosis of silicosis, which was applied to both the training and the testing data sets. The training cohort revealed significant differences in multiple hematologic parameters between silicosis patients and healthy individuals. Based on machine learning, 8 silicosis biomarkers were screened and identified from routine blood cell, biochemical and coagulation parameters. D-dimer (DD), Albumin/Globulin (A/G), lactate dehydrogenase (LDH) and white blood cells (WBC) were selected for constructing a logistic regression model for silicosis diagnostics. The model had a satisfactory performance in the training cohort with an area under the ROC curve (AUC) of 0.982, diagnostic sensitivity of 95.4%, and specificity of 92.2%. The model had a prediction accuracy of 0.936 with an AUC of 0.979 in the independent test cohort. Diagnostic accuracies of the logistic model in silicosis stages 1, 2, and 3 were 88.0, 95.4, and 94.3% with an AUC of 0.968, 0.983, and 0.990 for silicosis, respectively. The researchers concluded their model based on DD, A/G, LDH and WBC could be used to screen workers for silicosis because it is cheap, sensitive, specific, and offers a potential strategy for large-scale screening of silicosis.[103]

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[102] Ruiz ER, et al., "Clinical Validation of an AI System for Pneumoconiosis Detection Using Chest X-rays," *J. Occup. Environ. Med.* 2025; 67(4):e250-e256.

[103] Sun G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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B. Functional Testing

213. Functional testing is a complementary means of detecting interstitial lung disease, including silicosis. There are two basic types of functional testing: pulmonary function testing and cardiopulmonary exercise testing.

1. Pulmonary Function Testing

214. Pulmonary function testing (PFT) refers to a group of non-invasive tests that assess how well the lungs are working, including measurements of lung volume, airflow, and gas exchange capacity. These tests, such as spirometry and diffusing capacity for carbon monoxide (DLCO), are essential tools in the early detection of respiratory impairment. For workers exposed to respirable crystalline silica, particularly in the engineered stone industry, regular PFTs can help identify early signs of lung damage before symptoms appear or radiographic abnormalities develop.[104]

215. In Australia, it is recommended that workers in high-risk industries such as engineered stone fabrication undergo baseline pulmonary function tests (PFTs) at the start of employment, followed by annual testing to monitor for any decline in lung function over time. This approach is more rigorous than current U.S. OSHA requirements, which do not mandate routine pulmonary function surveillance for silica-exposed workers. The increased frequency of testing in Australia reflects the recognized rapid progression of silicosis in engineered stone workers and the need for more intensive monitoring. Both Safe Work Australia and the [Australian] National Dust Disease Taskforce emphasize that repeated PFTs allow for the identification of meaningful changes by establishing trends and distinguishing true physiological decline from normal variability. When significant changes are detected or clinical concerns arise, more frequent testing and referral to a respiratory specialist are warranted. As with imaging surveillance, this proactive approach to lung function monitoring is a critical strategy for early detection, prevention of disease progression, and

[104] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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protection of workers' respiratory health in this high-risk population.[105]

216. Pulmonary function testing in engineered stone workers can reveal a variety of abnormalities, with restrictive patterns being the most frequently observed. However, many individuals with CT evidence of silicosis may still have normal pulmonary function tests, particularly at the time of diagnosis. In an Italian case series, only 33% of workers with CT-confirmed silicosis had abnormal spirometry, whereas 50% had a reduced diffusing capacity for carbon monoxide (DLCO), highlighting the greater sensitivity of diffusion measurements. Similarly, in an Australian study, more than half of the individuals with progressive massive fibrosis showed normal spirometry results. These findings underscore the limited sensitivity of spirometry alone for early disease detection. Including DLCO in routine testing provides a more comprehensive assessment and improves the likelihood of detecting physiologic impairment. While pulmonary function testing is less sensitive than chest CT for diagnosing silicosis, it remains an important tool for monitoring disease progression and assessing functional disability—particularly when full testing, including DLCO, is performed.[106]

217. The Silicosis Center of Excellence of the University of California at San Francisco, recommends full pulmonary function testing which includes spirometry, lung volumes, diffusion capacity, and 6-minute walk test to be completed annually.[107]

2. Cardiopulmonary Exercise Testing (CPET)

218. Cardiopulmonary Exercise Testing (CPET) offers a valuable diagnostic advantage in dust-exposed workers by assessing the combined performance of the respiratory, cardiovascular, and muscular systems during exertion. Unlike resting spirometry or DLCO alone, CPET can detect

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[105] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[106] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[107] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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ventilatory inefficiency and reduced aerobic capacity even in individuals who appear normal at rest. For instance, in coal miners with small airway dysfunction, CPET revealed that at modest exercise workloads they used a significantly higher fraction of their maximal voluntary ventilation, had elevated ventilatory equivalents (VE/VO2 and VE/VCO2), and exhibited a 27% lower peak oxygen consumption—despite normal resting spirometry and DLCO.[108]

219. Similarly, in a cohort of former U.S. coal miners, resting DLCO strongly predicted abnormalities in CPET gas exchange measures such as elevated A-a gradient and reduced VO2 max, while FEV1 was less predictive. These studies highlight CPET's ability to unmask early functional limitation, even when resting pulmonary tests and imaging are relatively preserved. Incorporating CPET into surveillance of silica-exposed workers – such as those in engineered stone fabrication – can provide critical insights into subclinical impairment, guide targeted evaluations, and enhance early detection of disease progression and disability risk. Cardiopulmonary exercise testing (CPET) has been used to evaluate veterans exposed to burn pit smoke, providing a detailed assessment of exercise intolerance and revealing abnormalities in gas exchange, ventilatory efficiency, and cardiovascular response that may not be apparent on resting pulmonary function tests.[109]

220. Cardiopulmonary exercise testing is currently being used as part of expansive clinical protocols in the diagnosis of early lung disease in exposed workers, including the Department of Labor's Black Lung Program and the Veterans' Administration's Post-Deployment Cardiopulmonary Evaluation Network.[110]

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[108] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[109] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

[110] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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C. Tissue-Invasive Techniques

221. Tissue-invasive techniques have been used to obtain samples for pathological analysis. The surgical techniques to obtain tissue samples include the following:

1. Surgical Lung Biopsy (SLB);
2. Video-Assisted Thoracoscopic Surgery (VATS);
3. Transbronchial Lung Biopsy (TBLB);
4. Percutaneous Lung Biopsy (PCLB);
5. Ultrasound-guided Percutaneous Lung Biopsy (UPLB);
6. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TNA);
7. Transbronchial Cryobiopsy (TBCB);
8. Endobronchial Ultrasound-guided Transbronchial Mediastinal Cryobiopsy (EBUS-TMC);

222. The following analytical techniques are used to make diagnoses of silicosis from tissue samples obtained by surgical means:

9. Energy-Dispersive X-Ray Analysis (EDX);
10. Scanning Electron Microscopy (SEM);
11. Scanning Electron Microscopy (SEM) with Energy-Dispersive X-ray Spectroscopy (SEM-EDS);
12. Computer-Controlled Scanning Electron Microscopy with Energy-Dispersive X-ray Analysis (CC-SEM-EDX);
13. Field Emission Scanning Electron Microscopy (FE-SEM) and Energy Dispersive X-ray Spectroscopy (EDS)

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1. Surgical Lung Biopsy (SLB)

223. "Historically, surgical lung biopsy has been the gold standard for the diagnosis of ILD."[111] "The current recommendation by the American Thoracic Society/European Respiratory Society is for surgical lung biopsy in patients who are at acceptable risk to tolerate the procedure."[112]

224. "When diagnostic uncertainty persists, surgical lung biopsy may be required to confirm the diagnosis given the potential preventative, therapeutic, prognostic and legal implications of a diagnosis of occupational ILD. In such cases, a thorough review of the lung specimen by an expert pathologist looking for clues to exposures — of which the patient may not be aware, or may have forgotten, given the long latency of some exposure-related disease — by light microscopy, polarized light microscopy or [electron microscopy], as appropriate, is of outmost importance."[113]

225. In a study of surgical lung biopsies performed for interstitial lung disease from 2000 to 2011 in the United States, two-thirds of which were performed electively. In-hospital mortality was 1.7% for elective procedures but significantly higher for nonelective procedures (16.0%). The authors of the study recommended that identified risk factors for death should be taken into account when counseling patients on whether to pursue a histologic diagnosis for interstitial lung disease.[114]

226. "Lung biopsy should be avoided unless absolutely necessary . . . because surgical manipulation associates with unfavorable repercussions. However, lung biopsy is the only way to arrive at an accurate diagnosis when there is no occupational exposure history, disagreement between CXR [chest x-ray] and HRCT [high resolution computed tomography] imaging results, and atypical presentations cause physicians to consider other differential diagnoses."[115]

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[111] Kayatta MO, et al., "Surgical Biopsy of Suspected Interstitial Lung Disease Is Superior to Radiographic Diagnosis," *Ann. Thorac. Surg.* 20103; 96:399-402.

[112] *Id.,* citing King TE Jr, et al., American Thoracic Society/European Respiratory Society, "Idiopathic pulmonary fibrosis: Diagnosis and treatment," *Am. J. Respir. Crit. Care Med.* 2000; 161:646-664.

[113] Spagnolo P, et al., "Occupational interstitial lung diseases," *J. Intern. Med.* 2023; 294:798-815.

[114] Hutchinson JP, et al., "In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States: 2000 to 2011,"*Am J. Respir. Crit. Care Med.* 2016; 193(10):1161-1167.

[115] Li T, et al., "Early Identification, Accurate Diagnosis, and Treatment of Silicosis," *Canadian Respir. J.* 2022; 3769134.

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2. Video-Assisted Thoracoscopic Surgery (VATS)

227. "Presently, many surgical lung biopsies are performed by video-assisted thoracoscopic surgery (VATS). This approach is beneficial to patients by reducing length of stay in comparison with the traditional approach of open lung biopsy through a minithoracotomy."[116]

228. In a study of 194 patients undergoing video-assisted thorascopic lung biopsy for suspicion of interstitial lung disease from January 2003 to February 2012 at Emory University, a specific diagnosis was made after surgical biopsy in 88% of cases. Overall mortality of surgical biopsy was 6.7% (13/194). Major risk factors for death were preoperative supplemental oxygen, ventilator dependence, and age ($p < 0.0001$, $p < 0.0001$, and $p = 0.03$, respectively). Among patients with ventilator dependence preoperatively, the mortality rate was 100% versus 4.8% in patients not ventilator dependent. All biopsy specimens were concordant 91% of the time, and the first two biopsy specimens were concordant 96% of the time. The investigators concluded that surgical biopsy should remain the gold standard for diagnosis of interstitial lung disease.[117]

229. In a study of 66 patients with suspected interstitial lung disease who underwent VATS lung biopsies, a definite diagnosis was made in 74.2% of cases. A change in treatment was initiated in 47.2% of patients. A positive response to treatment was experienced in 58% of patients whom underwent a change in treatment. The investigators concluded that the study highlighted the effectiveness of performing VATS lung biopsies in patients with suspected interstitial lung disease inasmuch as the procedure led to a change in treatment of almost half of all patients. The investigators further concluded that VATS has been shown to be a relatively safe procedure and thus, should be performed in all patients with suspected interlung disease, indeterminate in type from prior CT imaging.[118]

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[116] Kayatta MO, et al., "Surgical Biopsy of Suspected Interstitial Lung Disease Is Superior to Radiographic Diagnosis," *Ann. Thorac. Surg.* 20103; 96:399-402.

[117] Kayatta MO, et al., "Surgical Biopsy of Suspected Interstitial Lung Disease Is Superior to Radiographic Diagnosis," *Ann. Thorac. Surg.* 20103; 96:399-402.

[118] Morris D, et al., "The efficacy of video-assisted thoracoscopic surgery lung biopsies in patients with interstitial lung disease: a retrospective study of 66 patients," *J. Cardiothoracic Surgery* 2014; 9:45.

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3. Transbronchial Lung Biopsy (TBLB)

230. "Although open lung biopsy is still the gold standard, transbronchial lung biopsy (TBB) through a flexible fibreoptic bronchoscope, has become widely used, as a less invasive procedure."[119]

231. "The flexible fiberoptic bronchoscope was initially conceived to visualize and obtain samples from the proximal airways; however, its reach has since been extended by the development of modern tools for navigation (e.g., electromagnetic navigation) and real-time visualization of the target lesion (e.g., radial endobronchial ultrasound imaging and digital tomosynthesis).[120]

232. In 2015, Chinese researchers evaluated the role of transbronchial lung biopsy (TBLB) pathology in the diagnosis of pneumoconiosis. A total of 418 patients exposed to dusts were examined with TBLB. The chest radiographs of all subjects showed pneumoconiosis-like opacities. Because the dust property or accumulated doses did not match with abnormality on chest radiographs or there were no series of chest radiographs, TBLB was required for diagnosis. Dust deposition, fibrosis and birefringent particles were found in TBLB pathological examinations. Among 379 subjects, 376 cases (99.2%) showed interstitial lung fibrosis, 228 cases (60.2%) showed dust deposition, 111 cases (29.3%) expressed the birefringent particles by polarized light microscopy. Birefringent particles positive rate was 37.8% (62/164) in 164 patients exposed to either silica or potter dusts or cement dusts or coal-silica dusts or foundry dusts – much higher than that (22.7%, 49/215) in patients exposed to other dusts (welding fume or asbestos or aluminum dusts) ($P < 0.05$). The rate of lung fibrosis in pneumoconiosis cases was significantly higher than that in non-pneumoconiosis cases ($P < 0.05$). The researchers concluded that TBLB can provide evidence of exposure to dusts and pathological changes that may be useful to the pneumoconiosis diagnosis.[121]

233. Transbronchial lung biopsy remains a useful, minimally invasive technique to obtain lung tissue samples that are adequate for diagnosing a substantial percentage of silicosis cases.

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[119] Descombes E, et al., "Transbronchial lung biopsy: an analysis of 530 cases with reference to the number of samples," *Monaldi Arch. Chest Dis.* 1997; 52(4):324-329.

[120] Gould MK, "Biopsy of Peripheral Lung Nodules – Inside Out or Outside In?" *New Engl J. Med.* 2025; 392(21):2162-2163, citing Panchabhai TS, et al., "Historical perspectives of bronchoscopy: connecting the dots," *Ann. Am. Thorac. Soc.* 2015; 12:632-641..

[121] Shi J, et al., [Application of transbronchial lung biopsy in pneumoconiosis diagnosis], *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2012; 30(4):261-264 [in Chinese with English abstract]

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4. Percutaneous Core Lung Biopsy (PCLB)

234. Percutaneous core biopsy of the lung "involves insertion of a hollow large bore needle, with a specially adapted cutting mechanism, into an organ to extract a piece of tissue for histologic evaluation."[122]

235. "While technically demanding, extensive experience documents PCBL as a safe and accurate procedure with limited morbidity and rare mortality."[123]

236. In 2012, Chinese researchers evaluated four cases of suspected silicosis by examining lung tissues obtained by percutaneous lung biopsy, to confirm the presence of pathogenic dust and corresponding characteristic changes in lung tissues or to obtain pathological evidence of other pulmonary diseases such as tuberculosis and lung cancer. Two of the four cases were diagnosed with silicosis, but the other two cases were diagnosed with hard metal lung disease and tuberculosis. The investigators concluded that obtaining pathological specimens through CT-guided percutaneous lung biopsy enabled diagnoses of all four patients, only two of whom actually had silicosis.[124]

237. In 2019, the same research group published a study of 63 patients with pneumoconiosis who underwent CT guided percutaneous lung biopsy, to investigate the safety and influencing factors of the procedure. 29 cases (46.03%) had complications, including 20 cases of pneumothorax (35.75%), 12 cases of bleeding (19.05%), and 3 cases of liquid pneumothorax (4.76%). The investigators concluded the main complications of the procedure are pneumothorax and bleeding.[125]

238. Although percutaneous lung biopsy will not enable diagnosis of all cases of silicosis, it can diagnose most cases of silicosis and distinguish them from other interstitial lung diseases.

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[122] McSweeney SE, et al., "Evaluation of the Efficacy and Safety of Percutaneous Biopsy of Lung," *Open Respir. Med. J.* 2012; 6:82-88.

[123] McSweeney SE, et al., "Evaluation of the Efficacy and Safety of Percutaneous Biopsy of Lung," *Open Respir. Med. J.* 2012; 6:82-88, citing Richardson CM et al., "Percutaneous lung biopsies: a survey of UK practice based on 5444 biopsies," *Br. J. Radiol.* 2002; 75:731-735.

[124] Dai WR, et al., "Application of percutaneous lung biopsy to diagnosis and differential diagnosis of pneumoconiosis: four case reports," *J. Environ. Occup. Med.* 2019; 36(3):282-286.

[125] Dai WR, et al. [Complications and influencing factors of pneumoconiosis patients undergoing CT guided percutaneous lung biopsy]; *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2019; 37(1):56-60.

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5. Ultrasound-guided Percutaneous Lung Biopsy (UPLB)

239. In 2018, Chinese researchers published a retrospective study evaluating the diagnostic accuracy and the factors influencing the diagnostic accuracy of 648 procedures of ultrasound-guided percutaneous needle biopsy (PNB) for peripheral pulmonary lesions (PPLs). They reviewed the histopathology results, clinical records and procedure reports of the 648 biopsies and final diagnoses of 637 PPLs to determine the diagnostic accuracy of ultrasound-guided PNB. Factors that influenced the diagnostic accuracy were assessed by analysis of the biopsy procedures, which were classified as diagnostic cases (true-positive and true-negative) and non-diagnostic cases (false-positive, false-negative and indeterminate). Statistical analyses of factors relating to patient demographic characteristics, lesion characteristics and biopsy details were performed to determine possible effects on diagnostic accuracy. Biopsies were successfully performed in all cases and 11 patients underwent second biopsies for the same lesions. Among the 637 PPLs, there were 326 (51.2%) malignant lesions, 272 (42.7%) benign lesions and 39 (6.1%) indeterminate lesions. Of the 272 benign lesions, 114 (41.9%) were found to be tuberculous. The overall diagnostic accuracy was 81.8%, and the rates of hemoptysis, symptomatic pneumothorax and chest-tube insertion were 8.0%, 1.7% and 0.9%, respectively. For lesions that measured ≤20 mm, 21–49 mm and ≥50 mm, the diagnostic accuracy was 72.0%, 86.8% and 79.7%, while sensitivity and specificity were 54.3%–79.2%, 88.3%–90.7% and 79.4%–89.5% and 77.3%–100%, 96.8%–100% and 58.6%–100%, respectively. Diagnostic accuracy was significantly affected by lesion size when lesion size was measured by ultrasound (p= 0.006) and computed tomography (CT) (p = 0.001). In the 3 lesion groups of ≤20 mm, 21–49 mm or ≥50 mm, diagnostic accuracy among each group was significantly different (p<0.001). When lesion size was measured by ultrasound (p<0.001) and CT (p<0.001) and the 3 groups were analyzed (p<0.001), there was a statistically significant relationship between lesion size and presence of necrosis. The rates of the presence of necrosis in lesions that measured ≤20 mm, 21–49 mm and ≥50 mm were 3.9%, 11.7% and 28.8%, respectively. The researchers concluded that ultrasound-guided PNB is an effective and safe diagnostic method for peripheral pulmonary lesions.[126]

[126] Guo Y-Q et al., "Ultrasound-Guided Percutaneous Needle Biopsy for Peripheral Pulmonary Lesions: Diagnostic Accuracy and Influencing Factors," *Ultrasound Med. Biol.* 2018; 44(5):1003-1011.

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240. In 2018, American researchers published a study in which they compared the efficacy and safety of biopsy guided by ultrasound (US) with biopsy guided by computed tomography for lung lesions with pleural contact. Among 1269 image-guided thoracic biopsies obtained at their institution between 2004 and 2016, 150 were US-guided for lung lesions with pleural contact. Of those, 94 were performed using US only; 56 had initial CT localization. A comparison cohort of 100 consecutive CT-guided biopsies for lung lesions with pleural contact was identified. Biopsy type, number of passes, sample adequacy, final pathologic results, complications, procedural time, lesion diameter, and pleural contact were recorded. US-guided biopsy was associated with fewer complications (7%) than CT-guided procedures (24%; $p < 0.001$). Mean procedure times (± SD) were shorter with US only (31 ± 16 min) than with CT only (45 ± 26 min; $p < 0.001$) or US with CT localization (45 ± 18 min; $p < 0.001$). Procedural times were longer for patients with small lesions and those with lesser pleural contact. Sample adequacy was best when core biopsy was performed with US and CT. Fewer passes were performed with US guidance than with CT guidance (mean, 3.1 ± 1.8 vs 4.4 ± 1.9, respectively, $p < 0.001$), with a trend toward improved pathologic adequacy (98% vs 93%, respectively, $p = 0.122$). Subgroup analysis showed fewer complications for lesions 31–50 mm ($p = 0.029$), improved sample adequacy for lesions 10–30 mm ($p = 0.0032$), and shorter procedural times for lesions 10–30 mm ($p = 0.0001$) with US than with CT. The investigators concluded that US guidance should be considered for biopsy of peripheral lung and pleural lesions larger than 10 mm, because it is safer, faster, and possibly more accurate than CT guidance.[127]

241. In 2019, Japanese researchers published a similar study, finding that the diagnostic rate for lesion size >40 mm was significantly higher in the US-guided group than the CT-guided group (P=0.009). They concluded that US-guided percutaneous needle biopsy for thoracic lesions adjacent to the chest wall is a feasible technique compared with CT-guided biopsy because of its higher diagnostic rate with longer lesion-pleura contact arc length and reduced complications.[128]

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[127] Lee MH, et al., "Ultrasound Guidance Versus CT Guidance for Peripheral Lung Biopsy: Performance According to Lesion Size and Pleural Contact," *Amer. J. Roentgenology* 2018; W110-W117.

[128] Yamamoto N, et al., "Efficacy and safety of ultrasound (US) guided percutaneous needle biopsy for peripheral lung or pleural lesion: comparison with computed tomography (CT guided needle biopsy," *J. Thorac. Dis.* 2019; 11(3):936-943.

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242. In 2018, Chinese investigators published an experimental study in which they sought to determine the clinical application value of percutaneous lung biopsy guided by ultrasound in the diagnosis of peripheral lung lesions of silicosis. Silicosis was induced in rabbits by the intratracheal administration of silica. Imaging changes were observed in 36 rabbits 60 days after intratracheal instillation of silica. To contrast with CT results, percutaneous lung biopsy of peripheral lesions was guided by ultrasound. The success rate of sufficient material, the diagnostic rate between biopsy and pathology, and the incidence of complications were calculated. Biopsy with sufficient material, biopsy findings coinciding with pathological results and no complications were defined as successful procedure. Each rabbit was intravenously administrated by 10 000 U of heparin for anticoagulation and sacrificed by fast injection of 10% KCl through jugular vein catheterization. Specimens from lung tissue were collected and stained with hematoxylin-eosin. Pathological changes of lung tissue were observed through an optical microscope. Of 36 silicosis rabbits, peripheral lung lesions of silicosis were observed in 30 rabbits. Biopsy procedures were performed with ultrasound guidance in 30 rabbits. The total success rate of biopsy was 70% (21/30). The success rate of sufficient material was 93% (28/30), the diagnostic rate between biopsy and pathology was 86% (24/28), and the incidence of complications was 10% (3/30) respectively. Compared with failure group, peripheral lesions in the successful biopsy group were larger, closer to the chest wall, and lower respiratory rate, the difference being statistically significant ($P<0.05$). There was no significant difference in weight, heart rate, temperature and stages of silicosis ($P>0.05$). The pathological results showed typical silicosis nodules. Silica-exposed rabbits also showed signs of vascular remodeling with pulmonary artery muscularization, vascular occlusion, and medial thickening. The investigators concluded that Ultrasound-guided percutaneous lung biopsy is an effective and safe technique in peripheral lung lesions of silicosis, and that it can serve as an important technical means to monitor the evolution of silicosis lesions and provide reference for the diagnosis of silicosis.[129]

243. Based on these studies, ultrasound-guided percutaneous lung biopsy is effective in obtaining lung tissue for pathological analysis and has utility as a less invasive technique than open lung biopsy and CT-guided percutaneous biopsy in diagnosing silicosis in silica-exposed workers.

[129] Zeng D, et al., "The clinical application value of ultrasound-guided percutaneous lung biopsy in the diagnosis of peripheral lung lesions of silicosis," *Chinese J. Ultrasonography* 2018; 12:524-528.

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6. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

244. "Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has emerged as a minimally invasive technique for evaluating the mediastinum and staging patients with lung cancer. In the hands of an experienced operator, the procedure is safe and provides excellent sensitivity, specificity, and predictive diagnostic values. In conjunction with endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), a nearly complete mediastinal evaluation can be performed in a minimally invasive fashion. This strategy results in improved lymph node staging, markedly reduced need for mediastinoscopy, and fewer futile thoracotomies compared with a traditional surgical staging procedure. The procedure is cost effective and provides excellent cytologic specimens that have proven well suited for ancillary testing, such as immunohistochemistry and tumor genotyping. EBUS-TBNA, initially used as a tool to sample the lymph nodes adjacent to the airway walls, has now become instrumental in sampling lesions in the mediastinum, hilum, and lung parenchyma, where previously more than one procedure would have been necessary."[130]

245. In 2013, researchers from Hong Kong described a case of chronic silicotuberculosis presenting with antituberculous therapy treatment failure despite microbiological confirmation. The diagnosis was made with EBUS-TBNA because radiologic features were inconclusive of silicosis.[131]

246. In 2018, Israeli researchers published a study of 28 patients with suspected silicosis referred for outpatient evaluation in three large tertiary hospitals. Patients with mediastinal lymphadenopathy underwent EBUS-TBNA, while others underwent transbronchial biopsy (TBB) and/or video-assisted thoracoscopic surgery. Eleven patients with mediastinal lymphadenopathy (39%) were evaluated using EBUS-TBNA. The diagnosis was accurate in all cases, demonstrating silica particles under polarized light, with no complications. The study demonstrated specificity of 100% and sensitivity of 88% for EBUS-TBNA in diagnosing silicosis in patients with consistent exposure histories. The investigators concluded that EBUS-TBNA is a useful and sufficient tool to

[130] VanderLaan PA, et al., "Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA): An Overview and Update for the Cytopathologist," *Cancer CytoPathol.* 2014; 122(8):561-576.

[131] Tung AH, et al., "Diagnosis of silicotuberculosis by Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA)," *Respirology* 2013; 18(2):383-384.

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diagnose silicosis in patients with mediastinal lymphadenopathy with compatible exposure history.[132]

247. In 2020, Thai researchers reported three cases of patients with silicosis who presented with abnormal chest radiography with mediastinal adenopathy without circumference calcification or eggshell calcification. Some also had no lung parenchymal lesion on computed tomography of the thorax. EBUS revealed mediastinal lymph nodes of various sizes in each patient. EBUS-TBNA was performed and mediastinal lymph node tissue was obtained for pathology and cytology. Pathology revealed fibrotic stroma with anthracotic pigment and silica particles. The researchers concluded EBUS-TBNA is useful for confirming the diagnosis of silicosis in an early stage of the disease.[133]

248. In 2025, American researchers published a retrospective study of patients with occupational silica exposure who underwent EBUS-TBNA to evaluate mediastinal and/or hilar lymphadenopathy (MHL) on computed tomography. Cytology specimens were re-examined by an independent pathologist under polarized microscopy. Eighty-four patients (mostly coal miners) with silica exposure underwent EBUS-TBNA to evaluate MHL. Birefringent silica particles (BSP) were identified in 82 (97.62%), silicotic nodules (SN) in 26 (30.95%), and granulomas in 21 (25%). EBUS-TBNA demonstrated a diagnostic yield of 95.2% for lymph node silicosis, and supported the diagnosis of parenchymal silicosis with a sensitivity of 97.6%. The investigators concluded that EBUS-TBNA effectively identifies lymph node silicosis and confirms the diagnosis of parenchymal silicosis in the appropriate clinical-radiologic context. They observed that granulomas can be seen in cytologic specimens of patients with silicosis. They concluded that in patients with well-defined silica exposure and suspected silicosis, EBUS-TBNA does not impact the presumed diagnosis of silicosis and that EBUS-TBNA should be reserved for cases in which alternative diagnoses are more likely.[134]

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[132] Shitrit D, et al., "EBUS-TBNA is Sufficient for Successful Diagnosis of Silicosis with Mediastinal Lymphadenopathy," *Lung* 2018; 196(4):441-445.

[133] Thanthitaweewat VLN, et al., "Silicosis: Role of Endobronchial Ultrasound and Transbronchial Needle Aspiration," *Eur. Respir. J.* 2020; 56:3155 [conference abstract]

[134] Aljarod TM, et al., "Utility of EBUS-TBNA in Evaluating Mediastinal and Hilar Lymphadenopathy in Patients With Silica Exposure: A Retrospective Single-center Study," *J. Broncol. Intervent. Pulmonol.* 2025; 32:e01016.

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7. Transbronchial Cryobiopsy (TBCB)

249. In 2018, European researchers published a review regarding Transbronchial Lung Cryobiopsy (TBLC), which they referred to as "a new bioptic approach in diffuse parenchymal lung diseases," that "is considered to overcome the limitations of conventional forceps biopsies."[135]

250. "The equipment needed for TBLC is quite simple and consists of a main unit connected to a tank containing a cooling agent, a pedal, and the probe. The entire system is easily transportable. The cryosurgical equipment works by the Joule-Thompson effect; hence, expansion of the gas from the compressed state leads to a change in temperature. The cooling agent, which is mainly carbon dioxide (CO_2), is applied under high pressure through the central canal of the probe.... When the gas passes the end of the central canal, it expands due to the sudden difference in pressure which results in an immediate drop of temperature to less than 0° C at the tip of the probe."[136]

251. The procedure is less costly than surgical biopsy.[137]

252. Studies have reported that the procedure provides a high diagnostic yield.[138] A higher diagnostic yield than surgical lung biopsy has been reported in some,[139] but not all studies.[140]

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[135] Colella S, et al., "Transbronchial Lung Cryobiopsy in Interstitial Lung Diseases: Best Practice," *Respiration* 2018; 95(6):383-391.

[136] Colella S, et al., "Transbronchial Lung Cryobiopsy in Interstitial Lung Diseases: Best Practice," *Respiration* 2018; 95(6):383-391.

[137] Sharp C, et al., "Use of transbronchial cryobiopsy in the diagnosis of interstitial lung disease - a systematic review and cost analysis," *Quarterly J. Med.* (*QJM)* 2017; 110(4):207-214.

[138] Pajares V, et al., "Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: A randomized trial," *Respirology* 2014; 19:900-906; Johannson KA, et al., "Diagnostic Yield and Complications of Transbronchial Lung Cryobiopsy for Interstitial Lung Disease: A Systematic Review and Metaanalysis," *Ann. Am. Thorac. Soc.* 2016; 13(10):1828-1838; Harari S, et al., "Lung Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: A Series Contribution to a Debated Procedure," *Medicina* 2019; 55:606; Rodrigues I, et al., "Diagnostic yield and safety of transbronchial lung cryobiopsy and surgical lung biopsy in interstitial lung diseases: a systematic review and meta-analysis," *Eur. Respir. Rev.* 2022; 31:210280; Freund O, et al., "Transbronchial Cryobiopsy is Superior to Forceps Biopsy for Diagnosing both Fibrotic and non-Fibrotic Interstitial Lung Diseases," *Respiration* 2023; 102:852-860.

[139] Pajares V, et al., "Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: A randomized trial," *Respirology* 2014; 19:900-906; Freund O, et al., "Transbronchial Cryobiopsy is Superior to Forceps Biopsy for Diagnosing both Fibrotic and non-Fibrotic Interstitial Lung Diseases," *Respiration* 2023; 102:852-860.

[140] Mehrad M, et al., "Transbronchial Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Disease," *Arch. Pathol. Lab. Med.* 2020; 144:1501-1508.

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253. The diagnostic accuracy of the procedure is high.[141] Diagnostic accuracy superior to that of surgical lung biopsy has been reported in some,[142] but not all studies.[143]

254. Many studies have reported transbronchial lung cryobiopsy to be safe.[144] Procedure-related mortality, severe bleeding, prolonged air leak, acute exacerbation, respiratory failure, and respiratory infection are rare.[145] Morbidity and mortality are lower than surgical lung biopsy.[146]

255. "Among patients with undiagnosed or unclassified ILD requiring tissue biopsy for diagnosis, transbronchial cryobiopsy represents a reliable alternative to surgical lung biopsy with decreased incidence of various clinical adverse events."[147]

256. In at least one study the procedure has been used in diagnosing silicosis.[148]

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[141] Unterman A, et al., "High Diagnostic Accuracy of Transbronchial Cryobiopsy in Fibrotic Interstitial Lung Diseases Compared to Final Explant Diagnosis," *Respiration* 2019; 98(5):421-427; Hetzel J, et al., "Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial," *Eur. Respir. J.* 2020; 56:1901520; Troy LK, et al., "Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective comparative study," *Lancet Respir. Med.* 2020; 8(2):171-181.

[142] Colella S, et al., "Transbronchial Lung Cryobiopsy in Interstitial Lung Diseases: Best Practice," *Respiration* 2018; 95(6):383-391; Freund O, et al., "Transbronchial Cryobiopsy is Superior to Forceps Biopsy for Diagnosing both Fibrotic and non-Fibrotic Interstitial Lung Diseases," *Respiration* 2023; 102:852-860.

[143] Romagnoli M, et al., "Poor Concordance between Sequential Transbronchial Lung Cryobiopsy and Surgical Lung Biopsy in the Diagnosis of Diffuse Interstitial Lung Diseases," *Am. J. Respir. Crit. Care Med.* 2019; 199(10):1249-1256.

[144] Casoni GL, et al., "Transbronchial Lung Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Diseases," *PLOS One* 2014; 9(2):e86716; Cooley J, et al., "Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease," *Respiratory Med.* 2018; 140:71-76; Hagmeyer L, et al., "Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction," *Thorax* 2019; 74:711-714; Harari S, et al., "Lung Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: A Series Contribution to a Debated Procedure," *Medicina* 2019; 55:606; Maldonado F, et al., "Transbronchial Cryobiopsy for the Diagnosis of Interstitial Lung Diseases: CHEST Guideline and Expert Panel Report," *Chest* 2020; 157(4):1030-1042; She S, et al., "Transbronchial Cryobiopsy in Interstitial Lung Disease: Safety of a Standardized Procedure," *J. Bronchology Interv. Pulmonol.* 2020; 27(1):36-41; Rodrigues I, et al., "Diagnostic yield and safety of transbronchial lung cryobiopsy and surgical lung biopsy in interstitial lung diseases: a systematic review and meta-analysis," *Eur. Respir. Rev.* 2022; 31:210280.

[145] Kheir F, et al., "Transbronchial Lung Cryobiopsy in Patients with Interstitial Lung Disease: A Systematic Review," 2022; *Ann. Am. Thorac. Soc.* 19(7):1193-1202.

[146] Mehrad M, et al., "Transbronchial Cryobiopsy in the Diagnosis of Fibrotic Interstitial Lung Disease," *Arch. Pathol. Lab. Med.* 2020; 144:1501-1508.

[147] Zayed Y, et al., "Role of Transbronchial Lung Cryobiopsy in the Diagnosis of Interstitial Lung Disease: A Meta-analysis of 68 Studies and 6300 Patients," *J. Bronchol. Interv. Pulmonol.* 2023; 3092):99-113.

[148] Bango-Álvarez A, et al., "Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases - how to do it," *ERJ Open Res.* 2017; 3:00148-2016 [12 cases of silicosis diagnosed in a series of 106 ILD cases].

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8. Endobronchial Ultrasound-guided Transbronchial Mediastinal Cryobiopsy

257. Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy (EBUS-TMC) is a recent enhancement of EBUS-TBNA, which facilitates the acquisition of larger and better-preserved tissue samples from the mediastinum, while maintaining an excellent safety profile.[149]

258. In 2020, Polish researchers published a multi-center study regarding 114 interstitial lung disease patients from whom endobronchial ultrasound guided transbronchial lung cryobiopsies were obtained over a period of 2.5 years. Histopathology was conclusive for final diagnosis in 90 (79%) cases. The most common histological diagnosis was sarcoidosis, in 32 cases. Silicosis was diagnosed in 9 cases. Complications included only 5 cases of pneumothorax requiring chest tube drainage and minor and moderate bleeding in a few cases.[150]

259. In 2023, Spanish researchers published a study of 50 patients who underwent EBUS-TBNA and EBUS-guided TMC in a single procedure between January and August 2022. Patients with mediastinal lesions greater than 1 cm were recruited and EBUS-TBNA and TMC were performed in the same lymph node station. The diagnostic yield was 82% and 96% for TNA and TMC respectively. In 5 cases they had to make 5 passes of TBNA prior to performing the cryobiopsy, because it was not possible to penetrate the bronchial wall. This problem occurred in patients with suspected silicosis, where the bronchial wall is more rigid and cartilaginous. The investigators concluded that EBUS-TMC is a minimally invasive, feasible and safe technique that seems to offer a higher overall diagnostic yield compared to EBUS-TBNA.[151]

260. In 2024, Italian researchers published a retrospective study of 48 patients who underwent both EBUS-TBNA and endobronchial ultrasound-transbronchial mediastinal cryobiopsy (EBUS-TMC) between August 2021 and October 2023. The overall diagnostic yield of EBUS-TMC

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[149] Ramarmuty HY, et al., "Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy: a narrative review," *Mediastinum* 2024; 8:2.

[150] Gnass M, et al., "Transbronchial lung cryobiopsy guided by radial *mini-probe* endobronchial ultrasound in interstitial lung diseases – a multicenter prospective study," *Adv. Respir. Med.* 2020; 88:123-128.

[151] Ariza-Prota M, et al., "Endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: safety, feasibility and diagnostic yield - experience in 50 cases," *ERJ Open Res.* 2023; 9:00448-2022.

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surpassed that of EBUS-TBNA (95.8% vs 54.1%). Silicosis diagnoses were made in 2 cases.[152]

261. In 2024, Swiss researchers published a study of 137 patients who underwent ultrasound-guided transbronchial cryobiopsy for suspicious mediastinal and hilar lesions. Of the 137 patients, 77 had benign disorders; 44 were diagnosed with sarcoidosis and 33 were diagnosed with silico-/anthracosis.[153]

262. In 2024, Malaysian researchers published a study published a study of 30 patients who underwent EBUS-TBMC in a teritary center in Malaysia. They concluded: "EBUS-TBMC potentially offers a higher diagnostic yield than EBUS-TBNA. It has the advantage of minimising the need for repeat biopsies and delay in diagnosis, which could translate into overall cost savings."[154]

263. In 2025, Spanish researchers published a study summarizing 178 EBUS-TBNA and CryoEBUS procedures that they conducted over a two year period. The patients had a mean age of 63 years and a male predominance of 72.5%. The primary indication for the sampling procedure was lung cancer in 106 patients. Other indications included lymphoproliferative disorders (22 cases), sarcoidosis (18 cases), reactive lymphadenopathy (17 cases), suspected extrapulmonary metastasis (10 cases), as well as additional cases involving silicosis and tuberculosis. The article includes a series of images from microscopic evaluation of EBUS-TBNA cytologic and CryoEBUS tissue samples. The last image, using dark field microscopy, shows the presence of silica crystals. The investigators concluded that combined implementation of the WHO Reporting System for Lymph Node Cytopathology and the simultaneous use of CryoEBUS resulted in enhanced performance and diagnostic accuracy, reducing non-diagnostic samples to less than 3%.[155]

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[152] Poletti V, et al., "EBUS-guided cryobiopsy in the diagnosis of thoracic disorders," *Pulmonology* 2025; 30:459-465.

[153] Mangold MS, et al., "Ultrasound-guided transbronchial cryobiopsy of mediastinal and hilar lesions: a multicenter pragmatic cohort study with real-world evidence," *BMJ Open Respir. Res.* 11:e002617.

[154] Soo IS, et al., "Technical tips, diagnostic yield and safety of endobronchial ultrasound-guided transbronchial mediastinal cryobiopsy," *Med. J. Malaysia* 2024; 79(4):490-493.

[155] Fernández FLM, et al., "EBUS-TBNA and CryoEBUS of the mediastinal lymph node. One hundred seventy-eight cases. Validation of the WHO Reporting System for Lymph Node Cytopathology. Proposed CryoEBUS diagnostic flow chart and indications. The view of the interventional pathologist," *Rev. Esp. Patología* 2025; 58:100799.

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9. Energy-Dispersive X-Ray Analysis (EDX)

264. In 1984, researchers from North Carolina published a review of recently developed analytical techniques for studying the interaction between the lung and the various exogenous materials to which it is exposed. They observed that analytical problems requiring elemental sensitivity or specificity beyond the range of that offered by conventional scanning electron microscopy and energy dispersive X-ray analysis are particularly appropriate for the application of these newer techniques. They commented that electron energy loss spectrometry, Auger electron spectroscopy, secondary ion mass spectrometry, and laser microprobe mass analysis each offer unique advantages in this regard, but also possess their own limitations and disadvantages. They also noted that diffraction techniques provide crystalline structural information available through no other means.[156]

265. Also in 1984, researchers from the Clement J. Zablocki Veterans Administration Medical Center in Milwaukee, Wisconsin, published a study in which they used energy-dispersive x-ray analysis to study pulmonary specimens from 10 normal subjects and 3 patients with various lung diseases. The amount of silicon in the pulmonary tissue was determined and expressed as a silicon/sulfur (Si/S) ratio. This Si/S ratio was below 0.2 in the ten normal subjects and in 14 patients who had various interstitial pulmonary diseases but had no previous history of exposure to silica or other dusts known to cause pulmonary fibrosis. The Si/S ratio was greater than 0.3 in 19 of 22 patients who had a history of exposure to silica dust and had clear-cut histologic evidence of silicosis. The Si/S ratio was less than 0.2 in 12 and between 0.2 and 0.3 in two of the 14 patients who had a history of exposure to silica dusts but no clinical or histologic evidence of silicosis. The investigators concluded that the determination of the silicon content of tissue by energy-dispersive x-ray analysis is useful in separating fibrosis due to silicosis from other causes of pulmonary fibrosis.[157]

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[156] Roggli VL, et al., "New Techniques for Imaging and Analyzing Lung Tissue," *Environ. Health Perspect.* 1984; 56:163-183.

[157] Funahashi A, et al., "Value of in situ elemental microanalysis in the histologic diagnosis of silicosis," *Chest* 1984; 85(4):506-509.

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266. In 1992, Italian researchers evaluated the possibility of quantifying alveolar dust burden in conditions of exposure to silica by performing bronchoalveolar lavage (BAL) on four groups of subjects: 10 healthy control subjects, 39 diffuse interstitial lung disease (DILD) patients never exposed to dust, 23 silicotic patients, and 12 chronic bronchitis patients with a history of occupational exposure to silica dust. Five to ten million BAL recovered cells were analyzed using an energy-dispersive X-ray microanalysis (EDXA) system to determine the silicon content, expressed in a semi-quantitative way as silicon to sulphur (Si/S) ratio. The results were independent of smoking habit. The Si/S median values (interquartile range in brackets) for the four groups were 0.53 (0.5-0.65), 0.60 (0.41-0.8), 1.23 (1.06-1.39), 1.31 (1.11-1.97), respectively. Silicotics and simply exposed individuals did not show a significant discrepancy, but they were both significantly different in comparison to normal and DILD patients without history of exposure ($p < 0.001$). 14.3% false negative cases were found, and 4.1% false positive cases (none among normal subjects). The investigators did not observe any significant relationships between the amount of silicon and the duration of exposure or the degree of chest X-ray involvement. A study of cytocentrifuge slides from the same subjects by polarizing light microscopy revealed a lower sensitivity (34% false negative cases). The investigators concluded that (1) it is possible to quantify the alveolar silicon burden on BAL samples, thus avoiding more invasive sampling techniques; (2) in the experimental conditions of the study, a Si/S level >0.95 (i.e., 95th percentile value of all nonexposed subjects) is, in most cases, indicative of significant exposure to silica and/or silicates, compatible with pneumoconiosis but of no definitive diagnostic value, since nonsilicotic exposed subjects share the same values with silicotics; (3) a Si/S value < 0.95 is typical of a nonexposure condition, but may underestimate a marked dust inhalation in about 14% of cases.[158]

267. In 1997, Spanish researchers sought to measure silica and non-fibrous silicates in bronchoalveolar lavage (BAL) fluid from populations with different exposures to inorganic dust, and to determine whether such measurement is useful for diagnostic purposes. BAL samples from 19 subjects with only environmental exposure to inorganic dust (group A, mean (SD) age 50.7 (15.2)),

[158] Lusuardi M, et al., "Semi-quantitative X-ray microanalysis of bronchoalveolar lavage samples from silica-exposed and nonexposed subjects," *Eur. Respir. J.* 1992; 5:798-803.

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23 subjects with normal chest x ray films exposed to silica or silicates at work (group B, mean (SD) age 52.0 (12.4)), and 15 subjects with a previous diagnosis of silicosis (group C, mean (SD) age 68.0 (6.5)) were studied. Absolute and relative cell counts were found, and the samples were prepared for microanalysis by electron microscopy (EM). Semiquantitative x ray microanalysis was performed to find the level of silicon (Si) (peak/background Si) and this was followed by microanalysis of individual particles by EM. Variables related to the level of Si detected were assessed with multivariate analysis. Detected levels were higher in group B (2.09, 95% CI 1.56 to 2.82) and C (1.50, 95% CI 1.07 to 2.12) than in group A (0.87, 95% CI 0.66 to 1.16) ($P<0.05$, Dunett *t* test). A first multivariate analysis showed that exposure to silica or silicates was the only determinant of the level of Si expressed as log peak/background Si, when adjusted for age, sex, smoking habit, and cell count. A second multivariate analysis with micro-analysis of individual particles as an independent variable showed the silica count to be the main predictor of detected concentration of Si. Silica and non-aluminium silicates together explain 55.5% (R2) of the variation in detected levels of Si. The investigators concluded that detected levels of Si in BAL fluid depend on silica count and are higher in subjects with exposure to inorganic dust at work, but will not discriminate between exposed subjects with and without silicosis. Because semiquantitative x ray microanalysis does not accurately define exposure to non-silica inorganic particles, this measurement must be followed by EM microanalysis of individual particles in most cases, especially when exposure to silicates or metal dust is suspected.[159]

[159] Monsó E, et al., "Electron microscopic microanalysis of bronchoalveolar lavage: a way to identify exposure to silica and silicate dust," *Occup. Environ. Med.* 1997; 54:560-565.

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10. Scanning Electron Microscopy

268. "Scanning Electron Microscopy (SEM) is a powerful technique designed to examine a material's surface. In SEM, an electron beam with acceleration voltages of up to 30 kV is focused on the specimen. The interactions between the electron beam and the specimen emit signals from the specimen, and detectors collect them. The recorded signals are combined to form an image .... SEM is a highly versatile tool for the structural characterization of biobased materials."[160]

269. "It is an effective method in analysis of organic and inorganic materials on a nanometer to micrometer (μm) scale. SEM works at a high magnification reaches to 300,000x and even 1000000 (in some modern models) in producing images very precisely of [a] wide range of materials."[161]

270. "SEM can provide information on surface topography, crystalline structure, chemical composition and electrical behaviour of the top 1 μm or so of specimen."[162]

271. "[A]dvantages of SEM over optical microscopy include:

- SEM benefits from a large depth of field so most of the specimen surface is simultaneously in focus whatever the surface roughness. Optical microscopes operating at high magnification have a very small depth of field so image quality is very dependent on the surface being smooth.

- Much higher magnifications can be achieved (up to 1,000,000x), with an ultimate resolution of 1 nm. The maximum useful magnification in an optical microscope is around 1000x.

- The possibility of getting more information than just the surface topography, e.g. crystal structure, chemical composition and electrical properties. Switching between different imaging techniques enables information to be cross-correlated with confidence."[163]

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[160] Rodriguez Herrero Y, et al., "Characterization of biobased materials," Chap. 4 in Ahmed S, et al., eds., *Advanced Applications of Biobased Materials: Food, Biomedical, and Environmental Applications* (Elsevier 2023).

[161] Mohammed A, et al., "Scanning Electron Microscopy (SEM): A Review," *Proc. 2018 Int. Conf. Hydraulics Pneumatics* 2018.

[162] Vernon-Parry KD, "Scanning Electron Microscopy: an introduction," *III-Vs Rev.* 2000; 13(4):40-44.

[163] Vernon-Parry KD, "Scanning Electron Microscopy: an introduction," *III-Vs Rev.* 2000; 13(4):40-44.

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11. Scanning Electron Microscopy with Energy-Dispersive X-ray Spectroscopy

272. "Scanning electron microscopy/energy dispersive X-ray spectrometry (SEM/EDS) is a widely applied elemental microanalysis method capable of identifying and quantifying all elements in the periodic table except H [Hydrogen], He [Helium], and Li [Lithium]."[164]

273. "Energy dispersive X-ray spectroscopy (EDS) in electron microscopy has been widely used in many research areas since it provides precise information on the chemical composition of subcellular structures that may be correlated with their high resolution images."[165]

274. In 1994, Spanish researchers studied the elemental inorganic content in pleura and lung tissue of exposed non-pneumoconiotic and silicotic populations by Scanning Electron Microscopy (SEM) with Energy-Dispersive X-ray Analysis (EDXA). Samples of parietal pleura, visceral pleura, and lung in 11 subjects with no measurable exposure to inorganic dust and of visceral pleura and lung samples of 10 exposed non-pneumoconiotic individuals and eight silicotic patients were examined. Constant depositions of silicon and calcium were detected in visceral pleura, parietal pleura, and lung of the reference group and in visceral pleura and lung of the exposed non-pneumoconiotic and silicotic groups. Other elements, such as aluminum and iron, were also detected in the exposed non-pneumoconiotic and silicotic patients and, less frequently, in the reference group. There was no difference in silicon content between parietal and visceral pleura in the reference group. Silicon content in silicotic patients was higher and more irregularly distributed in the pleura ($p = 0.005$ and $p < 0.01$, respectively) and in the lung ($p = 0.005$ and $p < 0.01$, respectively) than in the reference group. Comparison of the silicon content in pleura between silicotic and exposed non-pneumoconiotic subjects showed a nonsignificant probability of difference ($p = 0.052$), whereas there were no differences with respect to the silicon content in the lung.[166]

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[164] Newbury DE, et al., "Is Scanning Electron Microscopy/Energy Dispersive X-ray Spectrometry (SEM/EDS) Quantitative?" *Scanning* 2013; 35:141-168.

[165] Wyroba E, et al., "Biomedical and Agricultural Applications of Energy Dispersive X-Ray Spectroscopy in Electron Microscopy," *Cell. Mol. Biol. Lett.* 2015; 20:488-509.

[166] Ferrer J, et al., "Energy-dispersive X-ray analysis and scanning electron microscopy of pleura. Study of reference, exposed non-pneumoconiotic, and silicotic, population," *Am. J. Respir. Crit. Care Med.* 1994; 149(4):888-892.

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275. In 2024, American researchers published a study in which they used scanning electron microscopy with energy dispersive-x-ray spectroscopy (SEM EDS) to quantify the pulmonary parencyhmal burden of silica, silicates, and metal particles in 45 Texas oilfield pipe sandblasters who were biopsied between 1988 and 1995. They also evaluated pulmonary function tests, chest x-rays, high-resolution computed tomography (HRCT) and Gallium-67 scans of the sandblasting workers. The workers had clinical deterioration after <10 years exposure in dusty workplaces. Although initial CXR was normal in 54%, Gallium 67 scans were positive in 68% of those with normal CXR, indicating pulmonary inflammation. The histology of accelerated silicosis is diffuse interstitial infiltration of macrophages filled with weakly birefringent particles with or without silicotic nodules or alveolar proteinosis. Lung silica concentrations were among the highest in the investigators' database, showing a dose–response relationship with CXR, HRCT, and pathologic changes (macrophages, fibrosis, and silicotic nodules). Radiographic scores and diffusing capacity worsened during observation. Silica exposure was intensified, patients presented younger, with shorter exposure, more severe clinical abnormalities, higher lung particle burdens, and more rapid progression in a subset of patients exposed to recycled blasting sand. The investigators concluded that accelerated silicosis may present with a normal chest x-ray despite significant histopathology. Multivariable analyses showed silica, and not other particles, was the driver of observed radiologic, physiologic, and histologic outcomes.[167]

276. This study is especially relevant to the diagnosis of silicosis in artificial stone countertop fabricators for two reasons. First, like the sandblasters of recycled sand who largely developed accelerated silicosis, this type of silicosis is the predominant type of silicosis among countertop fabricators exposed to engineered stone dust. Second, like the sandblasters of recycled sand, stone countertop fabricators are exposed to extremely fine silica particles that are more toxic to the lungs than larger respirable particles. Just as the sandblasters were exposed to very fine silica particles from recycled sand, stone countertop fabricators are exposed to very fine silica particles because engineered stone is manufactured by pulverizing quartz to extremely small particles, which are further reduced in size when fabricators cut engineered stone with electric powered tools.

[167] Crawford JA, et al., "Accelerated silicosis in sandblaster: Pathology, mineralogy, and clinical correlates," *Am. J. Ind. Med.* 2024; 67:179-199.

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277. In 2021, Spanish researchers published a study in which they analyzed the compositional content of engineered stone brands that 7 patients diagnosed with silicosis had worked with during the years prior to their silicosis diagnoses and compared the results with analyses of the workers' lung tissue. These investigators used X-ray diffraction (XRD), X-ray fluorescence (XRF) and inductively coupled plasma mass spectrometry (ICP-MS) to analyze the constituents of the countertop materials, Scanning Electron Microscopy with Energy-Dispersive X-Ray Spectroscopy (SEM-EDS) to analyze the inorganic chemical composition of their lung tissue, and other techniques to analyze the organic content of the countertop samples. The different countertop materials were composed of silicon dioxide in percentages between 87.9 and 99.6%, with variable relationships of quartz and cristobalite depending on the sample. The most abundant elements in the countertop samples were aluminum, sodium, iron, calcium, and titanium. The most frequent volatile organic compounds were styrene, toluene and m-xylene, and among the polycyclic aromatic hydrocarbons, phenanthrene and naphthalene were detected in all samples. Samples obtained from lung biopsies most frequently showed well or ill-defined nodules, composed of histiocytic cells and fibroblasts without central hyalinization. All tissue samples showed a high proportion of Silica and Aluminum at the center of the nodules, becoming sparser at the periphery. In a preparation of a lung sample from a control patient, who had not been occupationally exposed to silica, no silicon or aluminum was detected. The investigators observed that some of the volatile organic compounds, polycyclic aromatic hydrocarbons and metals detected in the countertop samples hade been described as causative of lung inflammation and respiratory disease. They also noted that among the inorganic constituents, aluminum has been a prevalent component within the silicotic nodule, reaching atomic concentrations even higher than silicon in some cases. The concentration of both metals showed a decreasing tendency from the center of the nodule towards its frontier. The results of this study established a correlation between the chemical composition of engineered stone materials and volatile organic compounds emitted from the materials during fabrication processes and the chemical composition of inhaled particles in the nodules within the lungs of exposed workers with silicosis.[168]

[168] León-Jiménez A., et al., "Compositional and structural analysis of engineered stones and inorganic particles in silicotic nodules of exposed workers," *Particle Fibre Toxicol.* 2021; 18:41.

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12. Computer-Controlled Scanning Electron Microscopy with Energy-Dispersive X-Ray Analysis (CC-SEM-EDX)

278. In 2015, researchers from Virginia Tech published a paper describing a standard methodology for characterization of respirable coal mine dust that used scanning electron microscopy (SEM) with energy dispersive X-ray (EDX) and an automated spreadsheet program for computational analysis. In this preliminary study the researchers provided preliminary verification of the dust characterization method using three samples collected in the field.[169]

279. In 2017, researchers from the Department of Mining and Minerals Engineering of Virginia Tech, published a paper presenting a computer-controlled technique of SEM-EDX. They acknowledged that SEM-EDX can be used to estimate particle characteristics, but that "[i]f conducted manually, such work can be very time intensive, limiting the number of particles that can be analyzed, and that potential exists for user bias in interpretation of EDX spectra. They proposed the use of a computer-controlled (CC) routine, that can allow similar analysis at a much faster rate, increasing total particle counts and reproducibility of results. Their paper described a CCSEM-EDX routine specifically developed for analysis of respirable dust samples from coal mines. The routine was verified based on reliability of results obtained on samples of known materials, and reproducibility of results obtained on a set of 10 dust samples collected in the field. They also discussed characteristics of field samples with respect to mine occupational environments.[170]

280. In 2019, researchers from Virginia Tech presented data from 76 unique sampling events in which respirable dust samples were collected in key locations of eight underground coal mines in Appalachia. They data that they presented from each event described particle size and mineralogy class distributions across the ~100 - 10,000nm size range, which were determined using SEM-EDX. They also estimated mass concentrations of metals and trace elements.[171]

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[169] Sellaro R, et al., "A Standard Characterization Methodology for Respirable Coal Mine Dust Using SEM-EDX," *Resources* 2015; 4:939-957.

[170] Johann-Essex V, et al., "A Computer-Controlled SEM-EDX Routine for Characterizing Respirable Coal Mine Dust," *Minerals* 2017; 7:15.

[171] Sarver E, et al., "Characteristics of respirable dust in eight Appalachian coal mines: A dataset including particle size and mineralogy distributions, and metal and trace element mass concentrations," *Data in Brief* 2019; 25:104032.

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13. Field-Emission Scanning Electronic Electron Microscopy (FE-SEM) and Energy Dispersive X-Ray Spectroscopy (EDS)

281. In 2018, American researchers published a protocol for *in situ* characterization of the types and distribution of inorganic particles in biopsied lung tissue from three human groups using field emission scanning electron microscopy (FE-SEM) combined with energy dispersive spectroscopy (EDS). Many distinct particle types were recognized among the 13,000 particles analyzed. Silica, feldspars, clays, titanium dioxides, iron oxides and phosphates were the most common constituents in all samples. Particles were classified into three general groups: endogenous, which form naturally in the body; exogenic particles, natural earth materials; and anthropogenic particles, attributed to industrial sources. These in situ results were compared with those using conventional sodium hypochlorite tissue digestion and particle filtration. With the exception of clays and phosphates, the relative abundances of most common particle types were similar in both approaches. Nonetheless, the digestion/filtration method was determined to alter the texture and relative abundances of some particle types. The investigators concluded that SEM/EDS analysis of digestion filters could be automated in contrast to the more time intensive in situ analyses.[172]

282. In 2023, researchers from the Joint Pathology Center, Environmental Laboratory Services in Silver Spring, Maryland presented a protocol for automated *in-situ* analysis of inorganic inhaled particulate matter using field-emission scanning electron microscopy with energy dispersive X-ray spectroscopy. Over 120,000 particles of both a geological and manufactured nature were analyzed and characterized according to their chemistry and morphology. The most abundant particles were clays, feldspars, silica, titanium dioxides, and metals and were by and large less than 2.5 μm in the greatest dimension. They noted that automating the process allows for efficient *in-situ* analysis of thousands of particles daily and the development of large datasets.[173]

283. In 2024, American researchers presented data validating the Field Emission Scanning

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[172] Lowers HA, et al., "Method to characterize inorganic particulates in lung tissue biopsies using field emission scanning electron microscopy," *Toxicol. Mechanisms Methods* 2018; 28(7):475-487.

[173] Hayden L, et al., "Automated Particle Analysis Using Field-Emission Scanning Electron Microscopy (FE-SEM) and Energy Dispersive X-Ray Spectroscopy (EDS) to Characterize Inhaled Particulate Matter (PM) in Biopsied Lung Tissue," *Microscopy Microanalysis* 2023; 29:235-243.

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Electron Microscopy with Energy Dispersive X-Ray Spectroscopy (FESEM-EDS) technique. They programmed an automated FESEM-EDS procedure to collect particle size and elemental data, using lung tissue from 10 underground coal miners with PMF and 4 control cases. A statistical clustering approach was used to establish classification criteria based on particle chemistry. Data were correlated to PMF/non-PMF areas of the tissue, using corresponding bright-field microscopy images. Results for each miner case were compared with a separate corresponding analysis of particles recovered following tissue digestion. In situ analysis of miner tissues showed higher particle number densities than controls and densities were generally higher in PMF than non-PMF areas. Particle counts were typically dominated by aluminum silicates with varying percentages of silica. Compared to digestion results for the miner tissues, in situ results indicated lower density of particles (number per tissue volume), larger size, and a lower ratio of silica to total silicates, probably due to frequent particle clustering in situ. The investigators concluded that Automated FESEM-EDS analysis of lung dust is feasible in situ and could be applied to a larger set of mineral dust–exposed lung tissues to investigate specific histologic features of PMF and other dust-related occupational diseases.[174]

284. To date, Computer-Controlled Scanning Electron Microscopy with Energy-Dispersive X-Ray Analysis (CC-SEM-EDX) and Automated Field Emission Scanning Electron Microscopy with Energy Dispersive X-Ray Spectroscopy (FESEM-EDS) have not been developed commercially and have only been used for medical and scientific research in research institutions. However, these analytical techniques have been validated and should become commercially available, because they provide substantial improvements in the efficiency of scanning electron microscopic analysis with energy-dispersive X-ray spectroscopy, the number of sample that can be rapidly analyzed, and the technique avoids potential researcher selection and other biases that are inherent in traditional laborious analysis by pathologists individually performing SEM-EDS analyses.

[174] Sarver E, et al., "In Situ Lung Dust Analysis by Automated Field Emission Scanning Electron Microscopy With Energy Dispersive X-ray Spectroscopy: A Method for Assessing Inorganic Particles in Lung Tissue From Coal Miners," *Arch. Pathol. Lab. Med.* 2024; 148:e154-169.

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D. Clinical Occupational Medicine Assessment

285. Occupational questionnaires are a critical component in the evaluation of engineered stone workers for their risk of developing silicosis. These tools systematically capture detailed information about work history, job tasks, duration and intensity of exposure, use of personal protective equipment, and the presence or absence of dust control measures in the workplace. In the context of engineered stone fabrication - an industry associated with exceptionally high levels of respirable crystalline silica - questionnaires provide essential context that imaging and pulmonary function testing alone cannot offer. They help identify high-risk workers who require more frequent medical surveillance or earlier diagnostic evaluation, even in the absence of symptoms. Standardized occupational questionnaires can guide exposure mitigation strategies and inform regulatory response. When used as part of a comprehensive surveillance program, occupational questionnaires enhance the early detection and prevention of silicosis by ensuring that clinical assessments are informed by accurate and detailed exposure histories. Given the complexity of diagnosing and managing silicosis, particularly in workers exposed to high concentrations of respirable crystalline silica from engineered stone, it is essential that affected individuals be evaluated by specialists in occupational and pulmonary medicine with experience in silica-related lung disease. These specialists are uniquely trained to interpret the nuanced interplay between work history, radiographic findings, pulmonary function data, and symptom progression. Accurate diagnosis is particularly challenging in early or atypical cases, where imaging and pulmonary function testing may be equivocal. Misclassification can lead to either under-recognition of at-risk individuals or unnecessary anxiety and over-treatment. Evaluation by experienced clinicians ensures appropriate interpretation of clinical data, timely removal from exposure when needed, and the initiation of interventions to slow disease progression. Ideally, such assessments should occur within dedicated Silicosis Centers of Excellence, where multidisciplinary teams can provide standardized, high-quality care, and facilitate early detection through advanced diagnostics. These centers play a critical role in ensuring that best practices are applied consistently and that affected workers receive expert, coordinated care.[175]

[175] Silicosis Center of Excellence of University of California San Francisco, Ideal Medical Monitoring Program, at https://silicosis.ucsf.edu/content/ideal-medical-monitoring-program-silicosis-center-of-excellence.

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E. Biomarkers of Silicosis and Other Silica-Related Diseases

286. In recent years various biomarkers have been used to detect silicosis in early stages of the disease, before silicosis is detectable with chest radiographs and even computed tomography. Multiple biomarkers that can be obtained from blood, serum, and urine have been identified, which enable pre-clinical detection of silicosis, allowing early interventions to prevent disease progression. Non-invasive breath tests and electronic nose technologies can also be used to detect early silicosis.

287. During the past twenty years, studies have been published regarding a large variety of potential silicosis biomarkers, which studies are the subject of several published reviews.[176]

[176] Tiwari RR, "Biomarkers of silicosis: Potential candidates," *Indian J. Occup. Environ. Med.* 2005; 9(3):103-106; Gulumian M, et al., "Mechanistically identified suitable biomarkers of exposure, effect, and susceptibility for silicosis and coal-worker's pneumoconiosis: a comprehensive review," *J. Toxicol. Environ. Health B Crit. Rev.* 2006; 9(5):357-395; Syslová K, et al., "Rapid and easy method for monitoring oxidative stress markers in body fluids of patients with asbestos or silica-induced lung diseases," *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* 2009; 877(24):2477-2486; Pandey JK, et al., "Biomarkers: A potential prognostic tool for silicosis," *Indian J. Occup. Environ. Med.* 2012; 16(3):101-107; Cheepsattayakorn A, et al., "Silicosis: Pathogenesis and Biomarkers," *Ann. Clin. Pathol.* 2018; 6(5):1147; Miao R, et al., "Proteomic profiling change during the early development of silicosis disease," *J. Thoracic Disease* 2016; 8(3):329-341; Mohammadi H, et al., "Evaluation of potential biomarkers of exposure to crystalline silica: A case study in an insulator manufacturer," *Toxicol. Ind. Health* 2018; 34(7):491-498; Nardi J, et al., "Inflammatory and oxidative stress parameters as potential early biomarkers for silicosis," *Clin. Chim. Acta* 2018; 484:305-313; Peruzzi CP, et al., "Inflammatory and oxidative stress biomarkers at protein and molecular levels in workers occupationally exposed to crystalline silica," *Environ. Sci. Pollut. Res. Int.* 2019; 26(2):1394-1405; Scalia Carneiro AP, et al., "Inflammatory and oxidative stress biomarkers induced by silica exposure in crystal craftsmen," *Am. J. Ind. Med.* 2020; 63(4):337-347; Austin EK, et al., "Early Detection Methods for Silicosis in Australia and Internationally," *Int. J. Environ. Res. Public Health* 2021; 18:8123;. Zhou M, et al., "Plasma metabolic profiling in patients with silicosis and asbestosis," *J. Occup. Environ. Med.* 2021; 63(9):787-793; Blanco-Pérez JJ, et al., "Serum levels of inflammatory mediators as prognostic biomarker in silica exposed workers," *Sci. Rep.* 2021; 11(1):13348; Yilmaz B, et al., "Determination of neopterin in urine of industrial workers by HPLC," *An. Acad. Bras. Cienc.* 2022; 94(Suppl. 4): e20220304; Peruzzi CP, et al., "Occupational exposure to crystalline silica and peripheral biomarkers: An update," *J. Appl. Toxicol.* 2022; 42(1):87-102; Calutu IM, et al., "Biomonitoring exposure and early diagnosis in silicosis: a comprehensive review of the current literature," *Biomedicines* 2022; 11:100; Wang H, et al., "Exploratory study on serum metabolic profiles of Chinese male patients with artificial stone silicosis, silicosis, and coal worker's pneumoconiosis," *Toxicol. Lett.* 2022; 356:132-142; Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ind. Med.* 2023; 66(11):984-995; Liu K, et al., "Combined application of multiple biomarkers for early auxiliary diagnosis of silicosis," *Toxicol. Ind. Health* 2023; 39(3):138-145; Zhang Z, et al., "Changes of biomarkers in plasma of patients with occupational silicosis and their diagnostic value," *China Occup. Med.* 2023; 6:701-705; Zhang Y, et al., "Candidate gene polymorphisms associated with silicosis and coal workers' pneumoconiosis: A systematic review and meta- analysis," *BMC Pulm. Med.* 2024; 24:580; Rezaei A, et al., "Systemic inflammation indices as hematological biomarkers of inflammatory response in non-silicotic workers exposed to respirable silica dust," *Toxicol. Lett.* 2024; 395:26-39; Ribeiro PC, et al., "Inflammatory biomarkers in workers exposed to silica dust: integrative review," *Rev. Bras. Med. Trab.* 2024; 22(3):e20231224; Wang Z, et al., "The value of single biomarkers in the diagnosis of silicosis: A meta-analysis," 2024; *iScience* 27:109948; Yao J., et al., "Exosomal proteomics and cytokine analysis distinguish silicosis cases from controls," *Environ. Pollution* 2024; 357:124469; Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694; Sun G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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1. Blood Cells

288. "Routine blood analysis has been proposed as a cost-effective and easily measurable technique for improving the diagnosis and prognosis of various pathologies,[177] such as some interstitial lung diseases, idiopathic pulmonary fibrosis,[178] or hypersensitivity pneumonitis."[179] Multiple studies over the past 40 years have evaluated peripheral blood parameters as a means of diagnosing silicosis and determining stage and progression of disease.

289. In 2022, Spanish researchers investigated circulating biomarker levels and systemic inflammatory indices in Engineered Stone (ES) silicosis patients whose exposure to ES dust ended several years ago. Ninety-one adult men, ex-workers in the manufacturing of ES, 53 diagnosed with SS and 38 with PMF, and 22 healthy male volunteers (HC) as controls not exposed to ES dust, were recruited. Circulating levels of lactate dehydrogenase (LDH), angiotensin-converting enzyme (ACE), protein C reactive (PCR), rheumatoid factor, alkaline phosphatase and fibrinogen were obtained from clinical reports after being measured from blood samples. As biochemical markers, only LDH (HC = 262 ±48.1; SS = 315.4 ±65.4; PMF = 337.6 ±79.3 U/L), ACE (HC = 43.1 ±18.4; SS = 78.2 ±27.2; PMF = 86.1 ±23.7 U/L) and fibrinogen (HC = 182.3 ±49.1; SS = 212.2 ±43.5; PMF = 256 ±77.3 U/L) levels showed a significant sequential increase. Moreover, several systemic inflammation indices neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), aggregate index of systemic inflammation (AISI) derived from

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[177] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694, citing Bodaghi A, et al., "Biomarkers: promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases,"*Heliyon* 2023; 9(2):e13323.

[178] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694, citing Zinellu A, et al., "The aggregate index of systemic inflammation (AISI): a novel prognostic biomarker in idiopathic pulmonary fibrosis," *J. Clin. Med.* 2021; 10(18):4134 and Kreuter M, et al., "Monocyte count as a prognostic biomarker in patients with idiopathic pulmonary fibrosis," *Am. J. Respir. Crit. Care Med.* 2021; 204(1):74-81.

[179] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694, citing Barratt SL, et al., "Use of peripheral neutrophil to lymphocyte ratio and peripheral monocyte levels to predict survival in fibrotic hypersensitivity pneumonitis (fHP): a multicentre retrospective cohort study," *BMJ Open Respir Res.* 2021; 8(1):e001063.

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whole blood cell counts showed significant differences between the HC, SS and PMF groups. All these biomarkers were analyzed using receiver operating characteristic (ROC) curves, and the results provided moderately high sensitivity and specificity for discriminating between ES silicosis patient groups and healthy controls. The investigators concluded their study showed that some inflammatory biomarkers, easily available from routine blood analysis, are present in ES silicosis patients even several years after cessation of exposure to ES dust and could help assess disease progression.[180]

290. In 2023, Chinese researchers assessed changes to complete blood cell counts in 354 silicosis patients who were divided into stage I, stage II and stage III groups according to stage of silicosis. Based on the course of the disease, they were divided into groups of ≤3, >3-≤6, >6-≤9 and >9-≤12 years. Peripheral blood of the patients was collected for complete blood cell count analysis, and the influencing factors of complete blood cell count were analyzed by multiple linear regression model. The levels of hemoglobin and the average red blood cell hemoglobin in patients with silicosis at stage II and III groups were lower than those at stage I group (all $P<0.05$). The percentage and counts of neutrophils increased in patients at stage III group (all $P<0.05$), while the percentage and counts of lymphocytes decreased (all $P<0.05$) compared with those in stage I and II groups. The percentage of eosinophils in patients at stage III was lower than those at stage I group ($P<0.05$). The red blood cell count in the courses of silicosis >6-9 years group was lower ($P<0.05$), and the percentage of neutrophils was higher, while the percentage of lymphocytes was lower in the courses of silicosis >6-9 years group and >9-12 years group (all $P<0.05$) compared with the courses of silicosis ≤3 years and >3-6 years groups. The mean corpuscular volume of the courses of silicosis >6-9 years group and the neutrophil count of the courses of silicosis >9-12 years group increased (all $P<0.05$) compared with the courses of silicosis ≤3 years group. The results of multiple linear regression analysis showed that the silicosis stage and course of silicosis were influencing factors of erythrocyte count (all $P<0.05$), gender and age of first dust-exposure were influencing factors of hemoglobin level (all $P<0.05$), while age at diagnosis, duration of dust-exposure, age of first dust-exposure and comorbidities were influencing factors of neutrophil count (all $P<0.05$). Gender,

[180] Garcia-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

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comorbidities, smoking and silicosis stage were influencing factors of lymphocyte count (all $P<0.05$). The researchers concluded there are differences in complete blood cell count parameters in patients with silicosis at different stages and courses of the disease. Silicosis stage, course of disease, gender, age, smoking, comorbidities, duration of dust exposure and age of first dust exposure were influencing factors affecting complete blood cell count in silicosis patients.[181]

291. In 2023, Brazilian researchers evaluated the association of inflammatory markers with the presence of silicosis and lung function impairment in silica-exposed workers. Among 297 men, 51 were unexposed controls (G1), 149 were exposed to silica without silicosis (G2), and 97 were exposed to silica with silicosis (G3). Inflammatory marker levels were higher in G3 than in G2 and G1. Platelet/lymphocyte ratio, lactate dehydrogenase, soluble tumor necrosis factor II, and macrophage inflammatory protein-4 were associated with silicosis, and LDH, neutrophil/lymphocyte ratio, soluble tumor necrosis factor II, monocyte chemoattractant protein-1, soluble vascular cell adhesion molecule-1, and fibrinogen were negatively associated with lung function. The researchers concluded that blood inflammatory markers are associated with silicosis and impaired lung function.[182]

292. In 2024, Iranian researchers performed a cross-sectional study to assess whether systemic inflammatory indices, including systemic inflammation response index (SIRI), systemic immune inflammation index (SII), and aggregate index of systemic inflammation (AISI), can be considered as possible inflammatory markers in silica-exposed workers with no diagnosis of silicosis. They studied 371 non-silicotic workers exposed to respirable silica dust (RSD) and 1422 reference workers. The workers' exposure to RSD was assessed and inflammatory indices were compared between subgroups of the exposed workers based on the severity and duration of exposure. Correlations between inflammatory indices and pulmonary function parameters were investigated. The receiver operating characteristic (ROC) curve and Youden index were used to determine the cut-off values of the SII, SIRI, and AISI. Significant dose-response relationships were observed

[181] Bai X, et al., "Study on changes in complete blood cell count parameters of patients with occupational silicosis," *China Occup. Med.* 2023; 50(5):546-550.

[182] Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ind. Med* 2023; 66(11):984-995.

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between duration of exposure and all indices except monocytes and Lymphocyte-to-Monocyte Ratio (LMR). No significant interaction was observed between duration of exposure to RSD and smoking. Borderline significant correlations were observed between AISI and SIRI with forced expiratory volume (FEV1) and FEV1 to forced vital capacity (FVC) ratio. Higher AUCs were obtained for SII and AISI, respectively. The cut-off values for these biomarkers to be considered abnormal were > 348.48 for SII, > 183.78 for AISI, and > 0.768 for SIRI. The investigators concluded that SII, AISI, and SIRI are markers of inflammation in silica-exposed workers at risk of developing silicosis.[183]

293. In 2024, Spanish researchers assessed whether routine blood biomarkers, coupled with machine learning techniques, can differentiate between healthy individuals, subjects with Simple Silicosis and Progressive Massive Fibrosis. One hundred and seven men diagnosed with silicosis, ex-workers in the engineered stone (ES) sector, and 22 healthy male controls not exposed to ES dust were recruited. Twenty-one primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89% respectively. Angiotensin-converting enzyme (ACE), percentage of lymphocytes, and lactate dehydrogenase (LDH) indexes were revealed as blood biomarkers with significant cumulative importance for the machine learning models. Additionally, systemic immune-inflammatory index (SII) and neutrophil-lymphocyte ratio (NLR) were significantly different between healthy controls and patients with simple silicosis and between patients with simple silicosis and patients with progressive massive fibrosis. Table 3 from this study is reproduced below. The researchers concluded these biomarkers could detect chronic inflammatory status and serve as a tool for the diagnosis, monitoring, and early detection of silicosis progression.[184]

[183] Rezaei A, et al., "Systemic inflammation indices as hematological biomarkers of inflammatory response in non-silicotic workers exposed to respirable silica dust," *Toxicol. Lett.* 2024; 395:26-39.

[184] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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	HC	SS	PMF
ACE	43.13 ± 13.29[a]	70.08 ± 27.22[b]	76.43 ± 24.60[c]
Lymphocytes (%)	34.79 ± 6.58[a]	27.25 ± 7.94[b]	23.97 ± 7.40[c]
LDH	191.05 ± 47.29[a]	217.06 ± 55.73[b]	262.06 ± 67.77[c]
Basophils (%)	0.59 ± 0.68	0.62 ± 0.34	0.62 ± 0.31
Eosinophils (%)	3.10 ± 1.79	2.67 ± 1.48	2.70 ± 2.06
Platelets	228.67 ± 56.35	244.74 ± 58.76	244.10 ± 48.85
Monocytes (%)	8.34 ± 1.87[ab]	7.88 ± 2.38[a]	9.22 ± 2.37[b]
SII	355.13 ± 141.00[a]	629.75 ± 419.44[b]	762.88 ± 506.15[c]
NLR	1.56 ± 0.45[a]	2.57 ± 1.45[b]	3.08 ± 1.74[c]
Leukocytes	6.35 ± 1.42[ab]	6.87 ± 1.76[a]	6.55 ± 1.58[b]
ALP	68.68 ± 19.80	76.13 ± 17.70	75.66 ± 24.63

Abbreviations: ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; HC, healthy subjects; LDH, lactate dehydrogenase; PMF, pulmonary massive fibrosis; NLR, neutrophil/lymphocyte ratio; SII, systemic immune-inflammation index; SS, simple silicosis; TP, true positive.

294. In 2025, Chinese researchers published results of a case-control study in which they screened biomarkers for the diagnosis of silicosis. A total of 612 subjects (half cases, half controls) were randomly divided into training and test groups in a 2:1 ratio. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to construct a multiple biomarker-based model for the diagnosis of silicosis, which was applied to both the training and the testing data sets. The training cohort revealed significant differences in multiple hematologic parameters between silicosis patients and healthy individuals. Based on machine learning, 8 silicosis biomarkers were screened and identified from routine blood cell, biochemical and coagulation parameters. D-dimer (DD), Albumin/Globulin (A/G), lactate dehydrogenase (LDH) and white blood cells (WBC) were selected for constructing a logistic regression model for silicosis diagnostics. The model had a satisfactory performance in the training cohort with an area under the ROC curve (AUC) of 0.982, diagnostic sensitivity of 95.4%, and specificity of 92.2%. The model had a prediction accuracy of 0.936 with an AUC of 0.979 in the independent test cohort. Diagnostic accuracies of the logistic model in silicosis stages 1, 2, and 3 were 88.0, 95.4, and 94.3% with an AUC of 0.968, 0.983, and 0.990 for silicosis, respectively. The researchers concluded their model could be used to conduct large-scale screening of workers for silicosis because it is cheap, sensitive, and specific.[185]

[185] Sun G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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a. Basophils

295. Similar to but "[u]nlike mast cells, which mature and reside in tissues, basophils are released into circulation from the bone marrow (constituting 1% of leukocytes), only to infiltrate tissues under specific inflammatory conditions. Evidence is emerging that basophils mediate non-redundant roles in allergic disease and, unsuspectingly, are implicated in a variety of other pathologies [e.g., myocardial infarction, autoimmunity, chronic obstructive pulmonary disease, fibrosis, cancer, etc.]. Recent findings strengthen the notion that these cells mediate protection from parasitic infections, whereas related studies implicate basophils promoting wound healing. Central to these functions is the substantial evidence that human and mouse basophils are increasingly implicated as important sources of IL-4 and IL-13. Nonetheless, much remains unclear regarding the role of basophils in pathology vs. homeostasis. In this review, we discuss the dichotomous (protective and/or harmful) roles of basophils in a wide spectrum of non-allergic disorders."[186]

296. In 2024, Spanish researchers assessed whether routine blood biomarkers, coupled with machine learning techniques, can differentiate between healthy individuals, subjects with Simple Silicosis and Progressive Massive Fibrosis. 107 men diagnosed with silicosis, ex-workers in the engineered stone (ES) sector, and 22 healthy male controls not exposed to ES dust were recruited. Twenty-one primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Percent basophils was one of the biomarkers used in this study to build the machine learning models. Percent basophils was 0.59 ± 0.68 in healthy controls, but was increased in patients with simple silicosis (0.62 ± 0.34) and progressive massive fibrosis (0.62 ± 0.31). Based on this study, percent basophils appears to have some utility in diagnosis and screening of silicosis.[187]

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[186] Poto R, et al., "Basophils beyond allergic and parasitic diseases," *Front. Immunol.* 2023; 14:1190034.

[187] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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b. Eosinophils

297. In 1945, a tuberculosis researcher from West Virginia was perplexed with a series of patients with eosinophilia which could not be attributed to any hematopoietic or allergic diseases or parasitic infestations. Noting that the patients were predominantly coal miners, he conducted a diligent search of the literature that failed to reveal any mention of eosinophilia in coal miners or its association with silicosis. He therefore gathered data for male patients who had been admitted to the "sanitorium" in a recent two-year period and compared eosinophilia in 134 miners and 582 non-miners as controls. He found a 51.2 percent incidence of eosinophilia in coal miners with silicosis, compared to a 16.1 percent incidence in coal miners with tuberculosis and a 5.9 percent incidence in the control group. Based on these differences, he concluded that eosinophilia is frequent in patients with silicosis.[188]

298. In 1948, French researchers also reported eosinophilia in silicosis patients.[189]

299. In 1959, Romanian researchers from Bucharest studied 22 gold-miners for two years after they first began mining. Six men working in the dustiest part of the mine (8,000 to 45,000 particles/ml all sizes, in rock containing 72% free and combined silica) showed a progressive increase of blood silica, a decrease in erythrocytes, and an increase in eosinophils and monocytes. The changes observed were statistically significant only in those exposed to the highest concentrations of dust and occurred before abnormalities were detectable in the chest radiograph.[190]

300. In 1965, Egyptian researchers examined bone marrow specimens from 7 workers who had been exposed to dust of a calcareous sandstone consisting of 56.3% free silica. They observed generalized hyperplasia and high figures for the myeloid series, reticulum cells, and plasma cells along with a slight but definite increase of eosinophils. These changes were considered to be related to silicosis, because other diseases causing stimulation of the bone marrow had been adequately

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[188] Habeeb WJ, "Eosinophilia in Silicosis," *Am. Rev. Tuberculosis* 1945; 52(4):337-341.

[189] Martin E, et al., [Eosinophilia in silicosis], *Med. Usine Rev. Hyg. Ind. Mal. Prof.* 1948; 10(4):150-152.

[190] Velican C, et al, "Investigations Concerning the Pre-Radiological Stage of Silicosis," *Brit. J. Industr. Med.* 1959; 16:40-42.

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excluded. The findings correlated with the histopathological changes that are reported to occur in the lungs of silicotic patients, indicating a high degree of stimulation of the reticulo-endothelial system. The investigators concluded that if these changes were considered together with the industrial history and clinical and laboratory data, they may provide a clue to the diagnosis of silicosis and help in the differential diagnosis of other diffuse pulmonary lesions.[191]

301. In 2021, Ukrainian researchers compared blood counts in 25 workers who had pneumoconiosis and chronic obstructive pulmonary disease and 29 employees as controls. They found a 17.2% increase in eosinophil levels among the silicotic workers compared to the controls.[192]

302. In 2023, the same Ukrainian researchers published a study in which they examined the cellular immunity status of 99 patients with pneumoconiosis and COPD, 21 patients with pneumoconiosis, 515 patients with occupational COPD, and a control group of 212 healthy workers. The individuals with pneumoconiosis combined with COPD showed elevated levels of rod-nuclear leukocytes and eosinophils, along with an increased erythrocyte sedimentation rate, which the investigators concluded indicated activity of non-specific systemic inflammation.[193]

303. In 2023, Chinese researchers studied changes of complete blood cell count parameters in patients with occupational silicosis. A total of 354 silicosis patients were divided into stage I, stage II, and stage III groups according to stage of silicosis. Based on the course of the disease, they were divided into groups of ≤3, >3-≤6, >6-≤9 and >9-≤12 years. Peripheral blood of the patients was collected for complete blood cell count analysis, and the influencing factors of complete blood cell count were analyzed by multiple linear regression. Among other findings in this study, the percentage of eosinophils in patients at stage III was lower than those at stage I ($P < 0.05$).[194]

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[191] Warraki SE, et al., "Bone Marrow Changes in Silicosis," *Brit. J. Industr. Med.* 1965; 22:279-284.

[192] Rubtsov RV, "The Effect of the Comprehensive Treatment on Some Indicators of the Inflammatory Activity and Tentative Assessment of the Immune Status of Employees of the Ore Mining and Steel Industries Suffering from Pneumoconiosis in Combination with the Chronic Obstructive Pulmonary Disease," *Bull. Problems Biol. Med.* 2021; 195(1):116-120.

[193] Kovalchuk TA, et al., "Evaluating Cellular Immune Indicators' Significance in Mining and Metallurgical Industry Workers and Patients with Combined Pneumoconiosis and Chronic Obstructive Pulmonary Disease," *Ukrainian J. Occup. Health* 2023; 1993):181-188.

[194] Bai X, et al., "Study on changes in complete blood cell count parameters of patients with occupational silicosis," *China Occup. Med.* 2023; 50(5):546-550.

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304. In another study published in 2023, researchers from Beijing evaluated the correlation between peripheral blood eosinophil (EOS) levels and clinical characteristics of patients with pneumoconiosis complicated with chronic obstructive pulmonary disease (COPD). From January 2007 to November 2020, newly diagnosed patients with pneumoconiosis complicated with COPD in Beijing Chaoyang Hospital, were retrospectively studied. The patients were stratified into EOS <100 cells/μl group and EOS ≥100 cells/μl group. Demographic characteristics, clinical symptoms, lung function and laboratory indexes were compared between the two groups. The median EOS count of patients with pneumoconiosis complicated with COPD was 100 (40, 180) cells/μl. 50.2% (160/319) had blood eosinophil counts ≥100 cells/μl, and 11.0% (35/319) had blood eosinophil counts ≥300 cells/μl. In comparison with EOS<100 cells/μl group, EOS≥100 cells/μl group were older (P = 0.035), had higher body mass index (P = 0.008), had lower forced respiratory volume in the first second (P = 0.017), had a higher ratio of residual volume to total lung volume (P=0.010), and had lower diffusing capacity of the lung for carbon monoxide (P = 0.008). Arterial partial pressure of oxygen was significantly reduced in the EOS≥100 cells/μl group (P = 0.039). The peripheral blood EOS count was negatively correlated with forced vital capacity, forced breathing volume in one second, carbon monoxide diffusion, peak expiratory flow, and maximum mid expiratory flow as a percentage of expected values (r(s)=-0.22, -0.18, -0.19, -0.19, -0.19, P=0.000, 0.001, 0.003, 0.008, 0.002), and positively correlated with the ratio of residual air volume to total lung volume (r(s)=0.17, P = 0.002). The researchers concluded there was a correlation between blood EOS count and lung function.[195]

305. In 2023, researchers from India investigated the association between respiratory symptoms and eosinophil levels between 75 quarry workers exposed to quarry dust and 45 age, sex, body mass index-matched unexposed controls. The results of this study indicated that the quarry dust particles produced inflammatory responses, significantly increasing the mean eosinophil level (7.56 ± 2.94), causing allergic respiratory symptoms such as rhinitis , chest tightness, wheeze, and sputum production, impairing lung function with a decline in FEV1 (80.84 ± 108.8) level in workers

[195] Fan YL, et al. [Blood eosinophils and clinical features of pneumoconiosis complicated with chronic obstructive pulmonary disease: A cross-sectional study], *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2023; 41(8):605-611.

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exposed to quarry dust compared to controls. The investigators concluded that the presence of increased levels of respiratory irritants in quarry sites may explain the higher prevalence of respiratory infections and exacerbated inflammatory reactions found to ascertain the link between increased eosinophil count and lung function impairment in quarry workers.[196]

306. In 2024, Spanish researchers evaluated 21 markers derived from peripheral blood extraction among 107 former workers in the engineered stone sector and 22 healthy male controls not exposed to engineered stone dust. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, showing high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Percentage of eosinophils was one of the 11 biomarkers included in the analysis. Mean eosinophil percentage was 3.10 ± 1.79 in healthy controls, but was reduced in patients with simple silicosis (2.67 ± 1.48) and patients with progressive massive fibrosis (2.70 ± 2.06). The researchers concluded that the 11 biomarkers could detect chronic inflammatory status and be used for diagnosis, monitoring, and early detection of silicosis progression.[197]

307. These studies show that percentage of peripheral blood eosinophils may be used as one of several blood biomarkers in screening and monitoring workers exposed to crystalline silica dust for silicosis.

[196] Rajanayagam B, et al., "Deterioration of lung function and its association with eosinophil count," *Bioinformation* 2023, 19(5):644-648.

[197] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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c. Erythrocytes

308. The major function of erythrocytes (red blood cells) is respiratory gas exchange, but other functions including interaction with the immune system have been attributed to these cells.[198]

309. In 1959, Romanian researchers studied 22 gold-miners for two years after they first began mining. Six men working in the dustiest part of the mine (8,000 to 45,000 particles/ml in rock containing 72% silica) showed a progressive increase of blood silica, a decrease in erythrocytes, and increased eosinophils and monocytes. The changes were significant only in those exposed to the highest dust concentrations and occurred before abnormalities were detectable by chest radiograph.[199]

310. In 1992, a Russian researcher investigated the effect of silica on erythrocytes and neutrophils in 140 coal miners who were divided into 4 groups for study: (1) 25 healthy, newly employed workers examined at a mine health center; (2) 21 patients with anthracosilicosis; (3) 36 with X-ray confirmed anthracosilicosis; (4) 58 facing the first stage of anthracosilicosis. Erythrocyte histidine and catecholamine levels, myeloperoxidase and beta-glucuronidase activities, data of lysosomal cation (LC) and NBT tests in neutrophils were evaluated. Miners in groups 2, 3, 4 showed increased beta-glucuronidase activity (by 47-73%) and NBT test values (37-96%), lowered levels of catecholamines (57-67%), histidine (48-60%), results of LC-test (29-32%) and myeloperoxidase activity (21-31%) in comparison with normal subjects. The author concluded his findings will help diagnose latent forms of anthracosilicosis before structural changes can be detected by X-ray.[200]

311. In 1999, Italian researchers investigated the interaction of aerosol particles with human erythrocytes by electron microscopy, with hemolysis and radio wave dielectric spectroscopy to elucidate the extent of morphological and functional modification induced by aerosol surface. Scanning electron microscopy and freeze-fracturing techniques were used to follow morphological and ultrastructural modifications and hemolysis tests and radio wave dielectric spectroscopy to monitor membrane damage. All results showed an effect depending on silica concentration and

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[198] Morera D, et al., "Is there a direct role for erythrocytes in the immune response?" *Vet. Res.* 2011; 42:89.

[199] Velican C, et al, "Investigations Concerning the Pre-Radiological Stage of Silicosis," *Brit. J. Ind. Med.* 1959; 16:40-42.

[200] Bazeliuk LT, [Cytochemical research on the peripheral blood erythrocytes and neutrophils of coal miners], *Gig. Tr. Prof. Zabol.* 1992; 5:31-33 [article in Russian]

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incubation time. The process is time-limited and reached saturation after 20 minutes. Limited damage was observed, especially when little aerosol surface per cell was available; strong membrane damage was obtained when aerosol surface was considerable. Due to the high surface/volume of the aerosol particles, considerable membrane damage with small weight concentrations was obtained.[201]

312. In 2007, an Egyptian researcher investigated plasma malondialdehyde (MDA) level, erythrocyte reduced glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (Gpx) activity levels as an index of antioxidant status in silicotic patients. The workers were divided into 3 groups according to intensity of exposure. Significant decreases of erythrocyte GSH, GPx and SOD were found, and a significant increase in MDA level was found in comparison with the controls. A functional disturbance in RBC membrane was shown by alteration in hemorheological and dielectric properties. The researchers concluded that the techniques were reliable, rapid and sensitive for detecting damage to erythrocytes and for use as biomarkers of silica exposure.[202]

313. In 2023, Chinese researchers assessed complete blood cell count parameter changes in 354 patients with occupational silicosis. The patients were divided into stage I, stage II and stage III groups according to stage of silicosis and, based on the course of disease, into groups of ≤3, >3-≤6, >6-≤9 and >9-≤12 years. Peripheral blood was collected for complete blood cell count analysis, and influencing factors of complete blood cell count were analyzed by multiple linear regression. Hemoglobin and average red blood cell hemoglobin levels in silicosis patients at stage II and III were lower than those at stage I (all $P<0.05$). Red blood cell count in the courses of silicosis >6-≤9 years group was lower, compared to courses of silicosis ≤3 years and >3-≤6 years groups. Mean corpuscular volume of the courses of silicosis >6-≤9 years group increased compared with the courses of silicosis ≤3 years group. Multiple linear regression showed that silicosis stage and course of silicosis were influencing factors of erythrocyte count, while gender and age of first dust-exposure were influencing factors of hemoglobin level ($P<0.05$).[203]

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[201] Diociaiuti M, et al., "Morphological and Functional Alterations of Human Erythrocytes Induced by SiO_2 Particles: An Electron Microscopy and dielectric Spectroscopy Study," *Environ. Res. Section A* 1999; 80:197-207.

[202] Ali MA, "Erythrocytes of Silicotic Patients," *Romanian J. Biophys.* 2007; 17(4):225-236.

[203] Bai X, et al., "Study on changes in complete blood cell count parameters of patients with occupational silicosis," *China Occup. Med.* 2023; 50(5):546-550 [in Chinese with English abstract].

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314. In 2023, Japanese researchers assessed the feasibility of constructing a screening system for proinflammatory potential prediction of silica particles based on erythrocyte hemolytic activity. They evaluated lysosomal membrane damage using the erythrocyte hemolysis assay, which was performed on silica particles of different sizes, crystallinity, and surface functional groups using erythrocytes from a healthy volunteer. Hemolytic activity of other elemental particles was compared with that of the silica particles and 27 types of commercially available crystalline silica products underwent screening trials. Hemolytic activity of silica particles was higher in the crystalline than the amorphous form and increased with decreasing size. The hemolytic reaction was particular to silica particles and rarely occurred in particles of other elements. The hemolytic activity was significantly suppressed if the surface of the silica particles was modified with metal ions (Fe3+, Al3+). Hemolytic activities of the crystalline silica products used industrially significantly differed. The researchers concluded that their study revealed that particle properties affect the hemolytic activity of silica particles. Particularly, the surface functional groups (silanol groups) that are unique to silica particles were founded to be strongly involved in hemolytic activities.[204]

315. In 2023, Serbian researchers published a study in which they sought to investigate inflammatory, hematological, and biochemical parameters as biomarkers for diagnosing and monitoring silicosis. They enrolled 14 workers with silicosis and 7 healthy controls (without exposure and silicosis). Serum levels of prostaglandin E2, C-reactive protein, fibrinogen, biochemical, and hematological parameters were measured. The receiver operating characteristic curve was used to determine diagnostic sensitivity of each biomarker. The silicosis patients had a significantly higher level of prostaglandin E2, erythrocyte, hemoglobin, and hematocrit than patients without silicosis. Prostaglandin E2, hemoglobin, and the erythrocyte count were significant in distinguishing silicosis cases from healthy controls. The investigators concluded that Prostaglandin E2 might be an adjuvant peripheral diagnostic biomarker of silicosis, while hematological parameters (erythrocytes, hemoglobin, and hematocrit) might be prognostic biomarkers.[205]

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[204] Amamoto T, et al., "Investigating erythrocyte hemolysis assay use for proinflammatory potential prediction of silica particles,"*Sangyo Eiseigaku Zasshi* 2023; 65:125-133.

[205] Milovanović APS, et al., "Serum Concentration of Prostaglandin E2 as a Diagnostic Biomarker in Patients With Silicosis: A Case-Control Study," *J. Occup. Environ. Med.* 2023; 65(7):546-552.

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d. Lymphocytes

316. In a study by French researchers of 58 silicosis patients, a highly significant decrease of total lymphocyte count ($P<0.001$) was found in silicotic patients compared to healthy controls.[206]

317. In a study by Chinese researchers of 354 silicosis patients, percentage of lymphocytes was significantly decreased in patients of 6-9 and 9-12 years, compared to patients of <3 and 3-6 years.[207] This study showed that the percentage of lymphocytes decreases with the course of disease.

318. In another Chinese investigators evaluated blood parameters and inflammatory markers in 148 male patients diagnosed with silicosis and 120 age and sex matched volunteers without allergic or renal disease, who were engaged in dust-related work. The patients diagnosed with silicosis were divided into three groups based on stage (severity) of disease. Percentage lymphocytes decreased monotonically with severity of disease: 33.86 ± 3.55 in healthy controls; 27.46 ± 9.38 in Stage I Silicosis; 22.51 ± 7.51 in Stage II Silicosis, and 21.78 ± 9.48 in Stage III Silicosis. A similar pattern emerged for lymphocyte counts. The decreasing trend for lymphocyte percentage and lymphocyte count were both highly significant ($P < 0.0001$).[208]

319. In a cross-sectional study, Brazilian researchers evaluated the association of inflammatory markers with the presence of silicosis and lung function impairment in individuals exposed to silica. Among 297 white men evaluated, 51 were unexposed hospital controls (G1), 149 were exposed to silica without silicosis (G2), and 97 were exposed to silica with silicosis (G3). Lymphocytes decreased as exposure to silica increased: Unexposed controls: 2048 (1632-2328); Exposed individuals without silicosis: 1950 (1656-2371); Individuals with Silicosis: 1647 (1339 - 1965). The trend was highly significant (p <0.001). The evaluation of hematological markers showed lower lymphocyte counts in individuals with silicosis than in unexposed and exposed

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[206] Subra JF, et al., "Lymphopenia in occupational pulmonary silicosis with or without autoimmune disease," *Clin. Exper. Immunol.* 2001; 126:540-544.

[207] Bai X, et al., "Study on changes in complete blood cell count parameters of patients with occupational silicosis," *China Occup. Med.* 2023; 50(5):546-550.

[208] He G, et al., "Modified Glasgow Prognostic Score, and Neutrophil/lymphocyte and Platelet/lymphocyte Ratios in Different Stages of Silicosis," *Biomed. Environ. Sci.* 2019; 32(5):376-379.

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individuals without silicosis, with no differences in neutrophil or platelet counts, similar to the He study. The investigators concluded that the data from their study suggest that the analysis of hematological markers, which are easy and cost effective to perform, and inflammatory markers can be employed to monitor workers exposed to silica to identify the disease in its subclinical phase and monitor its clinical evolution, thus contributing to reducing the morbidity and mortality rates of silicosis.[209]

320. In a study by Spanish researchers of 107 former workers in the engineered stone sector and 22 healthy male controls not exposed to engineered stone dust, 21 primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Percentage of lymphocytes, angiotensin-converting enzyme, and lactate dehydrogenase indexes were revealed as blood biomarkers with significant cumulative importance for the machine learning models. The researchers concluded these biomarkers could detect chronic inflammatory status and serve as a tool for the diagnosis, monitoring, and early detection of silicosis progression.[210]

321. In a study by Chinese researchers, 306 silicosis patients and 306 normal participants were included in a training cohort. Whole blood samples were collected from all participants and hematological characteristics were determined. In the training cohort, 14 hematological indicators, including white blood cell count, were significantly different in silicosis patients.[211]

322. These studies show that lymphocytes, especially percentage of lymphocytes, can be utilized in the diagnosis of silicosis, but most especially in evaluating progression of the disease.

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[209] Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ind. Med.* 2023; 66(11):984-995.

[210] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

[211] Sun G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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e. Neutrophil-Lymphocyte Ratio

323. "The neutrophil-to-lymphocyte ratio (NLR), calculated as a simple ratio between the neutrophil and lymphocyte counts measured in peripheral blood, is a biomarker which conjugates two faces of the immune system: the innate immune response, mainly due to neutrophils, and adaptive immunity, supported by lymphocytes."[212]

324. "Neutrophils serve as precursors to the innate immune response, engaging in phagocytosis and releasing cytokines and mediators.[213] "They act as the main effectors in the early hyperdynamic phase of infection and contribute to adaptive immunity regulation."[214]

325. "Neutrophilia during systemic inflammation occurs due to neutrophil demargination, suppressed neutrophil apoptosis, and stem cell stimulation through growth factors such as G-CSF [Growth-Colony Stimulating Factor]. Endocrine stress responses marked by elevated serum cortisol and catecholamines, or triggered by sympathetic activation, can also raise neutrophil count."[215]

326. "Lymphocytopenia, a notable decrease in circulating lymphocyte count, is described after ... systemic inflammation.... The mechanisms responsible for lymphopenia ... involve margination and redistribution of lymphocytes within the lymphatic system, along with increased apoptosis .... Moreover, factors such as ischemia-reperfusion injury ... and upregulated pro-inflammatory cytokines ... contribute to lymphocytopenia."[216]

327. "Simultaneous yet opposite changes in neutrophil and lymphocyte counts reflect a multifactorial dynamic response, influenced by immunologic, neuroendocrine, humoral, and biological factors . . . . In addition, the early change (<6 h) in neutrophil and lymphocyte counts

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[212] Buonacera A, et al., "Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases," *Int. J. Mol. Sci.* 2022; 23:3636, citing Song M, et al., "Neutrophil-to-lymphocyte ratio and mortality in the United States general population," *Sci. Rep.* 2021; 11:464.

[213] Islam MM, et al., "Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index, and delta neutrophil index: An extensive literature review," *Turk. J. Emerg. Med.* 2024; 24:8-19, citing Mortaz E, et al., "Update on neutrophil function in severe inflammation," *Front. Immunol.* 2018; 9:2171.

[214] *Id.,* citing Li Y, et al., "The regulatory roles of neutrophils in adaptive immunity," *Cell. Commun. Signal.* 2019; 17:147.

[215] *Id.*

[216] *Id.*

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following acute physiological stress endows them as earlier markers compared to other laboratory parameters (e.g., white blood cell count and C-reactive protein [CRP]."[217]

328. "[I]t has been reported that the NLR is more reliable in predicting patient survival compared to neutrophil or lymphocyte counts alone."[218]

329. In a nationally representative sample of 9,427 American adults, the average NLR was 2.15. However, Hispanic participants had a significantly lower mean NLR 2.08 and Blacks had an even lower mean NLR of 1.76.[219]

330. In 2016, Turkish researchers sought to determine associations between laboratory parameters and silicosis. From 2010 to 2015 they collected demographic, laboratory, radiographic and lung function data for 330 silicosis cases and 229 controls from the same workplaces. The laboratory data included mean corpuscular volume, mean platelet volume, procalcitonin, neutrophil-lymphocyte ratio (NLR), ferritin, thyroxine (T4), and thyroid-stimulating hormone (TSH). Statistically significant differences were found for all laboratory parameters except MCV, which was of borderline significance. NLR, ferritin, and T4 levels were higher among the silicosis patients than the controls, while MPV and TSH levels were lower in the silicosis patients than the controls. Statistical significance was also seen in multivariate analysis for NLR and T4. The investigators commented that to the best of their knowledge, this was the first clinical study that demonstrated high levels of NLR in silicosis.[220]

331. In 2018, Romanian researchers conducted a retrospective study of silicosis cases from an occupational disease hospital. In total, 32 patients, 20 women and 12 men, were included in the analysis. Current data and data from 5 years before were recorded: demographics, initial diagnosis and silicosis stage, comorbidities, smoking habit, lung function, exposure and retention time and

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[217] *Id.*

[218] *Id.*, citing Menges T, et al., "Changes in blood lymphocyte populations after multiple trauma: Association with posttraumatic complications," *Crit. Care Med.* 1999; 27:733-740 and Kumarasamy C, et al., "Prognostic significance of blood inflammatory biomarkers NLR, PLR, and LMR in cancer - A Protocol for systematic review and meta-analysis," *Medicine (Baltimore)* 2019; 98: 3 14834.

[219] Azab B, et al., "Average Values and Racial Differences of Neutrophil Lymphocyte Ratio among a Nationally Representative Same of United States Subjects," *PLoS One* 2014; 9(11): e112361.

[220] Gunduzoz M, et al., "Elevated neutrophil lymphocyte ratio and T4 levels can be predisposing factors for silicosis," *Eur. Respir. J.* 2016; 48(suppl 60): PA4282.

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NLR. Patients were divided into 2 groups according to differences in radiological classification: group 1 included patients who presented with a more advanced stage of silicosis after 5 years of evolution; group 2 included those with no detectable signs of progression. (apparently stable disease). NLR of subjects in Group 1 was 2.9376 (mean) and 2.2565 (median), while NLR of subjects in Group 2 was 1.9203 (mean) and 1.6955 (median). All patients in Group 1 had a NLR above the average value reported for silicosis and 4 patients had NLR above the upper limit. They all progressed from stage I to stage I/II during the study period. In Group 2, 45.5% of the patients had a NLR higher than the average and 13.6% had a NLR above the upper normal limit. The median NLR in group 1 was 2.94 (IQR=0.89) and in group 2 it was 1.7 (IQR=0.84). A significantly higher mean NLR value was noted in the group presenting a progression of the radiological pattern after 5 years of follow-up (p=0.016, U=51, r=0.424). The investigators concluded that their results support the hypothesis that NLR might represent a predictive biomarker for silicosis progression.[221]

332. In 2019, Turkish researchers investigated the relationship between Neutrophil-lymphocyte ratio and Platelet-lymphocyte ratio with silicosis. They retrospectively analyzed the demographic and laboratory data of ceramic workers referred to their hospital between 2010 and 2018. A total of 573 patients with silicosis and 222 ceramic workers without silicosis were included in the study. The radiographic ILO classification of silicosis patients was: category 1 (71.5%), category 2 (19.2%), category 3 (7.5%). NLR and PLR in categories 2 and 3 were significantly higher when compared with the control group ($P < .005$). FEV , FEV %, FVC, FVC % and PEF were significantly lower in all silicosis patients and also in patients with subcategories (all $P < 0.005$). NLR and PLR showed significant negative correlations with FEV, FVC and PEF (all $P < 0.005$). The investigators concluded that NLR and PLR are significantly correlated with pulmonary function and severity of silicosis, especially in late radiographic profusion categories of disease.[222]

333. In 2019, Chinese researchers evaluated neutrophil-lymphocyte ratio and other biochemical and functional indicators of inflammation in 48 subjects with Stage I silicosis, 46

[221] Oţelea MR, et al., "The significance of the neutrophil to lymphocyte ratio in silicosis," *J. Contemporary Clin. Pract.* 2018; 4(2):53-58.

[222] Karatas M, et al. "Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as haematological indices of inflammatory response in ceramic workers' silicosis," *Clin. Respir. J.* 2019; 13(3):159-165.

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subjects with Stage II silicosis, 54 subjects with Stage III silicosis, and a control group of 120 age and sex matched volunteers without allergic disease or renal disease who were engaged in dust-related work. The results showed a monotonic increase in mean NLR with increasing severity of disease: 1.65 in healthy controls, 3.51 in Stage I silicosis, 4.10 in Stage II silicosis, and 4.91 in Stage 3 Silicosis. The difference in mean NLR among the groups was highly statistically significant (*P* value = 0.006). The researchers also observed increased platelet-lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS) with increasing severity of disease. ROC curves proved that NLR and PLR have certain value in assessing the severity of silicosis, but NLR was more sensitive than PLR for assessing disease activity. The investigators noted that in clinical practice, the detection of inflammation indicators is cumbersome and costly and single white blood cell indicators are sensitive to dehydration/hydration, dilution of blood samples and the impact of factors such as blood sample processing, and reasoned that NLR and PLR as a combination of other inflammatory indicators provided more stability for disease assessment. They concluded that NLR, PLR and mGPS can be used as indicators of inflammatory status and severity to evaluate the clinical prognosis of patients with silicosis and that MLR is more sensitive to assessing disease activity than PLR.[223]

334. In 2021, Turkish researchers retrospectively evaluated the frequency of hilar lymphadenopathy (HL) and both neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) in 76 male patients diagnosed with pneumoconiosis over a 5 year period. They determined the rate of HL as 29.3%. As the ILO (International Labor Organization) category rose, they observed an increase in the number of patients with HL. They found a statistically significant increase in NLR and TLR values in patients with HL compared to those without HL (2.38 ± 0.70; 1.97 ± 0.59 (p=0.016) and 133.79 ± 39,06; 109.03 ± 29.00 (p=0.005)). Another finding was that the albumin values of patients with HL were significantly lower (4.42 ± 0.41; 4.67 ± 0.29 p = 0.008). The investigators concluded that 29.3% of patients had HL and that NLR, TLV and albumin levels may have prognostic value in pneumoconiosis patients with lymphadenopathy.[224]

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[223] He LG, et al., "Modified Glasgow Prognostic Score, and Neutrophil/lymphocyte and Platelet/ lymphocyte Ratios in Different Stages of Silicosis," *Biomed. Environ. Sci.* 2019; 32(5):376-379.

[224] Hasanli YS, et al., "The Prevalence of Hilar Lymphadenopathy and Related Factors in Pneumoconiosis Patients of a University Hospital Occupational Diseases Polyclinic," *Acta Med.* 2021; 52(4):289-295.

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335. In 2022, Spanish researchers investigated circulating biomarker levels and systemic inflammatory indices in engineered stone silicosis patients whose exposure to engineered stone (ES) dust ended several years ago. Ninety-one adult men, ex-workers in the manufacturing of ES, 53 diagnosed with Simple Silicosis (SS) and 38 with Progressive Massive Fibrosis (PMF), and 22 healthy male volunteers (HC) as controls not exposed to ES dust, were recruited. Several systemic inflammation indices, including neutrophil-to-lymphocyte ratio (NLR), derived from whole blood cell counts, showed significant differences between the HC, SS and PMF groups. NLR values increased with disease severity: HC 16 ± 0.5, SS 2.4 ± 1, PMF 2.7 ± 1.5 ($p < 0.0001$). All these biomarkers were analyzed using receiver operating characteristic (ROC) curves; results provided moderately high sensitivity and specificity for discriminating between ES silicosis patients and controls. The researchers concluded that their study showed that some biomarkers, available from routine blood analysis, are present in ES silicosis patients even several years after cessation of exposure to ES silica dust and could be useful in assessing progression of disease in such workers.[225]

336. In 2023, Italian researchers evaluated inflammatory markers with silicosis and lung function impairment in individuals exposed to silica. Individuals exposed and not exposed to silica were assessed by occupational history, clinical findings, lung function, chest imaging findings, and inflammatory markers. Among 297 men evaluated, 51 were unexposed controls (G1), 149 were exposed to silica without silicosis (G2), and 97 were exposed to silica with silicosis (G3). Inflammatory marker levels were higher in G3 than in G2 and G1. Neutrophil/lymphocyte ratio (NLR), was negatively associated with lung function. The researchers investigators concluded that blood inflammatory markers are associated with silicosis and impaired lung function.[226]

337. In 2024, Spanish researchers evaluated 21 markers derived from peripheral blood among 107 former workers in the engineered stone sector and 22 healthy male controls not exposed to engineered stone dust. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, showing high performance with

[225] García-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

[226] Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ined. Med.* 2023; 66(11):984-995.

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sensitivities and specificities in the best case greater than 82% and 89%, respectively. Mean NLR values increased with increasing severity of disease: HC 1.56 ± 0.45, SS 2.57 ± 1.45, PMF 3.08 ± 1.74 ($p < 0.05$). The researchers concluded that the biomarkers could detect chronic inflammatory status and be used for diagnosis, monitoring, and early detection of silicosis progression.[227]

338. In 2024, Spanish researchers evaluated inflammatory markers in engineered stone patients with simple silicosis and progressive massive fibrosis. In addition to inflammatory markers, NLR was significantly elevated in both of the silicosis groups compared to healthy controls.[228]

339. In 2024, Chinese researchers conducted a case-control study of 177 silicosis patients at an occupational disease institute in Hunan. The patients, all coal mine workers over age 75, were into three groups based on stage of disease. The control group included 100 age and sex-matched volunteers without comorbidities who worked in dust-related occupations. The major purpose of the study was to evaluate the Prognostic Nutritional Index (PNI) in the silicosis patients. However, the investigators also evaluated the NLR in the patients. Mean NLR values significantly increased with increasing severity of disease: Healthy controls: 1.65 ± 0.17; Silicosis group I: 3.51 ± 1.03; Silicosis group II: 4.10 ± 2.01; Silicosis group III: 4.91 ± 2.64. The multivariate regression model showed that the increase in NLR was an independent risk factor for silicosis. The researchers concluded that nutritional status may be related to silicosis and that their machine learning model suggests PNI combined with other clinical indicators is a better model for predicting silicosis risk.[229]

340. Collectively, the studies show that NLR is a useful biomarker for diagnosing and assessing silicosis progression in stone countertop fabricators and other artificial stone workers.

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[227] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

[228] Jiménez-Gómez G, et al., "Analysis of Immune Cell Subsets in Peripheral Blood from Patients with Engineered Stone Silica-induced Lung Inflammation," *Int. J. Mol. Sci.* 2024; 25:5722.

[229] He LG, et al., "Prognostic Nutritional Index Associates with the Severity of Silicosis: A Study from a Tertiary Class A Prevention and Treatment Institute for Occupational Diseases in China," *Biomed. Environ. Sci.* 2024; 37(1):122-126.

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f. Platelet-Lymphocyte Ratio

341. "Both thrombocytosis and lymphocytopenia are linked to the extent of systemic inflammation, while the ratio of the platelet to lymphocyte count introduces a fresh marker that integrates both hematologic parameters."[230]

342. "Especially in conditions that are potent triggers of systemic inflammatory response . . . , platelet proliferation is induced by pro-inflammatory cytokines . . . . Thrombocytosis is linked to heightened inflammatory responses due to alterations in the body's microcirculation, augmented blood vessel permeability, platelet activation, and aggregation of a substantial number of platelets. Consequently, this exacerbates the overall inflammatory reaction with the body. . . ."[231]

343. PLR is closely associated with systemic inflammation and is a promising biomarker not only in rheumatologic diseases but also in . . . various respiratory diseases."[232]

344. In 2019, Turkish researchers investigated the relationship between the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with silicosis. They retrospectively analyzed the demographic and laboratory data of ceramic workers who were referred to their hospital between 2010 and 2018. A total of 573 patients with silicosis and 222 ceramic workers without silicosis were included in the study. The radiographic ILO classification of silicosis patients was: category 1 (71.5%), category 2 (19.2%), category 3 (7.5%). NLR and PLR in categories 2 and 3 were significantly higher when compared with the control group ($P < .005$). FEV , FEV %, FVC, FVC % and PEF were significantly lower in all silicosis patients and also in patients with subcategories (all $P < 0.005$). NLR and PLR showed significant negative correlations with FEV, FVC and PEF (all

[230] Islam MM, et al., "Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflamation response index, and delta neutrophil index: An extensive literature review," *Turk. J. Emerg. Med.* 2024; 24:8-19.

[231] Islam MM, et al., "Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflamation response index, and delta neutrophil index: An extensive literature review," *Turk. J. Emerg. Med.* 2024; 24:8-19.

[232] Islam MM, et al., "Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflamation response index, and delta neutrophil index: An extensive literature review," *Turk. J. Emerg. Med.* 2024; 24:8-19.

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P< 0.005). The researchers concluded that NLR and PLR are significantly correlated with pulmonary function and severity of silicosis, especially in late radiographic profusion categories of disease.[233]

345. In 2019, Chinese researchers evaluated the platelet-lymphocyte ratio and other biochemical and functional indicators of inflammation in 48 subjects with Stage I silicosis, 46 subjects with Stage II silicosis, 54 subjects with Stage III silicosis, and a control group of 120 age and sex matched volunteers without allergic disease or renal disease who were engaged in dust-related work. The results showed an increase in mean PLR with increasing severity of disease: 114.89 in healthy controls, 144.28 in Stage I silicosis, 180.72 in Stage II silicosis, and 204.64 in Stage 3 Silicosis. The difference in mean PLR among the groups was highly significant (*P* value = 0.001). ROC curves showed that NLR and PLR have certain value in assessing the severity of silicosis. The researchers observed that in clinical practice, the detection of inflammation indicators is cumbersome and costly and single white blood cell indicators are sensitive to dehydration/hydration, dilution of blood samples and the impact of factors such as blood sample processing, and reasoned that NLR and PLR as a combination of other inflammatory indicators provided more stability for disease assessment. They concluded that NLR, PLR and mGPS can be used as indicators of inflammatory status to evaluate the clinical prognosis of silicosis patients.[234]

346. In 2021, Turkish researchers retrospectively evaluated the frequency of hilar lymphadenopathy (HL) and both neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) in 76 male patients diagnosed with pneumoconiosis over a 5 year period. They determined the rate of HL as 29.3%. As the ILO (International Labor Organization) category rose, they observed an increase in the number of patients with HL. They found a statistically significant increase in NLR and TLR values in patients with HL compared to those without HL (2.38 ± 0.70; 1.97 ± 0.59 (p=0.016) and 133.79 ± 39,06; 109.03 ± 29.00 (p=0.005)). Another finding was that the albumin values of patients with HL were significantly lower (4.42 ± 0.41; 4.67 ± 0.29 p = 0.008).

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[233] Karatas M, et al. "Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as haematological indices of inflammatory response in ceramic workers' silicosis," *Clin. Respir. J.* 2019; 13(3):159-165.

[234] He LG, et al., "Modified Glasgow Prognostic Score, and Neutrophil/lymphocyte and Platelet/lymphocyte Ratios in Different Stages of Silicosis," *Biomed. Environ. Sci.* 2019; 32(5):376-379.

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The investigators concluded that 29.3% of patients had HL and that NLR, TLV and albumin levels may have prognostic value in pneumoconiosis patients with lymphadenopathy.[235]

347. In 2022, Spanish researchers investigated circulating biomarker levels and systemic inflammatory indices in engineered stone silicosis patients whose exposure to engineered stone (ES) dust ended several years ago. Ninety-one adult men, ex-workers in the manufacturing of ES, 53 diagnosed with Simple Silicosis (SS) and 38 with Progressive Massive Fibrosis (PMF), and 22 healthy male volunteers (HC) as controls not exposed to ES dust, were recruited. Several systemic inflammation indices, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), and aggregate index of systemic inflammation (AISI) derived from whole blood cell counts, showed significant differences between the HC, SS and PMF groups. NLR values increased with disease severity: HC 16 ± 0.5, SS 2.4 ± 1, PMF 2.7 ± 1.5 ($p < 0.0001$). All these biomarkers were analyzed using receiver operating characteristic (ROC) curves; results provided moderately high sensitivity and specificity for discriminating between ES silicosis patients and controls. The researchers concluded that their study showed that some biomarkers, available from routine blood analysis, are present in ES silicosis patients even several years after cessation of exposure to ES silica dust and could be useful in assessing progression of disease in such workers.[236]

348. In 2023, Italian researchers evaluated inflammatory markers with silicosis and lung function impairment in individuals exposed to silica. Individuals exposed and not exposed to silica were assessed by occupational history, clinical findings, lung function, chest imaging findings, and inflammatory markers. Among 297 men evaluated, 51 were unexposed controls (G1), 149 were exposed to silica without silicosis (G2), and 97 were exposed to silica with silicosis (G3). Inflammatory marker levels were higher in G3 than in G2 and G1. The platelet-lymphocyte ratio (PLR), increased with disease severity: 113.5 in unexposed workers, 115.9 in exposed workers without silicosis, and 142.3 in silicotic workers. The trend was highly significant ($P < 0.001$). The

[235] Hasanli YS, et al., "The Prevalence of Hilar Lymphadenopathy and Related Factors in Pneumoconiosis Patients of a University Hospital Occupational Diseases Polyclinic," *Acta Med.* 2021; 52(4):289-295.

[236] García-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

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researchers concluded that PLR and other biological markers could help to distinguish between exposed workers with and without silicosis, despite the moderate accuracy observed. [237]

349. In 2024, Spanish researchers evaluated 21 markers derived from peripheral blood extraction among 107 former workers in the engineered stone sector and 22 healthy male controls not exposed to engineered stone dust. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, showing high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. PLR was not one of the 11 biomarkers according to the Relief-F algorithm.[238]

350. In 2024, Chinese researchers conducted a case-control study of 177 silicosis patients at an occupational disease institute in Hunan. The patients, all coal mine workers over age 75, were into three groups based on stage of disease. The control group included 100 age and sex-matched volunteers without comorbidities who worked in dust-related occupations. The major purpose of the study was to evaluate the Prognostic Nutritional Index (PNI) in the silicosis patients. However, the investigators also evaluated the PLR in the patients. Mean PLR values significantly increased with increasing severity of disease: Healthy controls: 114 ± 44.68; Silicosis group I: 144.28 ± 68.88; Silicosis group II: 180.72 ± 71.35; Silicosis group III: 204.64 ± 61.01. The researchers concluded that nutritional status may be related to silicosis and that their machine learning model suggests PNI combined with other clinical indicators is a better model for predicting silicosis risk.[239]

351. These studies show that the Platelet-Lymphocyte Ratio is an earlier marker of silicosis and a marker of silicosis disease progression. It therefore has utility in monitoring stone countertop fabricators and other workers exposed to artificial stone dust for early diagnosis of silicosis and for progression of disease.

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[237] Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ined. Med.* 2023; 66(11):984-995.

[238] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

[239] He LG, et al., "Prognostic Nutritional Index Associates with the Severity of Silicosis: A Study from a Tertiary Class A Prevention and Treatment Institute for Occupational Diseases in China," *Biomed. Environ. Sci.* 2024; 37(1):122-126.

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2. Biochemical Blood Biomarkers

a. Albumin-Globulin Ratio

352. A low albumin-globulin ratio was first reported in silicosis patients in the 1950s and 1960s.

353. In 1953, Italian researchers compared the albumin-globulin ratio of 15 patients with simple silicosis with that of 5 normal subjects. They found that the albumin-globulin ratio in 13 of the 15 silicosis patients was well below normal (1.45), the lowest being 0.78 and the highest 1.06.[240]

354. In 1957, Italian researchers noted a reduced albumin-globulin ratio in 4 of 5 silicosis patients.[241]

355. In 1961, more researchers reported a decreased albumin-globulin ratio in silicosis patients.[242]

356. In 1969, researchers determined serum proteins by electrophoresis in 118 subjects (60 copper miners with silicosis, 12 minors without clinical or radiological evidence of silicosis, and 46 healthy workers employed in other jobs). They found that the albumin-globulin ratio was considerably reduced in workers with radiographic evidence of silicosis. They regarded the dyslipoproteinemia in the silicosis patients as an expression of metabolic changes in the silicotic process and the increase of serum γ-globulins as evidence of intense immunobiological activity, lending support to the theory of immune reaction to account for the development of silicosis. The researchers opined that the serum electrophoresis tests that they conducted could be used as complementary tests for the detection of a predisposition to silicosis and to detect the disease at an early pre-radiological stage.[243]

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[240] Sartorelli E, et al. [Time of Solution of Blood Clot (Fibrinolysis) in Silicosis] *Med. Lav.* 1953; 44(5):218-224.

[241] Rizzatti EM, et al. [Coagulation of the Blood in Silicosis], *Acta Med. Legalis Socialis* 1957; 10(3):327-346.

[242] Daniello L, et al., "Complex Dyhsproteinaemia Tests in Silicosis," *Rumanian Med. Rev.* 1961; 5(1):129-131.

[243] Szabó S, et al., "Investigations concerning the immunity and blood proteins in silicosis: III. The serum proteins, glycoproteins, lipoproteins and the cryoagglutinins in silicosis," *Arch. Roumaines Path. Exper. Microbiol.* 1969; 28(1):109-118.

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357. Contemporaneously, reduction of the albumin-globulin ratio was confirmed in animals.

358. In 1961, a Japanese researcher exposed rats and mice to silica dust 5 hours per day for 200-400 hours and did blood chemistry evaluations for one year. He reported a decrease of albumin content and albumin-globulin ratio and an increase of γ-globulin content in the exposed rodents.[244]

359. In 1963, French researchers repeatedly injected rabbits intravenously with 100 mg silica. Electrophoresis studies showed that the albumin/globulin ratio was decreased due to an increase of globulins.[245]

360. No studies regarding reduction of the albumin-globulin ratio appear to have been published over the next 40 years.

361. In 2009, Chinese researchers evaluated the feasibility of using pulmonary function tests and blood biochemical markers in monitoring coal dust-induced early lung damage and status of coal worker's pneumoconiosis (CWP). They evaluated 45 coal workers with CWP, 64 coal workers without active CWP (including a high exposure group of 34 tunneling workers, a moderate exposure group of 13 coal hewers), and a control group of 17 workers with minimal exposure to coal dust. Pulmonary function, routine blood biochemical parameters and 4 biomarkers were evaluated. Compared to coal workers without CWP, the CWP patients of all stages had lower pulmonary function, lower albumin levels and higher globulin levels. The researchers concluded that pulmonary function and globulin levels may be used as biomarkers to monitor coal dust-induced early lung damage and progression of CWP.[246]

362. In 2025, Chinese researchers conducted a case-control study to screen biomarkers from routine blood parameters to develop a multi-biomarker model for the early detection of

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[244] Yamada T, "The Prevention against Experimental Pulmonary Fibrosis and the Therapy for the Associated Infections," *Jap. J. Med.* 1961; 1(1):25-34.

[245] Mosinger M, et al., [Experimental Silicosis in the Rabbit brought about by Intravenous Administration of Silica] *Arch. Mal. Prof. Med. Trav. Sec. Soc.* 1963; 24(6);503-521.

[246] Jin Q, et al., "Pulmonary functions and blood biochemical markers for workers with and without coal worker pneumoconiosis," *Life Sci. J.* 2009; 6(2);33-39.

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silicosis. A sample of 612 subjects (half cases and half controls) were randomly divided into training and test groups in a 2:1 ratio. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to construct a multiple biomarker-based model for the diagnosis of silicosis. The training cohort revealed significant statistical differences ($P < 0.05$) in multiple hematologic parameters between silicosis patients and healthy individuals. Based on machine learning, eight silicosis biomarkers were screened and identified from routine blood cell, biochemical and coagulation parameters. Of the eight biomarkers four (D-dimer, albumin-globulin ratio, lactate dehydrogenase, and white blood cells were selected for constructing the logistic regression model for silicosis diagnostics. This model had a satisfactory performance in the training cohort with an area under the ROC curve (AUC) of 0.982, a diagnostic sensitivity of 95.4%, and a specificity of 92.2%. In addition, the model had a prediction accuracy of 0.936 with an AUC of 0.979 in the independent test cohort. Moreover, the diagnostic accuracies of the logistic model in silicosis stages 1, 2, and 3 were 88.0, 95.4, and 94.3% with an AUC of 0.968, 0.983, and 0.990 for silicosis, respectively. Thus, in this study, the albumin-globulin ratio was one of four biomarkers that the investigators concluded could best be utilized to detect early silicosis.[247]

363. Based on the consistent results of both the early and the recent published studies regarding the albumin-globulin ratio as a biomarker of silicosis, a substantially reduced albumin-globulin ratio in workers exposed to silica appears to be a useful biomarker for preclinical silicosis, especially when accompanied by other biomarkers that have been associated with the development of silicosis, as in the recently published study by Chinese investigators.

[247] Sun, G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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b. Alkaline Phosphatase

364. "Alkaline phosphatases (ALPs) are a group of isoenzymes located on the outer layer of the cell membrane. They catalyze the hydrolysis of organic phosphate esters found in the extracellular space. Zinc and magnesium are essential cofactors of this enzyme. Despite the diverse tissue distribution and varying physiochemical properties of ALPs, they are classified as true isoenzymes due to their shared ability to catalyze the same reaction."[248]

365. Alkaline phosphatases are categorized as 2 types: tissue-specific and tissue-nonspecific. ALPs are exclusively present in the intestine, placenta, and germinal tissue, specifically within the tissues where they are expressed under physiological conditions. Under specific conditions, the tissue-specific ALPs may also contribute to the circulating pool of serum ALP when there is increased stimulation of their production. The tissue-nonspecific ALPs are clinically significant, as they constitute most of the circulating fraction in serum. They are encoded by a single gene and expressed in the liver, bone, and kidneys. In contrast, intestinal ALP is coded by a distinct gene separate from the one responsible for placental ALP and the Regan isoenzyme."[249]

366. "Serum ALP levels exhibit age-related variations in healthy individuals. The levels are highest during childhood and puberty due to bone growth and development and then decrease as individuals age. The decline in serum ALP levels within the age group of 15 to 50 is slightly more pronounced in men than in women. These levels increase again during old age, with a notable gender distribution difference."[250]

367. Alkaline phosphatase was first studied in silicosis patients by Italian researchers in the 1950s.[251]

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[248] Lowe D, et al., "Alkaline Phosphatase," *StatPearls*, 2023.

[249] Lowe D, et al., "Alkaline Phosphatase," *StatPearls*, 2023.

[250] Lowe D, et al., "Alkaline Phosphatase," *StatPearls*, 2023.

[251] Carnazzo A, et al., "Alkaline phosphatase and lysozyme in blood in silicosis," *Boll. Soc. Ital. Biol. Sper.* 1952; 28(8-10):1634-1635; Capra Marzani P, [Quantitative and histochemical research on the activity of some enzymes in tuberculous infection and silicosis. II. Behavior of alkaline and acid phosphatases in the lung] *Arch. Sci. Med. (Torino)* 1953; 95(4):344-351; Sacchitelli F, et al., [On the behavior of intraleukocytic alkalinephosphatase and peroxidase in patients with silicosis and silico-tuberculosis], *Folia Med. (Napoli)* 1961; 44:1150-1162.

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368. In 1987, researchers from the National Institute of Environmental Health Sciences noted a 9-fold increase in alkaline phosphatase in the alveoli of lungs of rats exposed to silica.[252]

369. In 1988, researchers from National Jewish Medical Center used a biochemical assay to study the expression of alkaline phosphatase by type II cells. Based on the results of their study, they concluded that alkaline phosphatase is a marker of alveolar type II cell differentiation.[253]

370. In 1997, Italian researchers investigated whether alkaline phosphatase could be a marker of fibrosis in interstitial lung diseases. Alkaline phosphatase was determined in broncho-alveolar lavage of 140 subjects: 25 control subjects, 33 patients with silicosis, 38 with idiopathic pulmonary fibrosis (IPF), and 18 with Stage I, 16 with Stage II, and 10 with Stage III/IV sarcoidosis. A significant increase of alkaline phosphatase activity was observed in patients with IPF, as well as in Stages II and III/IV sarcoidosis. Albumin was higher in those with Stages I and II sarcoidosis, but was normal in the other groups. Therefore, a significant increase in the alkaline phosphatase:albumin ratio characterized IPF (median, 10.3; range 2.4 to 83.2) and Stage III/IV sarcoidosis (8.9, 4.4 to 103.1), compared to Stage I (2, 1.1 to 18) and Stage II (4.7, 0.7 to 26.6) sarcoidosis, silicosis (6.5, 0.5 to 42.7), and the nonsmoker (6.1, 2.9 to 12.9) and smoker (6.4, 2 to 15.2) control groups. The researchers concluded that an increased alkaline phosphatase: albumin ratio in bronchoalveolar lavage fluids from interstitial lung disease patients may reflect progression of fibrosis.[254]

371. In 2020, German researchers investigated the correlation between pulmonary alkaline phosphatase activity and markers of inflammation in invasively ventilated critically ill patients with or without acute respiratory distress syndrome (ARDS), and to investigate the effect of administration of recombinant alkaline phosphatase on pulmonary inflammation in a well-established lung injury model in rats. Bronchoalveolar lavage fluid (BALF) was collected from 83

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[252] Dethloff LA, et al., "Quantitation of cellular and extracellular constituents of the pulmonary lining in rats by using bronchoalveolar lavage. Effects of silica-induced pulmonary inflammation," *Am. Rev. Respir. Dis.* 1987; 136(4):899-907.

[253] Edelson JD, et al., "Alkaline phosphatase: a marker of alveolar type II cell differentiation," *Am. Rev. Respir. Dis.* 1988; 138(5);1268-1275.

[254] Capelli A, et al., "Lung alkaline phosphatase as a marker of fibrosis in chronic interstitial disorders," *Am. J. Respir. Crit. Care Med.* 1997; 155(1):249-253.

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patients – 10 patients with mild ARDS, and 15 with moderate to severe ARDS. Alkaline phosphatase activity correlated well with levels of IL-6 ® = 0.70), as well as with levels of other inflammatory mediators. Animals with acute lung injury had markedly elevated pulmonary alkaline phosphatase activity compared to healthy controls (2.58 [(2.18–3.59] vs 1.01 [0.80–1.46] U/L; $p < 0.01$). The investigators concluded that in ventilated critically ill patients, pulmonary alkaline phosphatase activity correlated well with markers of pulmonary inflammation such as IL-6 and IL-8, and that administration of recombinant alkaline phosphatase does not alter pulmonary inflammation and endothelial or epithelial dysfunction in the acute phase of a murine lung injury model.[255]

372. In 2024, Spanish researchers assessed whether routine blood biomarkers, coupled with machine learning techniques, can differentiate between healthy individuals, subjects with Simple Silicosis and Progressive Massive Fibrosis. One hundred and seven men diagnosed with silicosis, ex-workers in the engineered stone (ES) sector, and 22 healthy male controls not exposed to ES dust were recruited. Twenty-one primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Percentage of lymphocytes, angiotensin-converting enzyme, and lactate dehydrogenase indexes were revealed as blood biomarkers with significant cumulative importance for the machine learning models. Alkaline phosphatase was one of the 11 biomarkers which showed differences between healthy controls and silicosis patients. Mean alkaline phosphatase levels in the healthy controls were 68.68 ± 19.80, but significantly higher in the silicosis patients (76.13 ± 17.70 for patients with simple silicosis and 75.66 ± 24.63 for patients with progressive massive fibrosis. Based on this data, alkaline phosphatase appears to be a useful biomarker for diagnosing silicosis, but not for determining disease progression in silicosis patients.[256]

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[255] Juschten J, et al., "Alkaline phosphatase in pulmonary inflammation – a translational study in ventilated critically ill patients and rats," *Intensive Care Med. Experimental* 2020; 8(Suppl. 1):46

[256] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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c. Amino Acids

373. "Amino acids serve as the building blocks of proteins and are directly involved in metabolic processes. Glycine and proline constitute approximately 33 % and 13 % of collagen, respectively. In silicosis lesions, the excessive and aberrant deposition of collagen is likely associated with the alterations in the metabolic flux of its precursor amino acids."[257]

374. In 1959, Italian researchers investigated the chemical composition of lung tissue of silicosis patients. Chemical analyses showed that the hyaline substance in the lung tissue consisted of approximately 80% proteins, 17% lipids, and 3% carbohydrates. The amino acid composition of the proteins was studied and the results indicated that only about 40% of these proteins were due to collagen, the remaining 60% being due to proteins similar, in this respect, to beta or gamma serum globulins. The presence in the silicotic hyaline of comparatively high levels of globulins rich in aromatic amino acids was confirmed by ultraviolet spectrophotometry.[258]

375. In 1964, South African researchers studies the effect of silica on amino acids in guinea pig lung tissue. Using ion exchange chromatography, they quantitatively compared 18 amino acids in lung tissue of guinea pigs with the amino acid content of corresponding controls and with previously reported guinea pig lung tissue values. The lungs of the guinea pigs exposed to quartz dust increased in weight. The collagen content, measured by hydroxyproline, was also increased.[259]

376. In 1977, researchers from India studied the effect of intratracheal injection of quartz on amino acids of lung, serum and liver of rats before and after collagen formation. Amino acid metabolism was significantly altered in the lungs of silicotic rats. Changes in the body pool of amino acids appeared to be related to both collagen and non-collagen formation in silicotic lung. A central role for glutamic acid metabolism in the genesis of pulmonary fibrosis was observed.[260]

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[257] Xu H, et al., "Targeted metabolomics analysis of 21 amino acids in serum of silicosis patients using HILIC-MS/MS," *J. Chromatography B* 2025; 1264:124736.

[258] Vigliani EC, et al., "An Immunological Approach to Silicosis," *J. Occup. Med.* 1959; 1(6):319-328.

[259] Baily P, et al., "Biochemistry of Lungs in relation to Silicosis. II. The Effect of Quartz Dust on the Protein Amino Acids of Guinea Pig Lung Tissue," *Arch. Environ. Health* 1964; 8(4):547-554.

[260] Singh J, et al., "Amino acid changes and pulmonary response of rats to silica dust," *Environ. Res.* 1977; 14(3):452-462.

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377. In 2021, Chinese researchers investigated circulating metabolites in silicosis and asbestosis patients exposed to mineral dusts. Plasma of 30 silicosis and 30 asbestosis patients, and 20 healthy controls was analyzed using liquid chromatography-mass spectrometry. Compared with healthy controls, 37 and 39 dysregulated plasma metabolites were found in silicosis and asbestosis, respectively. In silicosis patients 13 of 23 lipids, 4 of 6 amino acids, and 7 of 8 carnitines were up-regulated. Three major pathways were identified, among which arginine and proline metabolism was identified as the most primary metabolic pathway. The researchers concluded that lipids, amino acids and carnitines were up-regulated metabolites, and differed between silicosis and asbestosis.[261]

378. In 2021, researchers from Beijing, China, sought to identify metabolic features in the plasma of patients with silicosis and dust-exposed workers without silicosis in metabolomics studies. Patients with silicosis, dust-exposed workers (DEWs) without silicosis and age-matched healthy controls were recruited in a case–control study. Metabolomics analyses by ultra-high performance liquid chromatography-mass spectrometry were conducted. Distinct metabolic features (DMFs) were identified in the pilot study and were validated in the validation study. The enriched signaling pathways of these DMFs were determined. Twenty-nine DMFs and 9 DMFs were detected and had the same trend in the pilot study and the validation study in the plasma of the DEW and silicosis groups, respectively. Sphingolipid metabolism was the major metabolic pathway in the DEWs, and arginine and proline metabolism was associated with silicosis. Twenty DMFs in the DEWs and 3 DMFs in the patients with silicosis showed a discriminatory ability with ROC curve analysis. The abundance of kynurenine was higher in Stage III silicosis than in Stage I or Stage II silicosis. l-arginine and kynurenine were both negatively correlated with the percentage of forced vital capacity predicted in silicosis. The investigators observed that distinct metabolic features in the plasma of DEWs and the patients with silicosis were different. Sphingolipid metabolism and arginine and proline metabolism were identified as the major metabolic pathway in the DEW and silicosis groups, respectively. l-arginine and kynurenine were correlated with the severity of silicosis.[262]

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[261] Zhou M, et al., "Plasma Metabolic profiling in Patients With Silicosis and Asbestosis," *J. Occup. Environ. Med.* 2021; 63(9):787-793.

[262] Xue C, et al., "Distinct metabolic features in the plasma of patients with silicosis and dust-exposed workers in China: a case-control study," *BMC Pulmonary Med.* 2021; 21:91.

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379. In 2024, researchers from Beijing used 16S rDNA sequencing and metabolomic analysis to study the role of lung microbiota in silicosis. They found that silica exposure leads to dysbiosis of lung microbiota and pulmonary fibrosis, which was alleviated by combination antibiotic intervention. Significant metabolic disturbances were found in silicosis, involving 85 differential metabolites among the 3 groups, mainly focused on amino acid metabolic pathways. The changed lung metabolites showed a substantial correlation with lung microbiota. The relative abundance of Pseudomonas negatively correlated with L-Aspartic acid, L-Glutamic acid, and L-Threonine levels. The investigators concluded that the results of their study indicate that dysbiosis in pulmonary microbiota exacerbates silica-induced fibrosis through impacts on amino acid metabolism.[263]

380. In 2025, researchers from Chengu, China, developed a specific serum amino acid metabolomics assay for identifying differential amino acids as biomarkers, providing a sensitive and reliable basis for diagnosing silicosis. A hydrophilic interaction liquid chromatography-tandem mass spectrometry (HILIC-MS/MS) method for the simultaneous quantification of 21 amino acids in serum was established by optimizing chromatographic and sample preparation conditions. The method validation results showed good linearity ® > 0.99), recovery (78.3 %–128.4 %) and precision (1.27 %–13.01 %). The developed method was utilized to detect the levels of 21 amino acids in the serum of the silicosis patient group (SP; n = 104) and the healthy control group (HC; n = 118). The concentration of four amino acids (glutamate, arginine, aspartic acid and ornithine) was significantly different between the SP and the HC. Single diagnostic biomarkers exhibited area under the curve (AUC) values ranging from 0.712 to 0.892, while the glutamate-arginine combination achieved superior performance (AUC = 0.915, 86.1% sensitivity, 90.0% specificity). The investigators concluded that the results of their study showed that of the 21 amino acids screened as potential biomarkers of silicosis, four amino acids had potential as biomarkers, with glutamate emerging as the most accurate single biomarker for predicting silicosis. The diagnostic performance was further enhanced by combining glutamate with arginine, which improved both sensitivity and specificity.[264]

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[263] Huo C, et al., "Silica aggravates pulmonary fibrosis through disrupting lung microbiota and amino acid metabolites," *Sci. Total Environ.* 2024; 945:174028.

[264] Xu H, et al., "Targeted metabolomics analysis of 21 amino acids in serum of silicosis patients using HILIC-MS/MS," *J. Chromatography B* 2025; 1264:124736.

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d. Angiotensin Converting Enzyme

381. "Angiotensin 1-converting enzyme (ACE, peptidyldipeptide hydrolase, EC 3.4.15.1) is a membrane-bound glycoprotein, which converts Angiotensin 1 to Angiotensin 2 and participates in bradykinin degradation. The ACE is bound to the luminal membranes of endothelial cells, and its action takes place mainly in the pulmonary circulation."[265]

382. Serum angiotensin-converting enzyme (ACE) was first reported to be increased in silicosis patients by Finnish investigators in the 1970s.[266] These findings were replicated by others.

383. In a study by other Finnish researchers of 135 male silicosis patients, mean ACE activity was higher in silicosis patients (46.6 ± 12.1 U/L) than patients exposed to silica (38.5 ± 8.1 U/L), and lumberjacks not exposed to silica (36.6 ± 9.7 U/L). In a retrospective side-by-side assessment of roentgenographic progression in 49 silicosis patients, ACE was higher in 18 patients with progression (50.5 ± 16.4 U/L) than in those with no progression (41.5 ± 9.5 U/L).[267]

384. In a study by Italian researchers of 76 silicosis patients and 30 healthy controls, mean ACE was found to be significantly higher in silicosis patients (129.8±4 U/ml) than controls (92.4 ± 22.7 U/ml); patients with more severe radiological changes tended to have lower ACE values.[268]

385. In a study by Polish researchers, mean ACE level was higher in 26 silicosis patients (45.2 ± 16.0 nmol/min X ml) than in 30 control subjects (38.1 ± 10.6 nmol/min X ml). Of the 26 silicosis patients, mean ACE level of 13 patients classified as having nodular silicosis was 44.2 and

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[265] Tiwari RR, "Biomarkers of silicosis: Potential candidates," *Indian J. Occup. Environ. Med.* 2005; 9(3):103-106, citing Soffer RL, et al., "Physiologic, biochemical, and immunological aspects of Angiotensin-converting enzyme," *Prog. Cardiovasc. Dis.* 1978; 21:167-175.

[266] Grönhagen-Riska C, et al., "Angiotensin-converting enzyme and lysozyme in silicosis and asbestosis," *Scand. J. Respir. Dis.* 1978; 59(4):228-231; .Grönhagen-Riska C, "Angiotensin-converting enzyme. I. Activity and correlation with serum lysozyme in sarcoidosis, other chest or lymph node diseases and healthy persons," *Scand. J. Respir. Dis.* 1979; 60(2):83-93.

[267] Nordman H, et al., "Increased Activity of Serum Angiotensin-converting Enzyme in Progressive Silicosis," *Chest* 1984; 86(2):203-207.

[268] Bucca C, et al., "Serum angiotensin converting enzyme (ACE) in silicosis," *Eur. J. Respir. Dis.* 1984; 65(7):477-480.

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10 patients classified as having progressive massive fibrosis was 39.4.[269]

386. In a study of 107 male silicosis by Japanese investigators, mean ACE activity was increased (47.4 ± 14.2 U/ml) in silicosis patients compared to controls (30.5 ± 8.6 U/ml).[270]

387. In another study by Japanese authors, mean ACE activity was significantly increased in silicosis patients (25.5 ± 9.3 nmol/min/ml) compared to controls (18.6 ± 6.0 nmol/min/ml).[271]

388. In a study by Egyptian researchers, mean ACE activity was significantly increased in 30 cement factory workers diagnosed with silicosis with mean exposure duration of 26.8 years (108.27 U/L), compared to 42 workers from the same factory not diagnosed with silicosis with mean exposure duration of 10.7 years (50.33 U/L), and 42 unexposed administrative workers (24.34 U/L). Differences in ACE levels among the 3 groups were highly significant (ANOVA p-value <0.0001).[272]

389. To study the role of ACE in silicosis, Chinese researchers treated wild-type mice, *hACE2*-transgenic mice which overexpress the *ACE2* gene, and mouse lung type II epithelial cells (MLE-12 cells) with diminazene aceturate (DIZEP), an ACE2 activator following induced fibrotic responses by silica. DIZE treatment and overexpression of ACE2 markedly inhibited the formation of silica-induced lung fibrosis and DIZE attenuated epithelial-mesenchymal transition (EMT) and collagen deposition induced by silica in MLE-12 cells. The investigators concluded that overexpression of ACE2 can ameliorate EMT in silicotic mice.[273]

390. In 2021, Australian researchers investigated ACE levels in 179 male workers from stone benchtop industry in Victoria diagnosed with artificial stone silicosis. All subjects had undergone assessments including respiratory function testing, high resolution CT chest and blood

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[269] Szechiński J, et al., "Serum angiotensin-converting enzyme levels in patients with silicosis," *J. Toxicol. Environ. Health* 1986; 17(1):73-79.

[270] Yano E, et al., "Serum Angiotensin Converting Enzyme Activity in Silicosis," *Ind. Health* 1987; 25:11-18.

[271] Inoue Y, et al., "Angiotensin converting enzyme in sarcoidosis and in silicosis," *Clin. Exper. Hypertension Part A: Theory and Practice* 1987; 9(2-3) 481-485.

[272] Beshir S, et al., "Serum levels of copper, ceruloplasmin and angiotensin converting enzyme among silicotic and non-silicotic workers," *Macedonian J. Med. Sci.* 2015; 3(3):467-473.

[273] Li S, et al., "ACE2 attenuates epithelial-mesenchymal transition in MLE-12 cells induced by silica," *Drug Design, Development Therapy* 2020; 14:1547-1559.

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tests panel, including sACE. Sixty workers with artificial stone silicosis had a higher median sACE level (64.1 U/L, IQR 51.5, 87.5), compared to 119 workers without silicosis (35.0 U/L, IQR 25.0, 47.0). Compared to those with a normal assessment, regression modelling noted significantly higher average differences in sACE levels for workers with lymphadenopathy alone (12.1 U/L, 95% confidence interval (CI): 1.3, 22.9), simple silicosis (28.7 U/L, 95% CI: 21.3, 36.0) and complicated silicosis (36.0 U/L, 95% CI 25.2, 46.9). The investigators concluded that sACE levels were higher in artificial stone workers with silicosis compared to those without disease and was highest in those with complicated silicosis. They also concluded that longitudinal follow up is required to evaluate sACE as a prognostic biomarker for workers with this rapidly emerging occupational lung disease.[274]

391. In 2022, Spanish researchers published a study of 91 male former engineered stone workers and 22 healthy male controls in which they investigated circulating biomarker levels and systemic inflammatory indices in engineered stone silicosis patients whose exposure to engineered stone dust ended several years previously. ACE levels were significantly increased among 38 former engineered stone workers diagnosed with progressive massive fibrosis (86.1 ± 23.7 U/L) and 53 former engineered stone workers diagnosed with simple silicosis (78.2 ± 27.2 U/L), in comparison to 22 healthy controls (43.1 ± 18.4 U/L). The investigators concluded that their data corroborate a progressive increase in circulating levels of ACE in former engineered stone workers with simple silicosis or progressive massive fibrosis in comparison to healthy controls. They also concluded that the increase in ACE levels persists for long periods of time (> 6–7 years) after the cessation of exposure to engineered stone dust and may help ascertain progression of engineered stone silicosis.[275]

392. In 2024, Spanish researchers determined levels of serum ACE in a cohort of patients with exposure to silica dust with and without silicosis to assess their impact on prognosis. The patients had been treated in a silicosis clinic from 2009 to 2018. ACE levels and pulmonary function tests were performed. Radiological progression was assessed in patients who had already had 2 X-rays of the thorax and/or two CT scans with at least a 1-year interval, from the time of inclusion in

[274] Hoy RF, et al., "Serum angiotensin converting enzyme elevation in association with artificial stone silicosis," *Respiratory Med.* 2021; 177:106289.

[275] Garcia-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

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the study. A total of 413 cases of silicosis were confirmed, as well as 73 with exposure to silica dust but without silicosis. Mean ACE levels were 74.5 ± 38.6 U/L for patients with complicated silicosis, 57.8 ± 31.3 U/L for patients with simple silicosis, 49.6 ± 24.2 U/L for exposed patients without silicosis, and 27.5 ± 7.3 U/L for the controls. The investigators concluded that ACE was elevated in patients with silicosis and the greater its severity of disease, the higher the ACE level, which was associated with disease progression measured radiologically or as a category change of silicosis.[276]

393. In 2024, researchers from Cadiz, Spain published a study in which they assessed 21 primary biochemical markers from peripheral blood to differentiate between healthy men and workers in the engineered stone sector diagnosed with silicosis. The study evaluated 107 former engineered stone (ES) workers with silicosis and 22 healthy volunteers as controls. Twenty-one primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-F features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Angiotensin converting enzyme was one of three biomarkers that showed significant potential for diagnosing and monitoring silicosis progression. Mean ACE levels were 76.43 ± 24.60 for former ES workers with progressive massive fibrosis, 70.08 ± 27.22 for former ES workers with simple silicosis, and 43.13 ± 13.29 for healthy controls. The investigators concluded that their study revealed blood-derived biomarkers that could detect chronic inflammatory status and potentially serve as a supportive tool for the diagnosis, monitoring, and early detection of the progression of silicosis, especially in initial disease phases where radiology is inconclusive or in exposed workers, to indicate the need for high resolution computed tomography in this subgroup of patients.[277]

394. In 2025, a Turkish researcher published a study in which he sought to determine whether serum sACE and CBC inflammatory markers can be used to diagnose silicosis and assess its severity. A total of 231 subjects who had been referred to Eskişehir City Hospital Occupational

[276] Blanco-Pérez J, et al., "Clinical usefulness of serum angiotensin converting enzyme in silicosis," *Pulmonology* 2024; 30(4):370-377.

[277] Sanchez-Morillo D., et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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Diseases Polyclinic between January 2021 and January 2024 were assigned to three groups: silicosis (n. 131), non-silicosis (n. 40) and controls (n. 40). sACE and CBC inflammatory markers were analyzed and ROC curves were assessed. sACE levels were markedly elevated (85.19±36.06 U/L) in cases with higher profusion scores and disease categories compared to control and non-silicosis groups. sACE has a high diagnostic value for silicosis detection and severity assessment (AUC:0.810, p=0.001). Platelet/Lymphocyte Ratio (PLR) and Monocyte/Lymphocyte Ratio (MLR) were significant predictors of advanced silicosis with large opacities (AUC for PLR: 0.796, p=0.001; AUC for MLR: 0.726, p=0.004). The author concluded that Serum ACE and CBC inflammatory indices serve as valuable biomarkers for diagnosing silicosis and determining disease severity.[278]

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[278] Akgunduz B, "Diagnostic Potential of Serum ACE and CBC Inflammatory Markers in Silicosis in the Ceramic Workers," *Sarcoidosis Vasculitis Diffuse Lung Dis.* 2025; 42(3): 16985.

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e. Club Cell Protein 16

395. "Club cell (formerly Clara cell) protein or CC16 (also known as CC10, club cell secretory protein, and uteroglobin) is a member of the secretoglobin family of small disulphide bridge dimeric proteins. It is secreted by non-ciliated epithelial club cells in the large and small airways and is the most abundant protein present in normal airway secretions.... Depletion of the club cell secretory protein population results in alveolar damage, oedema, and reduced lung repair."[279]

396. In 1994, Belgian researchers measured the concentration of CC16 in the serum of 86 miners and 86 controls matched for age, body mass index and smoking status. The workers were exposed to silica-rich dust in a quarry for 15.2 months on average. No difference between exposed and control workers was detected for respiratory symptoms, chest radiographs or lung function tests, but the concentration of CC16 in serum was decreased in silica-exposed workers (geometric mean 12.3 µg·l-1) compared to controls (16.3 µg·l-1). The decrease was found both in lifelong non-smokers (14.7 vs 21.9) and current smokers (11.3 vs 14.5). In the latter, smoking caused a decrease of serum CC16 additional to that associated with silica exposure. The researchers concluded that alterations in serum concentrations of CC16 probably reflect very early toxic effects of silica particles on the respiratory epithelium, reinforcing the view that serum CC16 is a sensitive marker that might facilitate detection of exposure to chemicals potentially harmful to the respiratory tract.[280]

397. In 2007, Chinese researchers investigated the roles of Clara cell protein 16 (CC16) and surfactant protein-D (SP-D) as serum biomarkers in the early diagnosis and the pathogenesis of silicosis. Thirty healthy volunteers, 30 silica-exposed workers, and 30 workers with suspected silicosis and phase I silicosis were included. Serum CC16 and SP-D concentrations were determined using the enzyme-linked immunosorbent assay. Serum CC16 concentrations decreased in silica-exposed workers when compared with controls, but serum SP-D levels increased. Discriminant analysis showed that the accuracies of classifying group membership into control, phase 0, phase 0+,

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[279] Celli BR, et al., "The club cell and its protein, CC16: time to shine," *Lancet Respir. Med.* 2013; 1(10):757-759.

[280] Bernard AM, et al., "Early decrease of serum Clara cell protein in silica-exposed workers," *Eur. Respir. J.* 1994; 7:1932-1937.

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and phase I were 86.7%, 46.7%, 66.7%, and 70%, respectively, and the total classification accuracy rate was 67.5%. The investigators concluded that serum CC16 and SP-D may be useful biomarkers for early diagnosis, and serum SP-D concentration may associate with the pathogenesis of silicosis.[281]

398. In 2019, Chinese researchers assessed the effect of silica dust exposure on the levels of serum CC16 to distinguish between patients with and without silicosis. 239 male workers were divided into three groups: silicosis group (n = 75), dust contact group (n = 75), and control group (n = 89). All the patients in the silicosis group were diagnosed as having phase I, II, or III silicosis using radiography according to the National Diagnostic Standard (GBZ70-2002) for Pneumoconiosis in China. The dust contact group comprised workers with an occupational history of silica exposure, but without abnormal findings based on their radiographs. The control group included healthy male volunteers without a history of silica exposure. CC16 was significantly lower in the silicosis group compared with the dust contact and healthy control groups and was also significantly decreased in the dust contact group compared with the controls. ROC curve analysis was used to determine the potential use of CC16 for silicosis diagnosis. The best cut-off value for CC16 was 16.21 ng/mL and the AUC for diagnosis of silicosis was 0.919 (P<0.001). The diagnostic sensitivity and specificity of CC16 for silicosis diagnosis was 81.10%, and 92.00%; the Kappa value was 0.731. The researchers concluded that long-term exposure to silica dust may result in a reduction in CC16 levels in serum and CC16 can be used as a biomarker for higher accuracy in the diagnosis of silicosis.[282]

399. In 2020, Indian researchers published a study of 121 persons of three groups: x-ray confirmed silicosis patients, ceramic factory workers with moderate dust exposure, and healthy unexposed controls. CC16 levels were quantified in serum samples through ELISA. Sensitivity and specificity of CC16 values at different cut-off points were calculated in both non-smokers and smokers. Serum CC16 level was significantly (P<0.01) decreased in X-ray confirmed advanced silicosis patients (4.7±3.07 ng/ml) followed by moderately exposed workers (10.2±1.77 ng/ml) as

[281] Wang S-X, et al., "Roles of Serum Clara Cell Protein 16 and Surfactant Protein-D in the Early Diagnosis and Progression of Silicosis," *J. Occup. Environ. Med.* 2007; 49(8):834-839.

[282] Liu J, et al., "The Effect of Silica Dust Exposure on the Serum Clara Cell Protein 16 Levels in Chinese Workers," *Biomed. Environ. Sci.* 2019; 32(1):47-50.

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compared to healthy non-exposed individuals (16.7±.81 ng/ml). Smoking also caused a significant decrease of serum CC16 concentration in healthy (10.2±1.12 ng/ml) and advanced silicosis workers (2.6±.28 ng/ml) compared to non-smokers. Sensitivity and specificity of CC16 values were ≥83% for screening all categories of individuals. The researchers concluded that due to its high sensitivity and specificity, serum CC16 could be used as predictive biomarker for early detection of silicosis.[283]

400. In 2020, Thai researchers investigated the association between respirable crystalline silica (RCS) exposure and plasma club cell protein 16 (CC16) and heme oxygenase-1 (HO-1) levels in 57 stone-carving workers and 20 unexposed workers. Cumulative exposure to RCS was individually estimated using a filter-based gravimetric method. Plasma CC16 and HO-1 levels were determined using commercial kits. The 8-hour time-weighted average for RCS in the exposed workers was significantly greater than in the unexposed workers ($p<0.001$). The health risk characterization for RCS exposure expressed as a hazard quotient (HQ) indicated that crystalline silica might be a risk factor where there is chronic exposure (HQ = 4.48). The exposed workers presented a significant decrease in CC16 and an increase in HO-1 levels compared to the unexposed workers ($p < 0.001$). In addition, a significant association between RCS concentration and plasma CC16 was found. only. The investigators concluded that their data indicated that CC16 might be a suitable biomarker to use to predict the health risk to stone-carving workers of exposure to RCS.[284]

401. In 2021, Mumbai researchers developed a lateral-flow assay for semi-quantitative estimation of serum CC16 level. Detection was performed using gold nanoparticles conjugated anti-CC16 monoclonal antibodies. 106 serum samples was taken to assess performance of the assay. A concentration of 6 ng/ml or less produced one band, 6.1–9 ng/ml produced two bands, while more than 9 ng/ml produced all the three bands at the test zone. The sensitivity of the assay was 100% while the specificity was 95%. The researchers concluded that the assay could be used as a sensitive

[283] Naha N, et al., "Club cell protein 16 as a biomarker for early detection of silicosis," *Indian J. Med. Res.* 2020; 151:319-325.

[284] Thongtip S, et al., "A suitable biomarker of effect, club cell protein 16, from crystalline silica exposure among Thai stone-carving workers," *Toxicol. Ind. Health* 2020; 36(4):287-296.

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tool for periodic screening of silica dust exposed workers for the early detection of silicosis.[285]

402. In 2021, Indian researchers estimated the lung damage in silicotic subjects and its relationship with serum CC16 to explore whether CC16 could be used as a screening tool for early detection of silicosis. Radiographs of 117 workers with radiological evidence of silicosis were evaluated in accordance with International Labour Organisation Classification of chest radiographs and were categorized as mild, moderate, and severe lung damage. The concentration of CC16 in serum was determined by enzyme-linked immunosorbent assay. Serum CC16 values were significantly decreased in relation to increasing lung damage. The mean ± standard deviation (SD) serum CC16 value in mild lung damage group was 8.4 ± 0.87 ng/mL, compared to 4.0 ± 2.10 ng/mL in moderate and 0.7 ± 0.21 ng/mL in high lung damage groups. The CC16 value of the healthy control population was 16.3 ± 3.8 ng/mL. The researchers concluded that serum CC16 could be used as a periodic screening tool for early detection of silicosis and for its secondary prevention.[286]

403. In 2022, Chinese researchers investigated changes of Club cell protein 16 (CC16) and surfactant protein D (SP-D) levels in serum and bronchoalveolar lavage fluid (BALF) in silicotic rats and explored their potential as early biomarkers for silicosis. Pulmonary fibrosis models of rats were constructed by exposing them to silica particles. BALF and serum were collected to determine CC16 and SP-D levels using enzyme-linked immunosorbent assay (ELISA) at different times after the exposure. Hydroxyproline (HYP) level in BALF and CC16 level in the lung tissues were also measured immunohistochemically. The BALF levels of CC16 decreased from 49.65 to 38.02 ng/mg after the rats were exposed to silica for 3 and 28 days, which were all significantly lower as compared with the controls (P<0.05), where the levels remained barely changed during the same period (61.27 to 56.76 ng/mg). The serum CC16 also showed a similar decrease from 9.8 ng/ml to 8.78 ng/ml during the period, while in the controls, the serum CC16 levels remained constantly between 11.04 and 10.96 ng/ml. The levels of SP-D in the serum of silica-exposed rats did not

[285] Nandi SS, et al., "A rapid point of care CC16 kit for screening of occupational silica dust exposed workers for early detection of silicosis/silico-tuberculosis," *Sci. Rep.* 2021; 11:23485.

[286] Sarkar K, et al., "Secondary prevention of silicosis and silico-tuberculosis by periodic screening of silica dust exposed workers using serum club cell protein 16 as a proxy marker," *Health Sci. Rep.* 2021; 4:e373.

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decrease compared with controls and BALF SP-D presented a parabolic curve change with silica exposure. Immunohistochemical examinations showed that the lung Club cells were severely damaged and CC16 expression was obviously decreased after silica exposure. BALF HYP level was higher in silica-exposed rats than in control only when the exposure was at 50 mg/ml. The investigators concluded that their study demonstrated that expressions of CC16 and SP-D are pulmonary tissue-specific and CC16 expression is down-regulated as a result of silica-exposure. They also concluded that the significant relationship between CC16 and silica dose indicates that CC16 may be exploited as an early biomarker to assess silica-induced pulmonary fibrosis.[287]

404. In 2023, researchers from the National Institute for Occupational Safety and Health published a study in which an immunoassay lab on a chip (LOC) was designed, developed and fully characterized for analyzing Clara cell protein 16 (CC16) in serum, which has been considered one of the potential biomarkers of lung inflammation or lung damage due to the respirable silica dusts. Sandwich immunoassay of CC16 was performed on the LOC developed with a custom-designed portable analyzer using artificial serums spiked with CC16 protein first and then human serums obtained from the coal mine workers exposed to the respirable silica-containing dusts. The dynamic range of CC16 assay performed on the LOC was in a range of 0.625–20 ng/mL, and the achieved limit of detection (LOD) was around 0.35 ng/mL. The assay results of CC16 achieved from both the developed LOC and the conventional 96 well plate showed a reasonable correlation. The correlation between the conventional reader and the developed portable analyzer was found to be reasonable, resulting in R2 ~ 0.93. The researchers concluded that their study showed that the LOC developed for the early detection of CC16 can be potentially applied for the development of a field-deployable point-of-care testing (POCT) for the early monitoring of workers who are exposed to silica aerosol.[288]

405. In 2023, Indian researchers published a study in which they assessed a semi-

[287] Yang L, et al., "Club cell secretory protein 16 is a potential biomarker for silica-induced pulmonary fibrosis," *Acta Biochimica Polonica* 2022; 69(4):697-702.

[288] Ahn C, et al., "Lab on a chip for detecting Clara cell protein 16 (CC16) for potential screening of the workers exposed to respirable silica aerosol," *Microfluid Nanofluidics* 2023; 17(11):1-10.

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quantitative and point-of-care CC16 detection kit using lateral flow immune chromatography jointly developed by the National Institute of Occupational Health and the National Institute of Virology. They reported that the test can be done from one drop of blood collected through a finger prick and that all trained peripheral healthcare workers can screen the silica dust-exposed workers periodically, under the national silicosis control program. Once early silicosis is detected, their sputum may be examined periodically by CB-NAAT/ True-NAT for early detection of silicotuberculosis. They noted that the serum CC-16 detection kit is the first of its kind for early detection of silicosis through periodic screening, approved by the Indian Council of Medical Research of the Ministry of Health. They also noted that since occupational silica dust exposure facilitates progressive fibrosis of lung tissue, a clinical trial using metformin may be the need of the day as animal experiments have already shown metformin's anti-fibroblastic effect in silica-induced animals.[289]

406. In 2023, Iranian researchers published a systematic review and meta-analysis of the relationship between occupational exposure to respirable crystalline silica and serum CC16 levels. Their search revealed 18 articles, of which eight were included for analysis. The overall effect estimate demonstrated that silicosis patients had lower serum level of CC16 (SMD: -3.58; 95% CI -5.14 to -2.3; I2 = 94.4% P-value <0.001) than the control group. Silicosis patients and exposed individuals had lower serum level of CC16 (SMD:-3.32; 95% CI -4.19 to -2.45; I2 = 88.6% P-value <0.001) compared to the control group. The silica exposure group had a lower CC16 level (SMD: -1.92; 95% CI -4.22 to 0.39; I2=97.5% P-value <0.001) than non-silicosis groups. The researchers concluded that their study demonstrated that occupational exposure to respirable crystalline silica is associated with the reduction of serum CC16 level and that reduced serum level of CC16 protein can be used to monitor the exposure levels of workers to respirable crystalline silica in workplaces.[290]

407. In 2024, Romanian researchers reviewed studies regarding Club Cell 16 as a bio-marker of silicosis. They found that most evidence points to a significant reduction in serum CC16

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[289] Sarkar B, et al., "Potential consequences of screening of occupational silica dust exposed workers for early detection of silicosis/silico-tuberculosis using a novel biomarker, club cell protein-16, with possible intervention by repurposing metformin," *Adv. Biomarker Sci. Technol.* 2023; 5:33-37.

[290] Arabzadeh H, et al., "Relationship between occupational exposure to respirable crystalline silica and serum CC16 level as a potential biomarker for preventing silicosis: A systematic review and meta-analysis study," *J. Air Pollut. Health* 2024; 9(2):225-234.

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levels in workers chronically exposed to silica dust, without respiratory symptoms and with normal chest x-rays and pulmonary function tests. They concluded: "These results recommend serum CC16 as a possible tool for detecting early asymptomatic silicosis in the silica-exposed population."[291]

408. In 2025, Chinese researchers explored whether CC16 levels can reflect early lung function changes. Cumulative dust exposure (CDE) levels of 1,461 coal miners were retrospectively assessed using a job-exposure matrix. Important factors affecting lung function and CC16 were selected by establishing random forest models. The potential of CC16 to reflect lung injury was explored from multiple perspectives. First, restricted cubic spline (RCS) models were used to compare the trends of changes in lung function indicators and plasma CC16 levels after dust exposure. Then mediating analysis was performed to investigate the role of CC16 in the association between dust exposure and lung function decline. Finally, the association between baseline CC16 levels and follow-up lung function was explored. Median CDE was 35.13 mg/m3-years. RCS models revealed a rapid decline in forced vital capacity, forced expiratory volume in one second, and their percentages of predicted values when CDE exceeded 25mg/m3-years. The dust exposure level (<5mg/m3-years) causing significant changes in CC16 was much lower than the level (25mg/m3-years) that caused changes in lung function indicators. CC16 mediated 11.1% to 26.0% of dust-related lung function decline. Workers with low baseline CC16 levels experienced greater reductions in lung function in the future. The investigators concluded that CC16 levels are more sensitive than lung indicators in reflecting early lung function injury, that CC16 levels have a mediating role in lung function decline induced by dust exposure, and that low baseline CC16 levels predict poor future lung function.[292]

409. In a comprehensive review of studies evaluating biomarkers for early diagnosis of silicosis, Romanian researchers concluded that CC16 detection seems the most promising of the biomarkers.[293]

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[291] Otelea MR, et al., "Club Cells – A Guardian against Occupational Hazards," *Biomedicines* 2024; 12:78.

[292] Wei J, et al., "Plasma club cell secretory protein reflects early lung injury: comprehensive epidemiological evidence," *Environ. Health Prev. Med.* 2025; 30:26.

[293] Calutu, I-M, et al., "Biomonitoring Exposure and Early Diagnosis in Silicosis: A Comprehensive Review of the Current Literature," *Biomedicines* 2023; 11:100.

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f. C-Reactive Protein

410. C-reactive protein is well-recognized as a sensitive biomarker of inflammation.[294]

411. The first article reporting detection of the C-reactive protein in silicosis patients was published by Italian researchers in 1958. In this early study the C reactive protein was determined in blood serum by means of the capillary technique of Anderson and McCarty in 70 cases of pulmonary silicosis, 22 of which were complicated with tuberculosis. C reactive protein was found in none of the examined cases of pure reticular, reticulo-nodular and nodular silicosis. C reactive protein was found in 18 out of 22 cases of silicotuberculosis (81.8%); it was also found in 5 out of 18 cases of confluent or massive silicosis in which a tubercular infection, although not manifest, was highly suspected. The investigators therefore concluded that the C reactive protein seems to be a factor of some importance in distinguishing cases of silicosis from cases of silicotuberculosis.[295]

412. Further studies regarding the C-reactive protein in silicosis were published later the same year by Italian investigators[296] and the following year by French researchers who detected the C-reactive protein in 12 of 40 silicosis patients, one of whom also had pulmonary tuberculosis.[297]

413. In 1971, German researchers published a study in which they measured CRP concentrations in the sera of patients with pneumoconiosis and chronic obstructive bronchitis. Positive CRP reactions were found in 70% of the cases examined using the immuno-diffusion method, which gave negative results in 97% of controls subjects of different age groups.[298]

414. In 1991, Spanish researchers studied several acute phase proteins in 62 coal miners,

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[294] Rizo-Téllez SA, et al., "C-reactive protein: a target for therapy to reduce inflammation," *Front. Immunol.* 2023; 14:1237729.

[295] Ghislandi E. [C Reactive Protein in Silicosis and Silico-Tuberculosis], *Med. Lav.* 1958; 49(3):173-181.

[296] Chiesura P, et al., [C-reactive protein in the serological diagnosis of silicosis & silicotuberculosis], *Folia Med. (Napoli)* 1958; 41(10):981-990; Morettu Em et al., "The Value of C-Reactive Protein Estimation in Silicosis and Silico-Tuberculosis," *Lotta contro la Tubercolosi* 1958; 28(8-9):851-859; Mazza V, et al.,]Milldeboork-Dubos reaction, C-reactive protein & erythrosedimentation rate in silicosis & silicotuberculosis], *Folia Med. (Napoli)* 1958; 41(11):1145-1154.

[297] Gaultier M, et al., "Investigations of the Serum of Silicotic Subjects for the Presence of C-Reactive Protein," *Arch. Mal. Prof. Med. Travail Sécurité Sociale* 1959; 20(1):90-94.

[298] Rasche B., et al., [Regarding the significance of C-reactive protein (CRP) in miners' pneumoconiosis with chronic obstructive bronchitis and in chronic obstructive bronchitis without pneumoconiosis] *Respiration* 1971; 28(5):457-570.

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19 of whom had not been diagnosed with pneumoconiosis, 23 who had simple pneumoconiosis, and 20 who had complicated pneumoconiosis with progressive massive fibrosis. C-reactive protein concentration was significantly higher in the miners with pneumoconiosis. The C-reactive protein concentration was above the upper normal value in 12 (27.9%) of 43 cases with simple and complicated pneumoconiosis, while only one case without pneumoconiosis was above the upper normal range (5.3%), a significant difference based on a stratified analysis for chronic bronchitis.[299]

415. In the 1990s, Romanian researchers published papers comparing several inflammatory factors in 68 silicosis patients divided into 3 subgroups according to stage of disease and 35 healthy controls. They found a high level of C-reactive protein in Stage III silicosis ($p < 0.001$).[300]

416. In 2006, Japanese researchers investigated whether Heme oxygenase-1 (HO-1), a rate-limiting enzyme in heme catabolism that has anti-oxidative, anti-apoptotic, and anti-inflammatory properties, might be involved in silicosis. They evaluated HO-1, c-reactive protein (CRP), and 8-hydroxydoxyguanosine in serum of 46 silicosis patients, 27 patients with COPD, and 42 healthy controls. Mean serum CRP mg/L levels were 5.39 ± 1.51 in silicosis patients, 2.56 ± 0.83 in COPD patients, and 0.66 ± 0.09 in the controls. The difference between CRP levels in the silicosis patients and the controls was highly significant ($P < 0.0001$).[301]

417. Subsequent studies also reported significantly increased CRP levels in silicosis patients compared to patients with chronic obstructive pulmonary disease and/or healthy controls.[302]

418. In 2011, the Japanese researchers determined annual lung function changes as well

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[299] Fernandez Rego, G., et al., "Presence of acute phase response in coal workers' pneumoconiosis," *Brit. J. Ind. Med.* 1991; 48:193-195.

[300] Cojocaru M, et al., "The role of certain immunologic parameters in silicosis," *Rom. J. Intern. Med.* 1995; 33(1-2):61-72; Cojocaru M, "Relationship between serum total sialic acid and C-reactive protein in silicosis," *Rom. J. Intern. Med.* 1997;35(1-4):77-82.

[301] Sato T, et al., "Heme Oxygenase-1, a Potential Biomarker of Chronic Silicosis, Attenuates Silica-induced Lung Injury," *Am. J. Respir. Crit. Care Med.* 2006; 174:906-914.

[302] Kalliny MS, et al., "Immune response due to silica exposure in Egyptian phosphate mines," *J. Health Care Poor Underserved* 2011; 22(4 Suppl):91-109; Miao R, et al., "Proteomic profiling differences in serum from silicosis and chronic bronchitis patients: a comparative analysis," *J. Thorac. Dis.* 2016; 8(3):439-450; Nardi J, et al., "Inflammatory and oxidative stress parameters as potential early biomarkers for silicosis," *Clinica Chimca Acta* 2018; 484: 305-313; Huang H-B, et al., "Clinically diagnosing and treating 119 cases of silicosis with organizing pneumonia," *J. Environ. Occup. Med.* 2019; 36(8):761-766.

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as HO-1 and CRP levels in the silicosis patients from their prior study. Among 33 evaluable patients with more than 5 years of available lung function tests, the 25 silicosis patients with elevated HO-1 levels showed a significantly slowed decline in FEV1 compared to those with normal HO-1 levels. There was no significant difference in the rate of FEV1 decline in subjects with high versus normal CRP levels. The investigators concluded that serum HO-1 levels (but not CRP levels) can be used to distinguish subjects with rapid decline of lung function in patients with chronic silicosis.[303]

419. In 2018, Chinese researchers published of a study in which they concluded that poor lung function (decreased FVC) in Chinese silicosis patients was associated with an increased risk of Type 2 diabetes. A table from this study showed that CRP levels increased with decreasing lung function in silicosis patients: CRP 4.03 ± 5.64 in silicosis patients with <30% decreased FVC; 7.25± 15.39 in patients with 30-60% reduced FVC, and 8.52±6.63 in patients with >60% reduced FVC.[304]

420. In 2020, Chinese researchers published a study regarding silicosis in 3190 excavation workers who participated in mining operations. They found that serum levels of C-reactive protein in Stage I silicosis patients were significantly lower than in Stage II-III silicosis patients ($P < 0.05$).[305]

421. In 2021, Spanish researchers conducted a prospective observational study in patients attending their pulmonology clinic from 2009 to 2018 to determine the clinical significance of specific biomarkers and to estimate their association with the development, severity and/or progression of silicosis. They assessed serum levels of several inflammatory markers including CRP. They also analyzed associations between the inflammatory mediators with lung function measurements and radiological severity of disease and their impact on prognosis. A total of 337 patients exposed to silica (278 with silicosis) and 30 subjects in the control group were included. Serum levels of CRP, IL-8, αAT, ferritin, and LDH levels were higher in silicosis than in those exposed to silica without silicosis. Mean serum CRP levels increased significantly with severity of

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[303] Sato T., et al., "Serum Heme Oxhygenase-1 As Marker of Lung Function Decline in Patients with Chronic Silicosis," *Am. J. Respir Crit. Care Med.* 2011; 183:A4788.

[304] Cheng HY, et al., "Poorer Lung Function Associated With Higher Risk of Type II Diabetes (DM) Among Chinese Adults With Silicosis," Circulation *2018*; 137(Suppl. 1), Abstract P060.

[305] Cao YM, et al., [Incidence of silicosis among excavation workers], *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2020; 38(9):686-688.

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disease: 6.87 in those exposed to silica without silicosis 7.5 in patients with simple silicosis, and 14.2 in patients with complicated silicosis ($P = 0.001$). CRP levels were also significantly associated with mortality ($P < 0.001$).[306]

422. Three recent studies did not find significantly increased CRP levels in silicosis patients compared to exposed patients without silicosis or unexposed controls, which the authors attributed to confounding by tuberculosis, chronic rather than acute inflammatory status, and small size of one of the studies.[307]

423. In 2025, researchers from the UK published a series of three cases of artificial stone silicosis, all of whom had mildly elevated C-reactive protein levels (31.9 - 47.7).[308]

424. In 2025, Chinese researchers conducted a case-control study to screen biomarkers from routine blood parameters to develop a multi-biomarker model for the early detection of silicosis. CRP was one of 21 biochemical parameters assessed among 204 silicosis patients and 204 controls. Mean serum CRP levels were significantly higher among the silicosis patients (19.87 ± 23.37) than the controls (1.48 ± 2.01) ($P < 0.001$). Nevertheless, these investigators did not include CRP as a parameter in constructing a logistic regression model based on selected biomarkers, because CRP is often increased by stochastic factors such as upper respiratory tract infections.[309]

425. Overall, these studies indicate that CRP serum levels may be used as confirmatory evidence in the diagnosis of silicosis, but not as an independent indicator of silicosis or of severity of disease among silicosis patients.

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[306] Blanco-Pérez JJ, et al., "Serum levels of inflammatory mediators as prognostic biomarker in silica exposed workers," *Sci. Rep.* 2021; 11:13348.

[307] Aloe CA, et al., "Excess iron promotes emergence of foamy macrophages that overexpress ferritin in the lungs of silicosis patients," *Respirology* 2022; 27:427-436; García-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211; Smărăndescu R-A, et al., "Serum concentrations of Krebs von den Lungen-6 as prognostic biomarker in patients with silicosis," *Front. Med.* 2025; 12:1579209.

[308] Khan AA, et al., "Artificial stone silicosis presenting as suspected Tuberculosis: A series of 3 cases at a district general hospital," *Clin. Infect. Pract.* 2025; 27:100495.

[309] Sun, G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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g. D-Dimer

426. "D-dimer is an indirect marker of fibrinolysis and fibrin turnover; this molecule exhibits unique properties as a biological marker of hemostatic abnormalities as well as an indicator of intravascular thrombosis. D-dimer is a soluble fibrin degradation product that results from the systematic degradation of vascular thrombi through the fibrinolytic mechanism. Because of this, the D-dimer serves as a valuable marker of activation of coagulation and fibrinolysis in a number of clinical scenarios."[310]

427. D-dimer generation requires the activity of three enzymes: thrombin, activated factor XIII (factor XIIIa), and plasmin. The process starts when thrombin generated by the coagulation system converts soluble fibrinogen to fibrin monomers. These monomers then form fibrin polymers through noncovalent interactions based on allosteric changes within the protein as a result of thrombin cleavage of fibrinopeptides from the N-terminal domain. Fibrin is strengthened through interactions with factor XIII, which, after activation by thrombin, cross-links the D domains of adjacent fibrin monomers. Plasmin digestion of the fibrin clot results in the D-dimer molecule.[311]

428. The presence of D-dimer molecules is suggestive of intravascular coagulation because it can only be generated after thrombin formation and subsequent degradation of cross-linked fibrin. Because of this, D-dimer measurements serve as a global marker of activation of the coagulation and fibrinolytic systems, and function as an indirect marker of thrombotic and thrombolytic activity.[312]

429. A normal D-dimer is considered less than 0.50 µg/mL (or 500 ng/mL). A positive D-dimer is 0.50 µg/mL or greater."[313]

430. In 2004, Chinese researchers published a case report of pulmonary alveolar

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[310] Johnson ED, et al., "The D-dimer assay," *Am. J. Hematol.* 2019; 94:833-839.

[311] Johnson ED, et al., "The D-dimer assay," *Am. J. Hematol.* 2019; 94:833-839, citing Francis CW, et al., "Plasmic degradation of crosslinked fibrin," *J. Clin. Invest.* 1980; 66:1033-1043..

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proteinosis in a foundry worker whose D-Dimer level was 1,618 ng/ML - more than 3 times the maximum normal level. Silicosis has long been associated with silica exposure at foundries, and pulmonary alveolar proteinosis is the morphologic feature of acute silicosis. The authors noted that pulmonary alveolar proteinosis is a rare disease and should be suspected from occupational inhalation of respirable silica.[314]

431. In 2018, Turkish researchers published a case report of a 53-year-old patient who had worked in the glass industry for 15 years and was suspected to have a pulmonary embolism based on radiology and a high D-dimer level of 798. A CT scan was therefore done, whereupon the patient was diagnosed with complicated silicosis with progressive massive fibrosis.[315]

432. In 2023, Turkish researchers published a case report of a 75-year-old patient who, at the age of 18, had worked in a lead mine blasting with dynamite for 4 months and then worked in tunnel and road construction, blasting, sand screening and transportation for 3 months. Chest x-ray showed nodular lesions bilaterally in the upper-middle zone and a mass in the upper zone of the right lung. His D-dimer level was high at 1770 ng/ml. HRCT showed nodular lesions consistent with pneumoconiosis and progressive massive fibrosis in bilateral upper-middle zones of the lung. The investigators noted that although chronic complicated silicosis is generally thought to develop with inorganic dust inhalation for more than 10 years and the patient only had occupational dust exposure for 7 months, they diagnosed him with pneumoconiosis with progressive massive fibrosis.[316]

433. In 2017, researchers from New York evaluated the relationship between elevated serum D-dimer level and acute exacerbation or preclinical acute exacerbation in patients with interstitial lung disease. The risk of developing acute exacerbation of interstitial lung disease was 10-fold higher in patients with elevated serum D-dimer level (aOR 10.46, 95% CI 1.24 - 88.11; p = 0.03). The researchers concluded that elevated serum D-dimer is associated with the risk of

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[314] Tsao S-L, et al., "Pulmonary Alveolar Proteinosis in a Foundery Worker: Report of One Case," *Changhua J. Med.* 2004; 9(1):38-42.

[315] Sarp Taymas Z, et al. [A case of Silicosis with a Radiology of Pulmonary Embolism], *Izmir Chest Hospital J.* 2018; 32(3):197-202.

[316] Özgün S, et al., "Pneumoconiosis accompanied by pulmonary thromboembolism: Case Report," *J. Deu Med.* 2023; 37(2):225-229.

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developing acute exacerbations of interstitial lung disease and that serum D-dimer may be used to predict acute exacerbation or recognize preclinical acute exacerbation of interstitial lung disease.[317]

434. In 2021, Italian researchers evaluated the possible role of three biomarkers (Carbohydrate Antigen CA 15.3, beta 2-microglobulin, and D-dimer) in a cohort of 100 patients with newly diagnosed idiopathic pulmonary fibrosis. The mean serum levels of all three biomarkers were higher than their reference values. The mean serum level of D-dimer was 548.3 ng/mL. At diagnosis, elevated serum levels of CA 15.3, beta 2m and D-dimer were significantly correlated with reduced lung function, assessed through the measurement of forced vital capacity (FVC) and total lung capacity (TLC), a reduction of DLCO, a decrease in 6MWD, and with more rapid progression of disease. The investigators concluded that at diagnosis, patients with altered values of the three biomarkers appear to be older, more symptomatic, with a more defined and compromised pattern of pathology, and present a more rapid progression of idiopathic pulmonary fibrosis.[318]

435. In 2022, Nigerian researchers evaluated 6 hemostatic parameters (activated partial thromboplastin time, D-Dimer, fibrinogen, international normalized ratio, prothrombin time, and Von-Willebrand factor) among 100 cement loaders and 100 individuals not exposed to cement dust. They reported a significant increase in D-Dimer, fibrinogen, and Von-Willebrand factor levels, as well as activated partial thromboplastin time in the cement-exposed group compared to the controls. The researchers noted that cement is made from silica, that silica causes silicosis, and that studies have shown that exposure to cement dust causes lung dysfunction, damage, and lung cancer.[319]

436. In 2024, Japanese researchers sought to confirm coagulopathy in acute exacerbations of interstitial lung disease (AE-ILD) by evaluating differences in clinical characteristics of coagulation/ fibrinolysis markers between stable ILD and AE-ILD. Overall, 81 patients were enrolled in this retrospective study and categorized into two groups: a chronic ILD group comprising

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[317] Ishikawa G, et al., "Elevated serum D-dimer level is associated with an increased risk of acute exacerbation in interstitial lung disease," *Respir. Med.* 2017; 128:78-84.

[318] Cavalli F, et al., "Biomarkers for possible early detection and progression of idiopathic pulmonary fibrosis," *Minerva Respir. Med.* 2021; 60(3):73-86.

[319] Nyebuchi J, et al., "Evaluation of Some Haemostatic Parameters among Cement Loaders in Port-Harcourt, Nigeria," *Arch. Current Res. Int.* 2022; 22(6):1-8.

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63 outpatients and an acute ILD group comprising 18 inpatients diagnosed with AE-ILD. Serum markers, including thrombin-antithrombin III complex (TAT), D-dimer, plasmin-2 plasmin inhibitor complex (PIC), and surfactant protein D (SP-D), were compared between the groups. A positive correlation was observed between SP-D levels and TAT, D-dimer, and PIC levels in acute ILD. Serum TAT, D-dimer, and PIC all showed good area under the receiver operating characteristic (ROC) curve (AUC) values in ROC analysis for the diagnosis of acute ILD. The investigators concluded that in the clinical setting of AE-ILD, it may be important to focus not only on alveolar damage markers such as SP-D but also on coagulation/fibrinolytic markers including TAT, D-dimer, and PIC.[320]

437. In 2025, Chinese researchers conducted a case-control study to screen biomarkers from routine blood parameters to develop a multi-biomarker model for the early detection of silicosis. A sample of 612 subjects (half cases and half controls) were randomly divided into training and test groups in a 2:1 ratio. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to construct a multiple biomarker-based model for the diagnosis of silicosis. The training cohort revealed significant statistical differences ($P < 0.05$) in multiple hematologic parameters between silicosis patients and healthy individuals. four (D-dimer, albumin-globulin ratio, lactate dehydrogenase, and white blood cells) were selected for constructing the logistic regression model for silicosis diagnostics. This model had a satisfactory performance in the training cohort with an area under the ROC curve (AUC) of 0.982, a diagnostic sensitivity of 95.4%, and a specificity of 92.2%. In addition, the model had a prediction accuracy of 0.936 with an AUC of 0.979 in the independent test cohort. Moreover, the diagnostic accuracies of the logistic model in silicosis stages 1, 2, and 3 were 88.0, 95.4, and 94.3% with an AUC of 0.968, 0.983, and 0.990 for silicosis, respectively. Thus, in this study, D-Dimer was one of four biomarkers that the investigators concluded could best be utilized to detect early silicosis.[321]

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[320] Takeshita Y, et al., "Usefulness of Combined Measurement of Surfactant Protein D, Thrombin-Antithrombin III Complex, D-Dimer, and Plasmin-α2 Plasmin Inhibitor Complex in Acute Exacerbation of Interstitial Lung Disease: A Retrospective Cohort Study," *J. Clin. Med.* 2024; 13:2427.

[321] Sun, G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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h. Fas/FasL

438. Fas ligand (FasL) is a membrane bound and shed protein belonging to the TNF gene family, and the natural counter-receptor for the death-promoting Fas molecule expressed by a variety of lymphoid and nonlymphoid tissues.[322] Lymphocyte apoptosis mediated by Fas/FasL interaction regulates immune responses,[323] and FasL-mediated apoptosis of leukocytes prevents inflammatory reactions at immune-privileged sites.[324]

439. The earliest studies regarding Fas in silicosis patients were undertaken by researchers from Okayama, Japan.

440. In 1997, the Japanese researchers investigated the serum sFas levels in 64 Japanese silicosis patients with no clinical symptoms of autoimmune diseases or malignant tumors, using ELISA for sFas. The serum sFas levels in the silicosis patients were significantly higher than those in healthy controls. Elevated serum sFas levels were also detected in patients with systemic lupus erythematosus but, unexpectedly, no difference was observed in sFas levels between progressive systemic sclerosis patients and healthy controls. There was no significant difference in the expression of Fas on peripheral blood lymphocytes between the patients with silicosis and age-matched healthy controls. These observations provided the first evidence that serum sFas levels are elevated in silicosis patients without clinical symptoms of autoimmune disease or malignant tumors.[325]

441. In 1998, the Japanese researchers investigated Fas and Fas-ligand message expression levels using the multiplex reverse transcription–polymerase chain reaction (RT–PCR) method with peripheral blood mononuclear cells from silicosis cases with no clinical symptoms of autoimmune

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[322] Borges VM, et al., "Fas ligand triggers pulmonary silicosis," *J. Exp. Med.* 2001; 194:155-164, citing Nagata S, "Fas ligand-induced apoptosis," *Annu. Rev. Genet.* 1999; 33:29-55.

[323] *Id.,* citing Lenardo M, et al., "Mature lymphocyte apoptosis: immune regulation in a dynamic and unpredictable antigenic environment," *Annu. Rev. Immunol.* 1999; 17:221-253; Krammer PH, "CD95's deadly mission in tn the immune system," *Nature* 2000; 407:789-795.

[324] *Id.,* citing Griffith TS, et al., "Fas ligand-induced apoptosis as a mechanism of immune privilege," *Science* 1995; 270:1189-1192.

[325] Tomokuni A, et al., "Elevated soluble Fas/APO-1 (CD95) levels in silicosis patients without clinical symptoms of autoimmune diseases or malignant tumours," *Clin. Exp. Immunol.* 1997; 110:303-309.

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diseases, to determine the role of the Fas/Fas ligand system in silica-induced immunological abnormalities. Although the relative expression levels of the Fas or Fas-ligand genes were not remarkably altered in these cases, the investigators observed that the sFas message was dominantly expressed compared with mFas expression. These results suggested that self-recognizing clones in cases with silicosis survive for decades, escaping the exclusion mechanisms induced by apoptosis and then cause the appearance of autoantibodies and the development of autoimmune diseases.[326]

442. In 1999, the Japanese researchers sought to establish a new clinical index for immunological abnormalities occurring in silicosis by investigating several clinical parameters related to Fas-mediated apoptosis: membrane Fas expression on peripheral blood lymphocytes (mFas), serum soluble Fas levels (sFas), serum soluble Fas ligand levels (sFasL), and soluble/membrane Fas mRNA expression ratios (s/mFas ExR) in peripheral blood mononuclear cells. Fifty-eight silicosis patients with no clinical symptoms of autoimmune diseases were the subjects of the study. Factor analysis was performed using 12 clinical parameters including four parameters related to Fas-mediated apoptosis. Two common factors were identified. Factor 1 which consisted of the following parameters; duration of exposure, symptomatic dyspnea, PO_2, PCO_2, and A-aDO_2, should be designated as the respiratory factor for cases with silicosis. The parameters of factor 2 were serum IgG, sFas with high factor loading, titer of ANA, sFasL, and s/mFasExR. These parameters of factor 2 are indicative of the immunological disorders occurring in silicosis cases. Some cases exhibited abnormalities in parameters of factor 2 but not factor 1. The investigators concluded that their analysis demonstrated that the parameters related to Fas-mediated apoptosis should be the most beneficial for predicting the pre-clinical status of complicated autoimmune diseases in silicosis.[327]

443. In 1999, the Japanese researchers examined the role of the Fas/FasL system in silica-induced immunological abnormalities by investigating serum soluble FasL levels (sFasL) in silicosis patients with no clinical symptoms of autoimmune diseases. Although the sFasL levels in patients

[326] Otsuki T, et al., "Soluble Fas mRNA is dominantly expressed in cases with silicosis," *Immunology* 1998; 94:258-262.

[327] Otsuki T, et al., "evaluation of cases with silicosis using the parameters related to Fas-mediated apoptosis," *Int. J. Mol. Med.* 1999; 4(4):407-411.

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with SLE were significantly higher than those in healthy controls and showed a slight positive correlation with serum sFas levels, those in silicosis patients exhibited no significant difference from those in healthy controls, and there was no correlation with serum sFas levels. However, sFasL levels were elevated in silicosis patients with slight dyspnea or normal PCO_2 among various clinical parameters of silicosis. The researchers concluded that the immunological disturbances presented by the abnormalities of apoptosis-related molecules in silicosis patients do not occur with a similar degree of respiratory involvement. This study suggests that serum FasL level might have utility as a biomarker for detecting early silicosis in asymptomatic workers without radiographic silicosis.[328]

444. In 2000, the Japanese researchers sought to detect alternatively spliced variants of the Fas gene. They found 4 deletional variant messages that were highly and frequently expressed in peripheral blood mononuclear cells (PBMC) derived from silicosis patients. All of these variants possess a signal peptide domain, but not a transmembrane or signal transducing domain. Functional mutations were not detected in Fas and FasL genes in PBMC from silicosis patients. The investigators concluded that alternative spliced variants of the Fas gene including typical sFas message appear to play an important role in immunological dysregulation in silicosis.[329]

445. In 2001, Brazilian researchers investigated the role of Fas ligand in murine silicosis. Wild-type mice instilled with silica developed severe pulmonary inflammation, with local production of tumor necrosis factor (TNF)-α, and interstitial neutrophil and macrophage infiltration in the lungs. Strikingly, Fas ligand–deficient generalized lymphoproliferative disease mutant (*gld*) mice did not develop silicosis. The *gld* mice had markedly reduced neutrophil extravasation into bronchoalveolar space, and did not show increased TNF-α production, nor pulmonary inflammation. Bone marrow chimeras and local adoptive transfer demonstrated that wild-type, but not Fas ligand-deficient lung macrophages recruit neutrophils and initiate silicosis. Silica induced Fas ligand expression in lung macrophages in vitro and in vivo, and promoted Fas ligand–dependent macrophage apoptosis.

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[328] Tomokuni A, et al., "Serum levels of soluble Fas ligand in patients with silicosis," *Clin. Exp. Immunol.* 1999; 118:441-444.

[329] Otsuki T, et al., "Detection of alternatively spliced variant messages of Fas gene and mutational screening of Fas and Fas ligand coding regions in peripheral blood mononuclear cells derived from silicosis patients," *Immunol. Letters* 2000; 72(2):137-143.

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Administration of neutralizing anti-Fas ligand antibody in vivo blocked induction of silicosis. The investigators concluded that Fas ligand plays a central role in induction of pulmonary silicosis.[330]

446. In 2003, Tunisian researchers examined the expression of Fas antigen, FasL and apoptosis in bronchoalveolar lavage fluid lymphocytes obtained from patients with silicosis. Ten patients with silicosis and 10 healthy controls were studied. Non-adherent cells were separated and analyzed by cytometry for the expression of Fas antigen, FasL, and the coexpression of Fas/FasL. By double staining, the FasL expression on CD4, CD8, CD56 and CD45RO-positive cells was evaluated. DNA fragmentation was investigated by the terminal deoxy(d) UTP nick end labelling (TUNEL) method. Fas and FasL expression in silicosis patients was significantly higher than in the healthy controls. Interestingly, 6-18% of lymphocytes from silicosis patients co-expressed Fas and FasL. In silicosis patients, FasL was highly expressed on CD4+, CD56+ and CD45RO+ bronchoalveolar lavage cells. Fas antigen expressing cells showed DNA fragmentation characteristic for apoptosis. The researchers concluded that FasL us significantly expressed on cytotoxic effector and memory cells and that the Fas/FasL system is implicated in the inflammatory process observed in silicosis patients.[331]

447. In 2006, Brazilian researchers investigated the importance of Fas-ligand (Fas-L) in human silicosis. They analyzed 23 lung biopsies from silicotic patients and five controls, quantifying Fas-L and Bcl-2 expression by inflammatory cells as well as mast cells and collagen and elastic fibers. They used immunohistochemistry and morphometry to evaluate the amount of Fas-L and Bcl-2. Silicotic lung stage was significantly related to Fas-L, mast cell and extracellular matrix remodelling. Fas-L expression was inversely associated with mast cells, collagen/elastic deposition and the silicotic lung. The investigators concluded that Fas-L, mast cell staining and collagen/elastic fiber quantities in silicotic lungs are strongly related to silicosis progression.[332]

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[330] Borges VM, et al., "Fas ligand triggers pulmonary silicosis," *J. Exp. Med.* 2001; 194:155-164.

[331] Hamzaoui A, et al., "Expression of Fas antigen and Fas ligand in bronchoalveolar lavage from silicosis patients," *Mediat. Inflamm.* 2003; 12:209-214.

[332] Delgado L, et al., "Apoptosis and extracellular matrix remodelling in human silicosis," *Histopathology* 2006; 49(3):283-289.

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448. In 2008, Chinese researchers conducted a case-control study of 183 silicosis patients and 111 silica-exposed miners to determine whether polymorphisms in FASL and other genes are associated with risk of silicosis. Analysis of haplotypes of polymorphisms in FAS showed there was a 2.71-fold increased risk (OR 2.71, 95% CI 1.22-6.03, $P = 0.011$) of silicosis for subjects with alleles of FAS-1377G and FAS-670G, compared with those carrying alleles of FAS-1377G and FAS-670A. The investigators concluded that extended haplotype FAS-1377G/-670G may play a role in the development of silicosis in the Chinese population.[333]

449. In 2011, Chinese researchers investigated the relationship between apoptosis of alveolar macrophages (AMs) and human silicosis. AM apoptosis was determined in whole-lung lavage fluid from 48 male silicosis patients, 13 male workers exposed to silica, and 13 male healthy volunteers. The relationships between apoptosis index (AI) and silica exposure history, soluble Fas (sFas)/membrane-bound Fas (mFas), and caspase-3/caspase-8 were analyzed. AI, mFas, and caspase-3 were significantly higher in lung lavage fluids from silicosis patients than those of exposed workers and healthy volunteers, but the level of sFas demonstrated a decreasing trend. AI was related to silica exposure, upregulation of mFas, and activation of caspase-3 and -8, as well as influenced by smoking status after adjusting for confounding factors. The investigators concluded that these results indicate that AM apoptosis could be used as a potential biomarker for human silicosis, and that the Fas/FasL pathway may regulate this process.[334]

[333] Wu F, et al., "Genetic polymorphisms of IL-1A, IL-1B, IL-1RN, NFKB1, FAS and FASL, and risk of silicosis in a Chinese occupational population," *Am. J. Ind. Med.* 2008; 51(11):843-851.

[334] Yao SQ, et al., "Fas/FasL pathway-mediated alveolar macrophage apoptosis involved in human silicosis," *Apoptosis* 2011; 16:1195-1204.

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i. Krebs von den Lungen-6 (KL-6)

450. "Krebs von den Lungen-6 (KL-6) is a kind of transmembrane mucoprotein, with high molecular weight, secreted by proliferating or damaged type II alveolar epithelial cells, which is specific in judging the function of type II alveolar epithelial cells."[335]

451. "KL-6 is mainly localized in the cytoplasm and membrane of alveolar type II epithelial cells and bronchial epithelial cells.[336] "KL-6 is also expressed in the cytoplasm of Clara cells and in bronchial glands."[337] "KL-6 can promote the proliferation and migration of fibroblasts, inhibit cell apoptosis, and increase the development of pulmonary fibrosis."[338]

452. Since at least 2005, Krebs von den Lungen-6 has been recognized as a biological marker for the activity of diffuse interstitial lung disease.[339] Krebs von den Lungen-6 has been reported to be a biomarker of pulmonary fibrosis,[340] interstitial lung disease,[341] idiopathic pulmonary

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[335] Qin H, et al., "Krebs von den Lungen-6 associated with chest high-resolution CT score in evaluation severity of patients with interstitial lung disease," *Pulmonology* 2019; 2593):143-148.

[336] Xue C, et al., "Serum concentrations of Krebs von den Lungen-6, surfactant protein D, and matrix metalloproteinase-2 as diagnostic biomarkers in patients with asbestosis and silicosis: a case-control study," *BMC Pulmonary Med.* 2017; 17:144, citing Ohnishi H, et al., "Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases," *Am. J. Respir. Crit. Care Med.* 2002;165:378-381.

[337] Xue C, et al., "Serum concentrations of Krebs von den Lungen-6, surfactant protein D, and matrix metalloproteinase-2 as diagnostic biomarkers in patients with asbestosis and silicosis: a case-control study," *BMC Pulmonary Med.* 2017; 17:144, citing Ohnishi H, et al., "Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases," *Am. J. Respir. Crit. Care Med.* 2002;165:378-381.

[338] Xue C, et al., "Serum concentrations of Krebs von den Lungen-6, surfactant protein D, and matrix metalloproteinase-2 as diagnostic biomarkers in patients with asbestosis and silicosis: a case-control study," *BMC Pulmonary Med.* 2017; 17:144, citing Ohshimo S, et al., "KL-6, a human MUC1 mucin, promotes proliferation and survival of lung fibroblasts," *Biochem. Biophys. Res. Commun.* 2005; 338:1845-1852.

[339] Morell EB, et al., "Multiple Pulmonary Nodules and Amiodarone. KL-6 as a New Diagnostic Tool," *Rev. Esp. Cardiol.* 2005; 58(4):447-449.

[340] Wang C, et al., "Krebs von den Lungen-6 (KL-6) as a diagnostic marker for pulmonary fibrosis: A systematic review and meta-analysis," *Clin. Biochem.* 2023; 114:30-38; Soccio P, et al., "Role of BAL and Serum Krebs von den Lungen-6 (KL-6) in Patients with Pulmonary Fibrosis," *Biomedicines* 2024; 12:269.

[341] Lederer C, et al., "Krebs von den Lungen-6 as a Potential Predictive Biomarker in Fibrosing Interstitial Lung Diseases," *Respiration* 2023; 102;591-600; Millan-Billi P, et al., "Diagnostic Value of Krebs von den Lungen (KL-6) for Interstitial Lung Disease: A European Prospective Cohort," *Arch. Bronchoneum.* 2024; 60:350-355; Navya C, et al., "Diagnostic value of Krebs von den Lungen-6, a serological biomarker in interstitial lung disease," *J. Curr. Res. Sci. Med.* 2024; 10:155-161; Song JH, et al., "Krebs von den Lungen-6 as a biomarker for distinguishing between interstitial lung disease and interstitial lung abnormalities based on computed tomography findings," *J.*

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fibrosis,[342] fibrotic interstitial pneumonia,[343] progressive pulmonary fibrosis,[344] hypersensitivity pneumonitis,[345] combined pulmonary fibrosis and emphysema,[346] systemic sclerosis,[347] sarcoidosis,[348] connective tissue disease associated interstitial lung disease,[349] rheumatoid arthritis associated interstitial lung disease,[350] and coal workers' pneumoconiosis.[351]

Thorac. Dis. 2025; 17(3):1377-1386.

[342] Aloisio E, et al., "Prognostic role of Krebs von den Lungen-6 (KL-6) measurement in idiopathic pulmonary fibrosis: a systematic review and meta-analysis," *Clin. Chem. Lab. Med.* 2021; 59(8):1400-1408; Li F, et al., "Elevated Serum Level of Krebs von den Lungen-6 Predicts Death in Patients with Comorbid Idiopathic Pulmonary Fibrosis and Obstructive Sleep Apnea," *Nature Sci. Sleep* 2025; 17:975-985.

[343] Yamakawa H, et al., "Evaluation of changes in the serum levels of Krebs von den Lungen-6 and surfactant protein-D over time as important biomarkers in idiopathic fibrotic nonspecific interstitial pneumonia," *Respir. Investig.* 2019; 57(5):422-429; Wakamatsu K, et al., "Prognostic performance of Krebs von den Lungen-6, surfactant protein A, surfactant protein D levels in the serum and bronchoalveolar lavage fluid in chronic fibrosing interstitial pneumonia: a retrospective study," *BMC Pulmonary Med.* 2024; 24:404.

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[345] He J, et al., "Krebs von den Lungen-6 as a clinical marker for hypersensitivity pneumonitis: A meta-analysis and bioinformatics analysis," *Front. Immunol.* 2022; 13:1041098.

[346] Kishaba T, et al., "A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema," *BMJ Open* 2012; 2:e000988; Demirdöğen E, et al., "serum Krebs von den Lungen-6: Promising Biomarker to Differentiate CPFE from IPF," *Sarcoidosis Vasculitis Diffuse Lung Diseases* 2022; 39(4): e2022035; Zhou A, et al., "Serum Krebs von den Lungen-6 as a potential biomarker for distinguishing combined pulmonary fibrosis and emphysema from chronic obstructive pulmonary disease: A retrospective study," *Heliyon* 2024; 10: e35099.

[347] Benyamine A, et al., "Elevated serum Krebs von den Lungen-6 in systemic sclerosis: a marker of lung fibrosis and severity of the disease," *Rheumatol. Int.* 2018; 38(5):813-819; Shirai Y, et al., "Clinical relevance of the Serial Measurement of Krebs von den Lungen-6 Levels in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease," *Diagnostics* 2021; 11:2007; Ibrahim NH, et al., "Significance of serum Krebs von den Lungen-6 in systemic sclerosis," *Egyptian Rheumatol. Rehab.* 2023; 50:59.

[348] Menon B, et al., "Serum krebs von den lungen-6 (KL-6): a promising biomarker in sarcoidosis," *MOJ Curr. Res. & Rev.* 2018; 192):44-47.

[349] Ma H, et al., "The value of serum Krebs von den Lungen-6 as a diagnostic marker in connective tissue disease associated with interstitial lung disease," *BMC Pulmonary Med.* 2020; 20:6.

[350] Hammoda RM, et al., "Krebs von den Lungen-6, a promising marker in evaluating the severity of interstitial lung disease in Egyptian rheumatoid arthritis patients," *Egyptian J. Immunol.* 2021; 28(4):241-249; Fotoh DS, et al., "Serum Krebs von den Lungen-6 and lung ultrasound B lines as potential diagnostic and prognostic factors for rheumatoid arthritis-associated interstitial lung disease," *Clin. Rheumatol.* 2021; 40(7):2689-2697.

[351] Hou Z, et al., "Serum Osteopontin, KL-6, and Syndecan-4 as Potential biomarkers in the Diagnosis of Coal Workers' Pneumoconiosis: A Case-Control Study," *Pharmacogenomics Personalized Med.* 2023; 16:537-549.

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453. Krebs von den Lungen-6 has been identified as a marker of progression in interstitial lung disease,[352] a marker of severity of interstitial lung disease,[353] and a marker of exacerbation of interstitial lung disease[354] and idiopathic pulmonary fibrosis.[355]

454. Krebs von den Lungen-6 has been associated with chest high-resolution CT score in patients with interstitial lung disease[356] and idiopathic pulmonary fibrosis.[357]

455. Importantly, serum Krebs von den Lungen-6 level has been shown to predict response to antifibrotic therapy treatment in patients with idiopathic pulmonary fibrosis.[358]

456. In 2014, Chinese researchers investigated the correlation between pulmonary fibrosis and Krebs von den Lungen-6 (KL-6) level in serum and bronchoalveolar lavage fluid (BALF) in mice exposed to silica. Sixty C57BL/6 mice were divided randomly into a silica-treated group and a control group. The mice in the silica-treated group were injected with silica suspension and those in the control with normal saline through the trachea. The mice were sacrificed at the 30th, 45th, 60th, 75, and 90th day after the silica exposure. KL-6 in the serum and BALF was determined with enzyme-linked immunosorbent assay (ELISA). The lung tissues were fixed and stained with Masson stain for the evaluation of pulmonary fibrosis. Collagen deposition in lung tissue was observed as early as 45 days after silica exposure. Compared with the mice 45 days after silica treatment,

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[354] Saeed ZH, et al., "Serum Krebs von den Lungen (KL-6) level as a marker of exacerbation of interstitial lung diseases," *Egyptian J. Bronchology* 2020; 14:41.

[355] Choe EJ, et al., "Role of blood Krebs von Lungen-6 in predicting acute exacerbation in patients with idiopathic pulmonary fibrosis," *PLoS One* 2025; 20(5): e 0323784.

[356] Qin H, et al., "Krebs von den Lungen-6 associated with chest high-resolution CT score in evaluation severity of patients with interstitial lung disease," *Pulmonology* 2019; 25(3):143-148.

[357] Sanjan G, et al., "Correlation of Serum Krebs von den Lungen-6 Levels with Fibrosis Score on High Resolution Chest Tomography and Pulmonary Function Parameters in Treatment Naive Idiopathic Pulmonary Fibrosis," *Sarcoidosis Vasculitis Diffuse Lung Dis.* 2024; 4193): e2024044.

[358] Choi MG, et al., "Blood Krebs von den Lungen-6 levels predict treatment response to antifibrotic therapy in patients with idiopathic pulmonary fibrosis," *Respir. Res.* 2022; 23:334.

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pulmonary fibrosis scores were all significantly increased for the silica-treated mice at the 60th, 75th, and 90th day after exposure ($P < 0.01$ for all). For the mice of 60, 75 and 90 days after the silica treatment, the serum KL-6 levels were obviously higher than that of the control and the mice of 45 days after silica exposure ($P < 0.01$). For the mice of 75 and 90 days after silica treatment, the KL-6 levels in BALF were obviously higher than those of the control and silica-treated mice 60 days after exposure ($p < 0.01$ for all) and serum and BALF KL-6 levels were positively correlated with the scores of pulmonary fibrosis ® = 0.866 or 0.737, $P < 0.01$). The investigators concluded that pulmonary fibrosis occurs 45 days after silica exposure and serum and BALF KL-6 level is positively correlated with the severity of pulmonary fibrosis in mice.[359]

457. In 2017, Chinese researchers evaluated Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D) and 3 matrix metalloproteinases as potential diagnostic biomarkers for asbestosis and silicosis. Serum concentrations were measured in 43 patients with asbestosis, 45 patients with silicosis, 40 dust-exposed workers without pneumoconiosis, and 45 healthy controls. Chest HRCT images were reviewed by experts blinded to the clinical data. According to the receiver operating characteristic (ROC) curve, the ideal level of each biomarker and its diagnostic sensitivity were obtained. Serum KL-6 concentrations were highest in patients with asbestosis and next highest in patients with silicosis; these concentrations were significantly different from those of the dust-exposed workers and healthy controls. Serum concentrations of KL-6 were not significantly different among the various stages of silicosis. The investigators concluded that KL-6, SP-D and MMP-2 are available biomarkers for the adjuvant diagnosis of asbestosis and silicosis and that the combination of all three biomarkers may improve the diagnostic sensitivity for asbestosis and silicosis.[360]

458. In 2019, Chinese researchers investigated the effects of long-term exposure to silica dust on serum CC16 and KL-6 levels in silicosis patients. Patients with stage I silicosis hospitalized at the researcher's hospital from April 2016 to April 2017 were the silicosis group. Silica dust-

[359] Xu E-Y, et al., "Correlation between pulmonary fibrosis and KL-6 level in silica-treated mice," *Chin. J. Public Health* 2014; 30(12):1536-1538.

[360] Xue C, et al., "Serum concentrations of Krebs von den Lungen-6, surfactant protein D, and matrix metalloproteinase-2 as diagnostic biomarkers in patients with asbestosis and silicosis: a case-control study," *BMC Pulmonary Med.* 2017; 17:144.

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exposed workers without silicosis given physical examinations at the hospital were the dust-exposed group. A healthy control group was comprised of patients without silica dust exposure who were physical examinations. The levels of CC16 and KL-6 in serum of all subjects were determined by enzyme-linked immunosorbent assay (ELISA) , and the levels of CC16 and KL-6 in serum were compared among the three groups. The level of serum KL-6 in the silicosis group was significantly decreased (P<0.01) compared with the control group, while the level of KL-6 in the serum of the dust-exposed group was significantly increased (P<0.01).[361]

459. In 2023, Chinese researchers analyzed changes of serum Krebs von den Lungen-6 and six other potential biomarkers in plasma of patients with occupational silicosis and explored their clinical value in determining the stage of silicosis. A total of 100 male silicosis patients were selected as the silicosis group (63 cases in stage I and 37 cases in stage II subgroups), and 100 male healthy individuals were selected as the control group in a 1:1 matched case-control study. Enzyme-linked immunosorbent assay was used to analyze levels of the biomarkers in plasma. Their clinical value for diagnosing silicosis was evaluated using receiver operating characteristic (ROC) curve, discriminant analysis stepwise method, and Fisher discriminant function analysis. Plasma levels of all the biomarkers in the silicosis group, silicosis stage I subgroups and stage II subgroups were higher than those in the control group (all P<0.05). KL-6 levels in the stage II subgroup were significantly increased compared to the stage I subgroup (P<0.05). The investigators concluded that KL-6 along with the other biomarkers could be used as biomarkers for the diagnosis of silicosis.[362]

460. In 2025, Romanian researchers investigated KL-6 as a diagnostic and prognostic biomarker in 108 silica-exposed workers and 25 healthy controls. Chest radiography, pulmonary function tests, inflammatory markers were collected. Progressive massive fibrosis (PMF) was defined according to the ILO classification. PMF was present in 23 subjects. Serum KL-6 levels were significantly higher in subjects with PMF than in controls, exposed workers or simple silicosis (p<0.001). In PMF, serum KL-6 positively correlated with C-reactive protein (CRP) and Erythrocyte

[361] Liu J, et al. ["The effects of long-term exposure to silica dust on serum CC16 and KL-6 levels," *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2019; 37(8):567-570 [in Chinese with English abstract].

[362] Zhang Z, et al., "Changes of biomarkers in plasma of patients with occupational silicosis and their diagnostic value," *China Occup. Med.* 2023; 50(6):701-705.

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sedimentation rate (ESR), and negatively with forced vital capacity (FVC) % predicted. At a cut-off of 436 U/mL, serum KL-6 differentiated exposed workers from PMF with a specificity and sensitivity exceeding 90% (p<0.0001), while a cut-off of 445 U/mL differentiated simple silicosis from PMF (p<0.0001). In the multivariate analysis, serum KL-6 levels were independently associated with risk of fibrosis. The investigators concluded that serum KL-6 appears to be a promising biomarker for the occurrence and progression of PMF in silica-exposed workers.[363]

461. In 2025, Chinese researchers evaluated levels of Krebs von den Lungen-6 (KL-6) in patients with early-stage silicosis and exposed its potential as a diagnostic biomarker. They collected blood samples from 40 stage I silicosis patients, 57 dust-exposed workers (DEWs), and 70 healthy controls (Hcs) and measured concentrations of KL-6, C-reactive protein (CRP), and angiotensin-converting enzyme (ACE). Receiver operating characteristic (ROC) curve analysis was utilized to evaluate the diagnostic efficacy of KL-6, in combination with other biomarkers for the early stage of silicosis. The association between lung function and KL-6 levels in silicosis patients was evaluated using partial correlation analysis. Serum levels of KL-6, CRP, and ACE were remarkably elevated in stage I silicosis patients compared to HCs and DEWs. KL-6 demonstrated an adjusted area under the curve (AUC) of 0.770 for distinguishing stage I silicosis patients from HCs, with a sensitivity of 80.0% and a specificity of 70.0%. When comparing silicosis patients to DEWs, KL-6 alone achieved an adjusted AUC of 0.735, with sensitivity and specificity of 45.0% and 89.5%, correspondingly. The integration of KL-6, CRP, and ACE demonstrated the highest diagnostic efficacy among all tested combinations. Furthermore, serum KL-6 levels were negatively correlated with vital capacity (VC) in silicosis patients. The investigators concluded that serum KL-6 may serve as a potential biomarker for early silicosis diagnosis, that its diagnostic performance is significantly improved when combined with CRP ad ACE, offering a potential multi-biomarker approach for enhanced detection in the early stages of the disease.[364]

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[363] Smărăndescu R-A, et al., "Serum concentrations of Krebs von den Lungen-6 as prognostic biomarker in patients with silicosis," *Front. Med.* 2025; 12:1579209.

[364] Nong Q, et al., "Serum Krebs von den Lungen-6 as a potential biomarker for early diagnosis of silicosis: a case-control study," *BMC Pulmonary Med.* 2025; 25:366.

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j. Lactate Dehydrogenase

462. In 1981, Indian researchers investigated the lactate dehydrogenase (LDH) isozenyme pattern in rat macrophages and studied the release of LDH isoenzymes from cultured macrophages exposed to silica dust and the pattern of serum LDH isoenzymes in silica exposed rats. They found that silica-exposed macrophages liberated LDH5 in the supernatant culture medium and this isoenzyme was increased in serum of silicotic rats during the early stages of disease development.[365]

463. The same year, researchers from Czechoslovakia monitored the activity of seven enzymes, including lactate dehydrogenase, of intermediary metabolism in lung tissues during the development of experimental silicosis in rats. They concluded that the lung tissues of silicotic rats have an enhanced capacity for anaerobic degradation of saccharides with lactate as the end product, which may be related to the activation of collagen prolyl hydroxylase.[366]

464. In 1990, researchers from Québec measured lactate dehydrogenase activities in lung lavage of 24 workers in the Québec granite industry and 25 control subjects. They found significant increases in LDH activities in the workers' lung lavage, even in the absence of established silicosis. They looked at a similar observation in the sheep model of early silicosis, measured quartz content of lung lavage, and found significant correlation with LDH levels ® = 0.64, $p < 0.001$). All of the quartz particles in human and sheep lung lavage were in the alveolar macrophages. To further test the relationship of macrophage damage from the cytotoxicity of quartz, they measured the release of LDH by sheep alveolar macrophage in 24 hour cell culture under control conditions, exposure to inert dust, titanium, minusil-5 quartz, or aluminum-treated quartz. LDH release was at control levels during titanium exposure and showed a significant dose-related increase during quartz exposure. The researchers concluded that their study showed a cytotoxic effect of quartz inhalation in humans and that this effect is related to the intensity of quartz retention in the lung macrophages.[367]

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[365] Bansal SK et al., "Lactate dehydrogenase isoenzymes in macrophages and serum during the development of pulmonary silicosis in the rat," *Toxicol. Lett.* 1981; 7(4-5):279-283.

[366] Miřejovská E, et al., "Enzyme changes during experimental silicotic fibrosis: II. Intermediary metabolism enzymes of the lungs," *Environ. Res.* 1981; 25(2):434-440.

[367] Larivée P, et al., "Enzyme activities of lung lavage in silicosis," *Lung* 1990; 168(3):151-158.

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465. In 1991, researchers from Pittsburgh studied total serum LDH concentrations and LDH isoenzyme fractions measured before and after whole lung lavage. Total serum LDH was elevated before lavage in 10 of 16 patients. Pre-lavage serum LDH and pre-lavage alveolar-arterial O2 gradient showed a significant correlation ® = 0.62, $p < 0.05$). A decrease in serum LDH was found after lavage in all patients in whom post-lavage data was available (paired t test, $p < 0.01$), although the magnitude of this decrease varied considerably. The isoenzyme pattern before lavage was isomorphic and was unchanged after whole lung lavage. This was in marked contrast to the LDH isoenzyme pattern observed in the lavage effluent, which showed a lower percent LDH1 and LDH2 and a higher percent LDH3, LDH4, and LDH5 compared to the corresponding pre-lavage isoenzyme percentages for serum (unpaired t test, $p < 0.001$). The researchers concluded that these data confirm that elevated serum LDH is a common finding in pulmonary alveolar proteinosis and that the LDH elevation found consistently in the alveolar fluid points to this as the source of the serum LDH.[368]

466. In 1996, researchers from the Netherlands published a review in which they concluded that that measurement of LDH activity levels and its isoenzyme pattern in pleural effusion and in bronchoalveolar lavage fluid would be informative of lung and pulmonary endothelial cell injury.[369]

467. The following year the same researchers investigated the serum LDH isoenzyme pattern after coal-dust exposure and its relation to pulmonary function tests. A total of 201 ex-coal miners with a history of coal-dust exposure more than 20 years, were included in the study. The serum LDH activity was found to be elevated in 79.1% of the ex-coalminers (634 C 245 U l^{-1}). In 196 of the 201 cases (97.5%), a high LDH_3 level (31 ± 4%) was demonstrated. A moderate negative relation was found between the forced expiratory volume in 1 second (FEV_1) and the LDH activity ® = 0.26; $P < 0.001$), as well as between FEV_1 and LDH_3 activity ® = - 0.23; $P < 0.001$), even in the subgroup (n=42) with a normal LDH. The investigators concluded that these results suggest that

[368] Hoffman RM, et al., "Serum and lavage lactate dehydrogenase isoenzymes in pulmonary alveolar proteinosis," *Am. Rev. Respir. Dis.* 1991; 143(1):42-26.

[369] Drent M, et al., "Usefulness of lactate dehydrogenase and its isoenzymes as indicators of lung damage or inflammation," *Eur. Respir. J.* 1996; 9:1736-1742.

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coal-dust, even many years after the actual exposure, causes an increase in the total serum LDH activity and changes in the LDH-isoenzyme pattern, mainly characterized by a high LDH_3 activity.[370]

468. In 2014, a researcher from India investigated total lactate dehydrogenase (LDH) activity in blood samples of silica-exposed agate workers as a non-invasive means of measuring silica-induced toxicity. Blood samples were collected from agate workers and control subjects. Total LDH activity was measured in the blood plasma and blood cells of the agate workers and the controls, using sodium pyruvate as a substrate. Reduction of pyruvate to L-lactate with the concurrent oxidation of nicotinamide adenine dinucleotide (NADH) during the assay was monitored by change in absorbance (or optical density) at 340 nm at the fixed interval of 10 min. The ratio of LDH activity (blood plasma/blood cells) in blood samples was calculated to detect cytotoxicity in exposed workers. LDH activity in blood plasma samples of exposed workers was increased about 25-fold, while the activity in the blood cells of silica-exposed agate workers was reduced to 10% of controls. The ratio of LDH activity (blood plasma/cells) was found to be 6.6 in the silica-exposed agate workers, while it was 0.02 in control (non-exposed) subjects. The investigators concluded that their study showed that total LDH activity and the LDH ratio (plasma/cells), along with occupational exposure history, are markers for silica exposure-induced toxicity in agate workers.[371]

469. In 2022, Spanish researchers investigated circulating biomarker levels and systemic inflammatory indices in Engineered Stone (ES) silicosis patients whose exposure to ES dust ended several years ago. Ninety-one adult men, ex-workers in the manufacturing of ES, 53 diagnosed with SS and 38 with PMF, and 22 healthy male volunteers (HC) as controls not exposed to ES dust, were recruited. Circulating levels of lactate dehydrogenase (LDH) and other enzymes were obtained from clinical reports after being measured from blood samples. As biochemical markers, lactate dehydrogenase was the only enzyme that showed a significant sequential increase (HC = 262 ±48.1;

[370] Cobben NAM, et al., "Serum lactate dehydrogenase and its isoenzyme pattern in ex-coalminers," *Respir. Med.* 1997; 91:616-623.

[371] Aggarwal BD, "Lactate dehydrogenase as a biomarker for silica exposure-induced toxicity in agate workers," *Occup. Environ. Med.* 2014; 71:578-582.

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SS = 315.4 ±65.4).[372]

470. In 2023, Brazilian researchers evaluated the association of inflammatory markers with the presence of silicosis and lung function impairment in silica-exposed workers. Among 297 men, 51 were unexposed controls (G1), 149 were exposed to silica without silicosis (G2), and 97 were exposed to silica with silicosis (G3). Platelet/lymphocyte ratio, lactate dehydrogenase, soluble tumor necrosis factor II, and macro-phage inflammatory protein-4 were associated with silicosis.[373]

471. In 2024, Spanish researchers assessed whether routine blood biomarkers, coupled with machine learning techniques, can differentiate between healthy individuals, subjects with Simple Silicosis and Progressive Massive Fibrosis. One hundred and seven men diagnosed with silicosis, ex-workers in the engineered stone (ES) sector, and 22 healthy male controls not exposed to ES dust were recruited. Twenty-one primary biochemical markers derived from peripheral blood extraction were obtained retrospectively from clinical hospital records. Relief-*F* features selection technique was applied, and the resulting subset of 11 biomarkers was used to build five machine learning models, demonstrating high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. Percentage of lymphocytes, angiotensin-converting enzyme, and lactate dehydrogenase indexes were revealed as blood biomarkers with significant cumulative importance for the machine learning models. The researchers concluded these biomarkers could detect chronic inflammatory status and serve as a tool for the diagnosis, monitoring, and early detection of silicosis progression.[374]

472. In 2024, Japanese researchers investigated bronchoalveolar lavage fluid (BALF) progressive fibrosing interstitial lung disease (PF-ILD) diagnosis and prognosis assessment. Overall, 120 patients with interstitial pneumonia who could be diagnosed with PF-ILD or non PF-ILD were enrolled in this retrospective study. PF-ILD was diagnosed according to Cottin's definition. All

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[372] Garcia-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

[373] Lombardi EMS, et al., "Biomarkers related to silicosis and pulmonary function in individuals exposed to silica," *Am. J. Ind. Med* 2023; 66(11):984-995.

[374] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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patients underwent bronchoscopy and BALF collection. Blood and BALF parameters, high-resolution computed tomography (HRCT) patterns, and spirometry data to identify factors influencing PF-ILD diagnosis and prognosis were evaluated. Multivariate logistic regression analysis revealed that in BALF lactate dehydrogenase (cut-off 275, AUC 0.69; sensitivity 0.57; specificity 0.78) correlated with death within 3 years.[375]

473. In 2025, Chinese researchers published results of a case-control study in which they screened biomarkers for the diagnosis of silicosis using LASSO regression, SVM and RF. A sample of 612 subjects (half cases and half controls) were randomly divided into training and test groups in a 2:1 ratio. Logistic regression analysis and receiver operating characteristic (ROC) curves were used to construct a multiple biomarker-based model for the diagnosis of silicosis, which was applied to both the training and the testing data sets. The training cohort revealed significant differences in multiple hematologic parameters between silicosis patients and healthy individuals. Based on machine learning, 8 silicosis biomarkers were screened and identified from routine blood cell, biochemical and coagulation parameters. D-dimer (DD), Albumin/Globulin (A/G), lactate dehydrogenase (LDH) and white blood cells (WBC) were selected for constructing a logistic regression model for silicosis diagnostics. The model had a satisfactory performance in the training cohort with an area under the ROC curve (AUC) of 0.982, diagnostic sensitivity of 95.4%, and specificity of 92.2%. The model had a prediction accuracy of 0.936 with an AUC of 0.979 in the independent test cohort. Diagnostic accuracies of the logistic model in silicosis stages 1, 2, and 3 were 88.0, 95.4, and 94.3% with an AUC of 0.968, 0.983, and 0.990 for silicosis, respectively. The researchers concluded their model based on DD, A/G, LDH and WBC could be used to screen workers for silicosis because it is cheap, sensitive, specific, and offers a potential strategy for large-scale screening of silicosis.[376]

[375] Watase M, et al., "Diagnostic and prognostic biomarkers for progressive fibrosing interstitial lung disease," *PLoS One* 2023; 18(3):e0283288.

[376] Sun G-K, et al., "Development of a multi-laboratory integrated predictive model for silicosis utilizing machine learning: a retrospective case-control study," *Front. Public Health* 2025; 12:1450439.

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k. Neopterin

474. "Neopterin is a biomarker of the activation of cellular immunity."[377] "As an early and valuable biomarker of cellular immunity, neopterin is a low-molecular-mass compound belonging to the class of pteridines. It is produced by guanosine triphosphate via interferon-γ, following the activation of T cells."[378] "Human macrophages and dendritic cells produce Neopterin derivates after stimulation with interferon-γ, and serve as a marker of activated cell-mediated immune response."[379]

475. "The production of neopterin by monocytes/macrophages has been reported to be closely related to the capacity of the cells to release toxic metabolites, especially ROS [reactive oxygen species], and there an increase in its concentration in body fluids could be an indirect estimate of cell-mediated oxidative stress."[380] "Neopterin was also shown to induce apoptosis in T lymphocytes,[381] and in alveolar epithelial cells."[382] "It is well known that neopterin levels show considerable alteration in various diseases such as autoimmune and inflammatory diseases, and malignancies."[383]

476. In 2003, Turkish investigators observed alteration of neopterin in silica exposure and

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[377] Heneberk O, et al., "Neopterin, the Cell-Mediated Immune Response Biomarker, in Inflammatory Periodontal Diseases: A Narrative Review of a More than Fifty Years Old Biomarker," *Biomedicines* 2023; 11:1294.

[378] Altindag ZZ, et al., "Neopterin as a new biomarker for the evaluation of occupational exposure to silica," *Int. Arch. Occup. Environ. Health* 2003; 76:318-322.

[379] Prakova G, et al., "The Potential Role of Neopterin as a Biomarker for Silicosis," *Trakia J. Sci.* 2005; 3(4):37-41.

[380] Gulumian M, et al., "Mechanistically Identified Suitable Biomarkers of Exposure, Effect, and Susceptibility for Silicosis and Coal-Worker's Pneumoconiosis: A Comprehensive Review," *J. Toxicol. Environ. Health, Part B* 2006; 9:357-395, citing Murr C, et al., "Increased neopterin concentrations in patients with cancer: Indicator of oxidative stress?" *Anticancer Res.* 1999; 19:1721-1728.

[381] Gulumian M, et al., "Mechanistically Identified Suitable Biomarkers of Exposure, Effect, and Susceptibility for Silicosis and Coal-Worker's Pneumoconiosis: A Comprehensive Review," *J. Toxicol. Environ. Health, Part B* 2006; 9:357-395, citing Wirleitner B, et al., "Induction of apoptosis in human blood T cells by 7,8-dihydroneopterin: The difference between healthy controls and patients with systemic lupus erythematosus," *Clin. Immunol.* 2003; 107:152-159.

[382] Gulumian M, et al., "Mechanistically Identified Suitable Biomarkers of Exposure, Effect, and Susceptibility for Silicosis and Coal-Worker's Pneumoconiosis: A Comprehensive Review," *J. Toxicol. Environ. Health, Part B* 2006; 9:357-395, citing Schobersberger W, et al., "Neopterin and 7,8-dihydroneopterin induce apoptosis in the rat alveolar epithelial cell line L2," *FEBS Lett.* 1996; 397:263-268.

[383] Altindag ZZ, et al., "Neopterin as a new biomarker for the evaluation of occupational exposure to silica," *Int. Arch. Occup. Environ. Health* 2003; 76:318-322.

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assessed whether screening of neopterin levels may be of use for assessment of occupational silica exposure. Serum and urinary neopterin levels, in 220 silica-exposed workers and 20 healthy volunteers, were investigated by ELISA, spectrophotometry and HPLC techniques. Serum neopterin levels of control and exposed groups were measured as 5.98±0.44 and 7.86±1.97 nmol/l, respectively (P<0.05). Urinary neopterin levels were also increased in the exposed group: 97.60±41.42 lmol/mol creatinine for controls and 165.59±78.20 lmol/mol creatinine for workers (P<0.05). Correlation between urinary neopterin levels, serum neopterin concentration and working years, smoking status, some complaints, and silica status in the working atmosphere were also evaluated. The investigators concluded that neopterin levels may have diagnostic value in silica-related diseases such as silicosis and that biological monitoring should be done in workplaces for clinical diagnosis and prognosis.[384]

477. In 2005, Bulgarian researchers sought to assess serum neopterin levels in patients with X-ray changes relating to silicosis. Serum neopterin concentrations were measured using ELISA in 60 patients with silicosis, according to conventional X-ray observation (ILO, 2002) and in16 healthy donors. Serum neopterin levels in silicosis patients (2.74 ± 1.12 ng/ml) were significantly higher (p<0.0005) in comparison with controls (1.56 ± 0.39 ng/ml). The investigators concluded that increased serum neopterin concentration could be used as a marker for silicosis.[385]

478. In a 2008, review, Indian researchers concluded that elevated levels of neopterin can be used as a biomarker of cell-mediated immunity, silicosis, and other occupational diseases.[386]

479. In 2009, Bulgarian researchers assessed serum neopterin levels in 60 silicosis patients, 92 male workers exposed to inorganic dust, and 43 controls. Neopterin levels in silicosis patients (2.74 ng/ml) and in exposed workers (3.22 ng/ml) were significantly higher (p<0.0005) compared to controls (1.5 ng/ml). A significant difference was also found between silicosis patients and exposed workers (p<0.005). The researchers concluded that increased serum neopterin levels could

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[384] *Id.*

[385] Prakova G, et al., "The Potential Role of Neopterin as a Biomarker for Silicosis," *Trakia J. Sci.* 2005; 3(4):37-41.

[386] Pingle SK, et al., "Neopterin: Biomarker of cell-mediated immunity and potent usage as biomarker in silicosis and other occupational diseases," *Indian J. Occup. Environ.* 2008; 12:107–111.

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be used as a marker for effect of exposure to inorganic dust containing more than 2% free crystalline silica.[387]

480. In 2011, Iranian researchers published a cross-sectional study in which they investigated the association of crystalline silica aerosols exposure with malondialdehyde in blood serum and urinary neopterin and explored their potential as biomarkers of their external exposure. Nonsmoking and healthy male glass sandblasters and controls were randomly selected and monitored for personal exposure to crystalline silica. High Performance Liquid Chromatography (HPLC) was used to measure malondialdehyde in blood serum, as well as urinary neopterin, and creatinine in all study participants. The mean of personal exposure to crystalline silica aerosols in glass sandblasters was 164 $\mu g/m^3$, compared with less than 0.006 mg/m^3 for controls that was below the detection limit. The mean of blood serum malondialdehyde of sandblasters (49.08±19.05μmole/l) was significantly (p<0.001) higher than that of controls (1.92±0.33 μmole/l). Urinary neopterin of sandblasters was 10.85±3.61 mmole/mole creatinine, which was also significantly (p<0.001) higher than controls 4.71±1.88 mmole/mole creatinine. The investigators concluded that serum malondialdehyde and urinary neopterin could be regarded as biomarkers of exposure to crystalline silica aerosols.[388]

481. In 2013, Turkish researchers investigated whether occupational silica exposure results in alterations in neopterin levels, tryptophan degradation, and activities of superoxide dismutase (SOD) and catalase (CAT), agents in the antioxidant defense system. Fifty-five male denim sandblasting workers and twenty-two healthy men as controls were included. Mean neopterin and kynurenine levels, kynurenine-to-tryptophan ratio, and SOD activity were higher in subjects with silicosis compared to non-exposed controls (all, p<0.05). Neopterin levels and kynurenine-to-tryptophan ratios were positively correlated (p<0.05), but no correlation was observed between length of employment and the measured parameters. The investigators concluded that the results of

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[387] Prakova G, et al., "Serum Neopterin in Silicosis Patients and Workers Exposed to Inorganic Dust," *Scripta Scientifica Medica* 2009; 41(1):91-94. See, also, Prakova G, et al., "Serum neopterin in workers exposed to inorganic dust containing free crystalline silicon dioxide," *Centr. Eur. J. Med.* 2009; 4(1):104-109; Prakova G, et al., "Serum Neopterin in Workers Exposed to Asbestos and coal Dust and Inpatients with Silicosis," *Trakia J. Sci.* 2010; 8:286.

[388] Azari MR, et al., "Serum Malondialdehyde and Urinary Neopterin Levels in Glass Sandblasters Exposed to Crystalline Silica Aerosols," *Int. J. Occup. Hyg.* 2011; 3(1):29-32.

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their study suggest that silica exposure activates cellular immune response and that increased neopterin levels and tryptophan degradation support their use as an indicator of cellular immune response.[389]

482. In 2015, Egyptian researchers sought to determine neopterin levels among workers exposed to marble dust and to assess the use of neopterin versus oxidative stress indicators as a screening tool for silica exposure and effect. The study involved 48 workers, 24 exposed to marble dust and 24 unexposed controls. The exposed workers were subjected to a questionnaire, clinical examination, and laboratory investigations including neopterin levels in urine and oxidative stress indicators (malondialdehyde MDA, and total sulfhydryl group SH) in urine. Comparison of neopterin levels between the studied groups revealed an elevated mean neopterin level among exposed workers with a highly significant statistical difference (p-value < 0.001). The investigators concluded that neopterin levels in urine are significantly increased in workers exposed to marble dust, suggesting use of neopterin as a simple non-invasive quantitative biological indicator for exposure and effect.[390]

483. In recent reviews, Romanian researchers concluded that overall studies showed that neopterin has great potential as a biomarker for early detection of silicosis[391] and Turkish researchers concluded that neopterin can be used to monitor the development and progression of silicosis in periodic examinations.[392]

[389] Palabiyik SS, et al., "Immunomodulation and oxidative stress in denim sandblasting workers: changes caused by silica exposure," *Arh. Hig. Rada Toksikol.* 2013; 64(3):431-437.

[390] Gaballah IMF, et al., "Neopterin Versus Oxidative Stress Indicators Among Egyptian Workers in Marble Industry," *Egypt. J. Occup. Med.* 2015; 39(1):67-83.

[391] Calutu IM, et al., "Biomonitoring exposure and early diagnosis in silicosis: a comprehensive review of the current literature," *Biomedicines* 2023; 11:100.

[392] Ergün R, et al., "Evaluation of neopterin, oxidative stress, and immune system in silicosis," *Turk. J. Biochem.* 2025; published online March 6, 2025.

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l. Systemic Immune-Inflammation Index

484. "The systemic immune-inflammation (SII) index, as a novel inflammation-related index, is a comprehensive combination based on peripheral lymphocyte, neutrophil, and platelet counts. It is calculated as follows: SII = platelet count × neutrophil/lymphocyte count."[393]

485. "The notion of the potential utility of this index is rooted in the special relationship between these cells, where neutrophils, lymphocytes, and platelets play pivotal roles in numerous inflammatory processes."[394]

486. "Unlike other inflammatory biomarkers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) . . . , the systemic immune-inflammation index [is] derived from complete routine tests" and "require[s] no special technique, making [it] . . . rapidly accessible."[395]

487. In 2022, Spanish researchers investigated circulating biomarker levels and systemic inflammatory indices in Engineered Stone (ES) silicosis patients whose exposure to ES dust ended several years ago. Ninety-one adult men, ex-workers in the manufacturing of ES, 53 diagnosed with SS and 38 with PMF, and 22 healthy male volunteers (HC) as controls not exposed to ES dust, were recruited. Circulating levels of lactate dehydrogenase (LDH), angiotensin-converting enzyme (ACE), protein C reactive (PCR), rheumatoid factor, alkaline phosphatase and fibrinogen were obtained from clinical reports after being measured from blood samples. Several systemic inflammation indices, including the systemic immune-inflammation index (SII), showed significant differences between the HC, SS and PMF groups. All these biomarkers were analyzed using receiver operating characteristic (ROC) curves, and the results provided moderately high sensitivity and specificity for discriminating between ES silicosis patient groups and healthy controls. The investigators concluded their study showed that some inflammatory biomarkers, easily available

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[393] Ruta VM, et al., "Neutrophil-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index – Biomarkers in Interstitial Lung Disease," *Medicina* 2020; 56:381, citing Zhang Y, et al., "Systemic immune-inflammation index is a promising noninvasive marker to predict survival of lung cancer," *Medicine* 2019; 98..

[394] Islam MM, et al., "Unraveling the clinical significance and prognostic value of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflamation response index, and delta neutrophil index: An extensive literature review," *Turk. J. Emerg. Med.* 2024; 24:8-19,

[395] Ruta VM, et al., "Neutrophil-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index – Biomarkers in Interstitial Lung Disease," *Medicina* 2020; 56:381.

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from routine blood analysis, are present in ES silicosis patients even several years after cessation of exposure to ES dust and could help assess disease progression.[396]

488. In 2024, Chinese researchers conducted a retrospective study to evaluate the systemic immune-inflammation index (SII) in silicosis. They used data from a large database platform of a tertiary general hospital in Beijing, which was established based on the electronic medical records of the hospital. The clinical data of adult patients diagnosed with silicosis at the Department of Occupational Medicine and Toxicology from 2013 to 2022 were collected. The data extracted from the database were in de-identified form. Only patients with a first diagnosis of silicosis and without conditions that might affect the parameters of routine blood tests were included in the analysis. Analyses were performed to assess the relationship between SII and the advanced stage of silicosis. A total of 246 participants were included in the study. Most of the patients were exposed to silica particles during excavation and digging (n = 149, 60.6%). SII level was significantly higher in patients with advanced stages of silicosis. A multivariate logistic regression analysis revealed that a higher SII level was associated with the advanced stage of silicosis [OR 1.002; 95% CI 1.000–1.003, $p < 0.001$] after adjusting for all covariates. The best cutoff value of SII was 444.1. The results of the subgroup analysis also showed a significant correlation between SII level over 444.1 and the advanced stage of silicosis in groups stratified by gender, smoking history and duration of silica exposure. The results also showed a significant but weak negative correlation between the level of SII and some lung function parameters in silicosis. The researchers concluded that a higher SII is associated with the advanced stage of silicosis and impaired lung function and that SII could be used to routinely assess the severity of silicosis among those occupationally exposed to silica.[397]

489. In 2024, Iranian researchers performed a cross-sectional study to assess whether the systemic immune inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI), could be considered as inflammatory markers in

[396] Garcia-Núñez A, et al., "Inflammatory indices obtained from routine blood tests show an inflammatory state associated with disease progression in engineered stone silicosis patients," *Sci. Rep.* 2022; 12:8211.

[397] Kang H-Y, et al., "The systemic immune-inflammation index is significantly associated with the severity of silicosis: a 9-year retrospective study in Beijing," *Front. Med.* 2024; 11:1351589.

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silica-exposed workers with no silicosis diagnosis. They studied 371 non-silicotic workers exposed to respirable silica dust (RSD) and 1422 reference workers. The workers' exposure to RSD was assessed and inflammatory indices were compared between subgroups of the exposed workers based on the severity and duration of exposure. Significant dose-response relationships were observed between duration of exposure and SII, SIRI and AISI. No significant interaction was observed between duration of exposure to RSD and smoking. Higher AUCs were obtained for SII and AISI. The cut-off values for these biomarkers to be considered abnormal were > 348.48 for SII, > 183.78 for AISI, and > 0.768 for SIRI. The researchers concluded that these systemic inflammation markers could be used as biomarkers for both the diagnosis of silicosis and progression of this disease.[398]

490. In 2024, Spanish researchers assessed whether routine blood biomarkers, coupled with machine learning techniques, can differentiate between healthy individuals and subjects with Simple Silicosis (SS) and Progressive Massive Fibrosis (PMF). A total of 107 men diagnosed with silicosis, ex-workers in the engineered stone (ES) sector, and 22 healthy male controls not exposed to ES dust were recruited. Twenty-one primary biochemical markers derived from peripheral blood were obtained from hospital records. Relief-*F* features selection technique was applied; the resulting subset of 11 biomarkers was used to build 5 machine learning models, showing high performance with sensitivities and specificities in the best case greater than 82% and 89%, respectively. SII was one of these 11 blood biomarkers. The researchers found that SII increased markedly with the onset of SS, being higher in the group of subjects with PMF, thereby indicating its utility as a readily accessible biomarker for diagnosing silicosis and for assessing disease progression.[399]

491. Based on these studies, the systemic inflammation index appears to be a useful biomarker for the diagnosis of silicosis and assessing stage of disease in workers who have been occupationally exposed to artificial stone dust.

[398] Rezaei A, et al., "Systemic inflammation indices as hematological biomarkers of inflammatory response in non-silicotic workers exposed to respirable silica dust," *Toxicol. Lett.* 2024; 395:26-39.

[399] Sanchez-Morillo D, et al., "Integrating routine blood biomarkers and artificial intelligence for supporting diagnosis of silicosis in engineered stone workers," *Bioeng. Transl. Med.* 2024; 9:e10694.

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F. Trace Elements

1. Copper

492. Copper is an essential trace element that is involved in multiple metabolic pathways. It is an essential component of several enzymes involved in the synthesis of adenosine triphosphate (ATP) in mitochondria. It is also required for the formation of connective tissues and in iron metabolism, for oxidizing ferrous iron to ferric ion.[400]

493. It has long been known that copper is increased in serum of silicosis patients. Several foreign language studies reported increased copper in serum of silicotics in the 1950s and 1960s.[401]

494. In 1981, Rumanian researchers investigation serum concentrations of copper, iron, and zinc in silicosis in relation to radiographic stage of the disease according to the I.L.O.-U/C 1971 pneumoconioses international classification), to TB complication, and to plasma proteins level. The determination of oligoelements and plasma proteins was performed in 15 subjects suspected of silicosis and in 141 silicotic patients, selected by three criteria: the type criterium (opacity size, p, q, r), category criterium (number of opacities, 1, 2, 3), and TB complication criterium. The levels of copper, iron, and zinc were also established in 28 active lung TB patients and in a control group. An increase of copper values in blood serum was observed, simultaneously with the progression of silicosis, the greatest change being found in subjects with silicotuberculosis and active TB. A decrease of serum iron was also recorded, parallel to silicosis evolution, as well as a hypozincemia

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[400] Coskun A, et al., "Systematic review and meta-analysis of within-subject and between-subject biological variation estimates of serum zinc, copper and selenium," *Clin. Chem. Lab. Med.* 2022; 60(4):479-482, citing Shenkin A, et al., eds., *Tietz textbook of clinical chemistry and molecular diagnostics*, 5th ed. Elsevier; 2012:895-983

[401] Gaultier M, et al, [Study of cupremia in silicotics], *Arch. Mal. Prof.* 1958; 19(6):592-595 [in French]; Gaultier M, et al., [Study of blood copper levels in silicosis], *Ann. Biol. Clin. (Paris)* 1959; 17(3-4):173-177 [in French]; Guyotjeannin C, [On the subject of the hypercupremia of silicotics], *Arch. Mal. Prof.* 1959; 20:396-399 [in French]; Fati S, et al., [The behavior of ceruloplasmin and of serum copper in pulmonary silicosis and in other diseaes of the respiratory tract], *Folia Med. (Napoli)* 1961; 44:731-751 [in Italian]; Rutgers VH, [Changes in levels of blood copper in coal miners], *Arch. Mal. Prof.* 1966; 27(6):483-490 [in French]; Granata A, et al., [Copper and iron levels in the serum in patients with severe pulmonary silicosis after a long interruption of the specific risk], *Folia Med. (Napoli)* 1968; 51(4):255-263 [in Italian]; Kvasov SE, [Copper and iron in the blood serum of healthy persons, and of patients with silicosis and silicotuberculosis] *Gig. Tr. Prof. Zabol.* 1968; 12(12):57-58 [in Russian].

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with no variations related to the stage of the silicosis. No correlations were found between changes of the oligoelements and the changes of plasma proteins.[402]

495. In 1985, Japanese researchers reported that pulmonary fibrosis is promoted by copper and depressed by zinc.[403]

496. In the late 1980s and early 1990s, Chinese researchers also reported increased copper levels in the serum of silicosis patients.[404]

497. In 1998, Chinese investigators reported increased levels of copper in the serum of silicosis patients, with copper levels increasing with stage of disease, as shown in a Table in the article.[405]

Table. Serum Cu, Zn or Cu/Zn ratio in silicotics (μmol/l)

Group	No. of cases	Cu	Zn	Cu/Zn
control	37	22.19 ± 3.90	16.70 ± 4.20	1.323 ± 0.852
stage I	33	27.31 ± 0.02*	28.41 ± 4.28*	0.962 ± 0.004*
stage II	19	31.83 ± 0.02*	28.86 ± 16.52*	1.103 ± 0.001
stage III	11	33.59 ± 0.02*	24.19 ± 10.17*	1.39 ± 0.002

*Every value in the silicosis group was compared with the corresponding control value and found different with $p<0.01$.

498. In 1999, Romanian researchers determined serum copper levels in 68 male silicosis patients and a control group of 35 healthy subjects. The patients were divided into three subgroups according to stage of disease. The mean value of serum copper increased gradually from stage to stage reaching in stage III the highest copper mean value ($p < 0.01$). Serum copper concentrations also increased with the severity of the disease. The investigators concluded that these changes

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[402] Niculescu T, et al., "Changes of copper, iron, and zinc in the serum of patients with silicosis, silicotuberculosis, and active lung tuberculosis," *Environ. Res.* 1981; 25(2):260-268.

[403] Konishi A, et al., "Changes of trace element copper and zinc in sera of cases with silicosis," *Gastroenterol.* 1985; 89:907-715.

[404] Liu BX, "Study on trace element in the serum of patient with silicosis," *Chinese J. Ind. Med.* 1989; 2:16-18 [in Chinese]; Bai Y, et al., "Changes of trace element copper and zinc in sera of cases with silicosis," *Chinese J. Ind. Hyg. Occup. Dis.* 1993; 11:280 [in Chinese with English abstract]; Ren ML, et al., "Detection of coal silicosis by radioimmunoassay used for ceruloplasmin," *Chinese J. Ind. Hyg. Occup. Dis.* 1993; 11:146 [in Chinese with English abstract].

[405] Wang W, et al., "Serum concentration of copper and zinc in patients with silicosis," *J. Occup. Health* 1998; 40:230-231.

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suggested that copper is directly responsible for the lung changes in silicosis and can be used as an indicator of the severity of the inflammatory reaction.[406]

499. In 2004, Indian researchers conducted a cross-sectional study of 134 workers of quartz stone crushing units to assess the serum copper activity among quartz stone workers. Demographic and occupational details of the subjects were recorded. Standard diagnostic criteria were used for diagnosing silicosis and tuberculosis. The pulmonary functions of the subjects were measured using Spirovit SP-10. The mean age for males was 26.63 ± 6.28 years while that for females was 21.93 ± 4.29 years, and for the whole group was 26.13 ± 6.26 years. Only one case of silicosis and seven cases of tuberculosis were found. The mean serum copper levels of those with respiratory disease was 91.5±19.8 µg/dl, while mean serum copper of those without respiratory disease was 86.8 ± 21.3 µg/dl. However, the difference was not quite statistically significant ($t = 0.64$, $df = 1$, $P>0.05$).[407]

500. The following year, the same researchers published a case report of an asymptomatic 22-year-old male nonsmoker who had worked in stone quartz crushing units for just 2 years. He was diagnosed with silicosis and found to have higher levels of serum angiotensin converting enzyme and serum copper that other subjects exposed to silica dust without observable disease. His serum copper level was 104 mg/dl -- much higher than the mean serum copper level of other silica-exposed workers without disease (86.64 ± 37.7 mg/dl).[408]

501. In 2012, researchers from India reviewed biomarkers of silicosis. They noted that copper plays a very important role in the progress of lung fibrosis, that it is directly related to copper level in serum, and that an increase in ceruloplasmin levels is one factor for the increase in copper

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[406] Cojocaru M, et al., "Silicosis related changes in serum copper," *Rom. J. Intern. Med.* 1999; 37(3):269-273.

[407] Tiwari RR, et al., "Serum copper levels among quartz stone crushing workers: A cross sectional study," *Indian J. Physiol. Pharmacol.* 2004; 48:337-342.

[408] Tiwari RR, et al., "Serum angiotensin converting enzyme activity and serum copper levels in covert silicosis," *Indian J. Occup. Environ. Med.* 2005; 9(3):124-126

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level. They concluded that increased copper and ceruloplasmin levels can help diagnose silicosis.[409]

502. In 2015, Egyptian researchers sought to measure serum levels of angiotensin converting enzyme (ACE), copper (Cu), and ceruloplasmin (Cp) in cement workers occupationally exposed to silica dust as biomarkers of exposure rather than biomarkers of effect for silicosis. Chest X-rays and pulmonary functions were done for 30 silicotic and 42 non-silicotic workers and 42 controls. CT scans were done for the exposed groups and serum levels of Cu, Cp and ACE were estimated. The results showed a highly statistically significant difference between the exposed groups and controls, and between the two exposed groups for the mean levels of all measured biochemical parameters:

Table 1: The mean values of measured serum biochemical parameters of the studied groups

	N	Mean	Std. Deviation	ANOVA F-ratio	ANOVA P-value	LSD
Serum ACE (U/L)	C 42	20.34	5.03			(N,S)
	N 42	50.33	12.45	53.06	P< 0.0001	(C,S)
	S 30	108.27	47.15			(C,N)
Serum Copper (µg/dl)	C 42	46.71	3.59			(N,S)
	N 42	81.01	5.13	88.65	P< 0.0001	(C,S)
	S 30	130.55	35.80			(C,N)
Serum Ceruloplasmin (mg/dl)	C 42	13.19	5.12			(S)
	N 42	15.61	8.58	6.34	P< 0.005	(S)
	S 30	21.95	10.16			(C,N)

C = control; N= non-silicosis; S = silicosis.

The pulmonary functions were significantly lower among silicotic workers than controls and non-silicotic groups. There was a significant positive correlation between duration of employment and serum ACE and Cu. The investigators concluded that the biochemical parameters (Cu, ACE and Cp) can be used as exposure biomarkers to silica dust, providing a better way to diagnose silicosis early.[410]

503. In 2016, researchers from India measured serum copper and zinc activity and correlated it with pulmonary function tests among coal mine workers to determine the extent of lung fibrosis. They conducted a cross-sectional study on two statistically similar groups consisting of 54

[409] Pandey JK, et al., "Biomarkers: A potential prognostic tool for silicosis," *Indian J. Occup. Environ.* 2012; 16:101-107.

[410] Beshir S, et al., "Serum levels of copper, ceruloplasmin and angiotensin converting enzyme among silicotic and non silicotic workers," *Maced. J. Med. Sci.* 2015; 3:467-473.

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dust exposed miners and 50 unexposed controls. Pulmonary function test values using spirometry and serum Cu and Zn levels were determined for all the test subjects. Serum Cu and Zn level increased significantly with duration of dust exposure among miners and their pulmonary function values suggested deterioration in lung. Smokers had significantly higher levels of serum Cu (87.38 ± 6.31µg/dl) and Zinc (80.07 ± 5.59 µg/dl) than non-smokers (81.50 ± 5.01 µg/dl and 78.62 ± 3.11 µg/dl) respectively. Alcoholic habit further deteriorated pulmonary function values and increased serum Cu and Zn values. The investigators observed that serum Cu and Zn concentrations were significantly higher in exposed workers, that they correlate well pulmonary function tests and are a more sensitive indicator for the status of miner's lung than pulmonary function tests. They concluded that the results of their study suggested a strong possibility of serum Cu and Zn as biomarkers for dust-related lung diseases like silicosis.[411]

504. In 2023, Iranian researchers published a systemic review and meta-analysis of studies regarding the relationship between occupational exposure to respirable crystalline silica and serum copper level as a biomarker for the early detection of silicosis. A total of 159 studies were identified, of which eight studies were included in the meta-analysis. Random effect meta-analysis of these eight studies showed that silicosis patients had higher copper levels than individuals without silicosis, with a pooled standardized mean difference (SMD) of 3.02 (95% confidence interval: 0.25, 5.78); I2 = 99.3%, *P* value < 0.001. The subgroup analysis showed that the corresponding figures in those with mean age >40 years and <40 years were 5.79 (2.06, 9.52) and −0.43 (−4.57, 3.70), respectively. No publication bias was found in the analyses. The investigators concluded that their meta-analysis demonstrated that silica exposure may be associated with increasing serum Cu levels.[412]

505. In 2022, researchers from Boston published an article in *Science* in which they showed that copper toxicity occurs via a mechanism that is distinct from all other known mechanisms of

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[411] Agarwal D, et al.. "Serum copper and zinc level as biomarker for dust exposed lung diseases among coal miners," *J. Bio. Env. Sci.* 2016; 8:65-74.

[412] Poormohammadi A, et al., "Relationship between Occupational Exposure to Respirable Crystalline Silica and Serum Copper Level as an Indicator of Silicosis: A Systematic Review and Meta-analysis," *Indian J. Occup. Environ. Med.* 2023; 27:4-8.

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regulated cell death including apoptosis, ferroptosis, pyroptosis and necroptosis. They explained that copper-induced cell death is regulated by mitochondrial ferredoxin 1-mediated protein lipoylation. In this article they proposed that this novel cell death mechanism be termed cuproptosis.[413]

506. In 2024, Chinese investigators noted that recent research had hinted at a potential connection between silicosis and cuproptosis. They sought to explore how cuproptosis-related genes (CRGs) may influence the development of silicosis and elucidate underlying mechanisms of this disease. They conducted an analysis of genes associated with both silicosis and cuproptosis. Key gene identification was achieved through the application of two machine learning techniques. Additionally, the correlation between these key genes and immune cell populations was explored and the critical pathways were discerned. To corroborate their findings, the expression of key genes was verified in both a publicly available silica-induced mouse model and their own silicosis mouse model. A total of 12 differentially expressed CRGs associated with silicosis were identified. Further analysis resulted in the identification of 6 CRGs, namely LOX, SPARC, MOXD1, ALB, MT-CO2, and AOC2. Elevated immune cell infiltration of CD8 T cells, regulatory T cells, M0 macrophages, and neutrophils in silicosis patients compared to healthy controls was indicated. Validation in a silica-induced pulmonary fibrosis mouse model supported SPARC and MT-CO2 as potential signature genes for the prediction of silicosis. These findings highlighted a strong association between silicosis and cuproptosis. Among CRGs, LOX, SPARC, MOXD1, ALB, MT-CO2, and AOC2 emerged as pivotal players in the context of silicosis by modulating CD8 T cells, regulatory T cells, M0 macrophages, and neutrophils.[414]

507. Shortly thereafter, other Chinese researchers observed that increased copper in the serum of silicosis patients suggests that the development of silicosis is accompanied by changes in copper metabolism, but whether cuproptosis is involved in the progression of silicosis had not yet been determined. To test this hypothesis, they screened the genetic changes in patients with

[413] Tsvetkov P, et al., "Copper induces cell death by targeting lipoylated TCA cycle proteins," *Science* 2022; 375(6586):1254-1261.

[414] Ma R, et al., "Cuproptosis-associated hub gene identification and immune cell infiltration patterns in silicosis," *Toxicology* 2024; 504:153762.

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idiopathic fibrosis by bioinformatics methods and predicted and functionally annotated the cuproptosis-related genes among them. Subsequently, they established a mouse silicosis model and detected the concentration of copper ions and the activity of ceruloplasmin (CP) in serum, as well as changes of the concentration of copper and cuproptosis related genes in mouse lung tissues. They identified 9 cuproptosis-related genes among the differential genes in patients with IPF at different times and the tissue-specific expression levels of ferredoxin 1 (FDX1) and Lipoyl synthase (LIAS) proteins. Furthermore, serum CP activity and copper ion levels in silicosis mice were elevated on days 7th and 56th after silica exposure. The expression of CP in mouse lung tissue elevated at all stages after silica exposure. The mRNA level of FDX1 decreased on days 7th and 56th, and the protein level remained in accordance with the mRNA level on day 56th. LIAS and Dihydrolipoamide dehydrogenase (DLD) levels were downregulated at all times after silica exposure. In addition, Heatshockprotein70 (HSP70) expression was increased on day 56. The investigators concluded that the results of their experiments demonstrated that elevated levels of copper loading are present during the development of experimental silicosis in mice, and the expression of core indicators of cuproptosis changes synchronously with serum copper loading levels. Finally, they concluded that cellular cuproptosis may exist in the inflammatory and fibrotic phases of silicosis.[415]

508. In conclusion, serum copper has potential as a biomarker for the detection of early silicosis and progression of the disease and is likely related to a new form of programmed cell death called cuproptosis, which appears to be a mechanism of the development of fibrosis in pulmonary silicosis.

G. Exhaled Breath Analysis

1. VOCs in Exhaled Breath

509. In 2007, Czech researchers measured 8-isoprostane, a marker of oxidative stress, and

[415] Xia J, et al., "Bioinformatics-based dynamics of cuproptosis-related indicators in experimental silicosis," *Ecotoxicol. Environ. Safety* 2024; 275:116286.

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leukotrienes B4, C4, D4, and E4, in exhaled breath condensate in silicosis patients. Sixty subjects were examined, mean age 66.7 years and mean silica exposure 23.6 years. The control group had 25 subjects, mean age 64.7 years. Exhaled breath was collected and 8-isoprostane and leukotrienes were analyzed by high-performance liquid chromatography/mass spectrometry. Several lung function parameters were impaired in silicotics compared to controls; ESR, α1-antitrypsin and proteinuria were higher in the silicotics. Antineutrophilic cytoplasmic antibodies were more frequent in silicotics (39%) than in controls (4%), p=0.0017. The mean level of 8-isoprostane in silicosis patients was 73.6 vs. 43 pg/ml in controls, p=0.0001. Silica exposure category (high, medium, none) was positively associated with 8-isoprostane level. In the patients with complicated silicosis, a high level of 8-isoprostane was found more frequently, p=0.0194. Leukotriene D4 was also increased in the silicotics 21.1 pg/ml vs. 14.7 in the controls, p=0.001. No significant effect of smoking or alcohol on markers examined was seen. The investigators concluded that exhaled breath condensate analysis is useful and contributes to elucidating processes in the respiratory system that derive from silicosis.[416] In a later study the Czech researchers showed that oxidative stress markers in exhaled breath condensate in pulmonary fibrosis are not significantly affected by systemic diseases.[417]

510. In 2016, Iranian researchers published a cross-sectional case-control study of exhaled breath of 69 subjects including 20 workers exposed to silica, 4 silicosis patients, 20 healthy non-smokers, and 25 healthy smokers. Seventy percent and 100% of the exposures to crystalline silica dust exceeded 8-hour time-weighted average Threshold Limit Values in case and positive control groups, respectively. A significant negative correlation was found between dust exposure intensity and FEV1/FVC when exposure and positive control groups were studied in a group (r2= -0.601, P<0.001). Forty VOCs were found in all exhaled breath samples. Among the VOCs, the mean of peak area acetaldehyde, hexanal, nonanal, decane, pentad cane, 2-propanol and 3-hydroxy-2-butanone were higher in exhaled breath of the workers exposed to silica and silicosis patients

[416] Pelclová D, et al., "8-isoprostane and leukotrienes in exhaled breath condensate in Czech subjects with silicosis," *Ind. Health* 2007; 45(6):766-774.

[417] Pelclová D, et al., "Oxidative Stress Markers in Exhaled Breath Condensate in Lung Fibroses Are Not Significantly Affected by Systemic Diseases," *Ind. Health* 2011; 49:746-754.

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compared to the healthy smoker and nonsmoker controls. In some cases the difference was significant ($P<0.05$). Based on the results of their study the investigators concluded that analysis of some VOCs in exhaled breath is an appropriate biomarker to determine exposure to silica.[418]

511. In 2022, researchers from China and Utah developed an engineering solution to breath tests using an electronic nose and evaluated its diagnosis accuracy for silicosis in a cross-sectional study of 221 miners with silicosis and 398 miners without silicosis. Exhaled breath was analyzed by 16 organic nanofiber sensors and a customized sample processing system. Principal component analysis was used to visualize the breath data, and classifiers were trained by two improved cost-sensitive ensemble algorithms (random forest and extreme gradient boosting) and two classical algorithms (K-nearest neighbor and support vector machine). All subjects were included to train the screening model, and an early detection model was run with silicosis cases in stage I. The association between personal smoking habits and classification was investigated by the chi-square test. Classifiers of ensemble learning performed well in both screening and early detection model, with an accuracy range of 0.817–0.987. There was no association between smoking habits and classification accuracy, supporting applicability of models in silicosis screening. The investigators concluded that their e-nose technique and breath analysis methods could provide quick and accurate screening for silicosis.[419]

512. In 2023, Chinese researchers conducted a study to establish regular screening and early diagnosis methods for silicosis. A total of 161 subjects were enrolled in the study, including 69 patients with silicosis and 92 healthy controls. Analysis of volatile organic compounds in exhaled breath was performed by solid-phase microextraction (SPME) combined with gas chromatography mass spectrometry (GC-MS). After excluding pollutants from sampling bags and instruments, 86 VOCs were identified in exhaled breath. Orthogonal partial least squares-discriminant analysis (OPLS-DA) was employed for screening potential biomarkers of silicosis. Components related to

[418] Jalali M, et al., "Oxidative Stress Biomarkers in Exhaled Breath of Workers Exposed to Crystalline Silica Dust by SPME-GC-MS," *J. Res. Health Sci.* 2016; 16(3):153-161.

[419] Xuan W, et al., "Engineering solutions to breath tests based on an e-nose system for silicosis screening and early detection in miners," *J. Breath Res.* 2022; 16:036001.

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smoking were excluded from the biomarkers. Nine possible biomarkers for silicosis were screened: 2,3-butanedione, ethyl acetate, chlorobenzene, o-cymene, 4-ethylhex-2-ynal,3,5-dimethyl-3-heptanol, hydroquinone, phthalic anhydride and 5-(2-methylpropyl)nonane. The nine biomarkers in exhaled breath were preliminarily screened for early diagnosis of silicosis. Based on these screened biomarkers, a predictive model for silicosis was generated with accuracy of 89.61%.[420]

513. In 2025, Australian researcher investigated a rapid, non-invasive diagnostic approach using atmospheric pressure chemical ionization-mass spectrometry (APCI-MS) to analyze volatile organic compounds (VOCs) in exhaled breath from 31 silicosis patients and 60 healthy controls. Six different interpretable machine learning (ML) models with Shapley additive explanations (SHAP) were applied to classify these samples and determine VOC features that contribute most significantly to model accuracy. The extreme gradient boosting classifier demonstrated the highest performance, achieving an area under the receiver-operator characteristic curve of 0.933 with the top ten SHAP features. The *m*/*z* 442 feature, potentially corresponding to leukotriene-E3, emerged as a significant predictor for silicosis. VOC sampling and measurement process took less than five minutes per sample, highlighting its potential suitability for large-scale population screening. Moreover, the ML models were interpretable through SHAP, providing insights into the features contributing to the model's predictions. The investigators concluded that their study suggests that APCI-MS breath analysis could enable early, non-invasive diagnosis of silicosis, helping to improve disease outcomes.[421]

514. The results of these studies shows that exhaled breath analysis can be used as a non-invasive technique for mass screening of individuals occupationally exposed to respirable crystalline silica dust to detect silicosis without radiography prior to the onset of respiratory symptoms and functional impairment.

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[420] Yi Z, et al., "Exploratory study on noninvasive biomarker of silicosis in exhaled breath by solid-phase microextraction-gas chromatography-mass spectrometry analysis," *Int. Arch. Occup. Environ. Health* 2023; 96(6): 857-868.

[421] Baker MJ, et al., "Rapid, non-invasive breath analysis for enhancing detection of silicosis using mass spectrometry and interpretable machine learning," *J. Breath Res.* 2025; 19(2): 026011.

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VII. TREATMENTS FOR SILICOSIS

A. Relevant Medical Literature

515. Although there is no cure for silicosis, there is an extremely large body of medical literature that is relevant to the treatment of silicosis, for two reasons. First, silicosis is a fibrotic lung disease, so studies regarding fibrotic lung disease are relevant to treatment. Second, silica not only causes silicosis, but also causes other chronic diseases by mechanisms that are common with silicosis, so treatments for these chronic diseases are also relevant to the treatment of silicosis.

516. Silicosis is one of many types of interstitial lung disease -- fibrotic lung disease that result from damage to the interstitium, the thin tissue between the air sacs of the lungs where gas exchange occurs. Gas exchange is the process whereby oxygen inhaled into the air sacs enters the bloodstream, and carbon dioxide exits the bloodstream into the air sacs whereupon it is exhaled.

517. There are two major categories of interstitial lung disease: Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis.

518. Idiopathic Pulmonary Fibrosis (IPF) is a type of interstitial lung disease that has a specific morphologic appearance called Usual Interstitial Pneumonia (UIP); IPF also has specific diagnostic criteria, one of which is the exclusion of all interstitial lung diseases of known cause.[422] Since silicosis is caused by silica and only by silica, by definition, silicosis is not IPF. However, a large number of epidemiologic studies show that IPF is consistently and significantly increased in persons exposed to silica dust.[423] The pathogenesis of IPF and silicosis is also similar, because IPF and silicosis share common mechanisms of action.[424] Because silica increases the risk of IPF and these diseases have common mechanisms of action, treatments for IPF are relevant to silicosis.

519. While fibrosis occurs in lung tissue from exposure to multiple and varied inhaled

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[422] See, Raghu G, et al., "An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis; Evidence-based Guidelines for Diagnosis and Management," *Am. J. Respir. Crit. Care Med.* 2011; 183:788-824.

[423] See, Park Y, et al., "Occupational and environmental risk factors of idiopathic pulmonary fibrosis: a systematic review and meta-analyses," *Sci. Rep.* 2021; 11:4318.

[424] See, Bellani S, et al., "What rationale for treatment of occupational interstitial lung diseases with the drugs approved for idiopathic pulmonary fibrosis?" *Curr. Opin. Allergy Clin. Immunol.* 2025; 25:95-104.

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toxins, fibrosis also occurs in tissues in other organs, including the kidney, heart, liver and skin.[425] Occupational exposure to silica has also been associated with fibrosis in other organs in humans, including the kidney,[426] heart,[427] liver,[428] and skin.[429] The effects of silica on these organs have been confirmed in animal studies.[430] Studies about fibrotic effects of silica in other organs and treatments for fibrosis in these organs are therefore relevant to evaluating such treatments for silicosis patients.

520. Progressive Pulmonary Fibrosis (PPF) is a classification term for interstitial lung diseases that first appeared in the published medical literature in 2021, when it was characterized as "a common denominator/phenotype of many interstitial lung diseases other than idiopathic pulmonary fibrosis, leading to clinical deterioration, decreased quality of life, and high mortality."[431] Since PPF is non-IPF, silicosis is a type of PPF, and is therefore relevant to treatments for silicosis.

521. As noted above, silica not only causes silicosis, but also causes multiple other chronic lung diseases, including Chronic Obstructive Pulmonary Disease (COPD), systemic sclerosis, sarcoidosis, lung cancer, and mycobacterial lung diseases, as well as other diseases including autoimmune diseases and kidney disease. Silica causes these various disease generally by disrupting the human immune system, which is how silica causes silicosis. Thus, studies regarding treatments for these other chronic human diseases caused by silica are also relevant to the treatment of silicosis.

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[425] Zeisberg M, et al., "Cellular Mechanisms of Tissue Fibrosis. 1. Common and organ-specific mechanisms associated with tissue fibrosis," *Am J. Physiol. Cell Physiol.* 2013; 304:C216-C225.

[426] Chen F-F, et al., "Renal involvement in a silicosis patient - case report and literature review," *Renal Failure* 2019; 41(1):1045-1053.

[427] Chakraborty P, et al., "Ventricular tachycardia," *JACC Case Rep.* 2020; 2(14):2256-2259.

[428] Montaldo S, et al., "Statistical evaluation of pathologies concomitant to pulmonary silicosis and their influence in determining death," *Rassegna Medica Sarda* 1984; 87-351-364; Forastiere F, et al., "Mortality pattern of silicotic subjects in the latium region, Italy," *Br. J. Ind. Med.* 1989; 46:877-880.

[429] Tang B, et al., "Silica's silent threat: Contributing to skin fibrosis in systemic sclerosis by targeting the HDAC4/Smad2/3 pathway," *Environ. Pollution* 2024; 355:124194.

[430] See, e.g., Guo J, et al., "Effects of silica exposure on the cardiac and renal inflammatory and fibrotic response and the antagonistic rule of interleukin-1 beta in C57BL/6 mice," *Arch. Toxicol.* 2016; 90(2):247-258.

[431] Selman M, et al., "From pulmonary fibrosis to progressive pulmonary fibrosis: a lethal pathobiological jump," *Am. J. Physiol. Lung Cell Mol. Physiol.* 2021; L600-L607.

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B. Overview of Silicosis Treatments

522. Treatments for silicosis include anti-fibrotic treatments (e.g., pirfenidone, nintendanib and nerandomilast), anti-inflammatory treatments (corticosteroids), antibiotics (e.g., azithromycin), immunomodulatory agents (e.g., thymalfasin), infection prevention, monoclonal antibodies (e.g., infliximab), psychological support, pulmonary rehabilitation, smoking cessation, stem cell therapies (e.g., mesenchymal stem cells), symptomatic treatment (bronchodilators, oxygen), tetrandrine (natural alkaloid calcium channel blocker), whole lung lavage, and lung transplantation.

523. Thus far there is no cure for silicosis. Treatments are provided to treat symptoms, to retard progression of disease, to prevent infections, and to provide physical and psychological support. Treatments include the use of bronchodilators and the administration of oxygen to improve respiratory symptomatology and vaccines and antibiotics to prevent infections.

524. In the initial stages of silicosis, the therapeutic interventions consist of smoking cessation, improving cardiovascular and respiratory conditions, psychological support, and whole lung lavage, which is used to treat pulmonary alveolar proteinosis.

525. Treatment recommendations include anti-inflammatory treatment, pulmonary rehabilitation, symptomatic treatment, and treatment for complications.

526. Short-term use of corticosteroids can relieve symptomatology without appreciable risk of infection.

527. Pulmonary rehabilitation has recognized benefits. Rehabilitation programs combine a series of physical exercises (e.g., gymnastics, walking, muscle-toning exercises), respiratory gymnastics, relaxation techniques, and nutritional advice. Several studies have shown a significant improvement in standard test results in patients with interstitial lung disease such as the 6-minute walk test, pulmonary function (maximum rate of oxygen consumption), and quality of life immediately after completion of the rehabilitation program.

528. Lung transplantation is the only treatment option for severe forms of silicosis. Lung transplantation has been shown to be an effective treatment for artificial stone countertop fabricators, with such patients doing better than other patients undergoing lung transplantation.

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C. Antifibrotic and Immunosuppressive Treatments

529. Antifibrotics have been approved for use in many countries based on the results of several phase III clinical trials in patients with Idiopathic Pulmonary Fibrosis, Systemic Sclerosis-associated Interstitial Lung Disease, and Progressive Pulmonary Fibrosis. In a recent study of anti-fibrotic use for the treatment of interstitial lung disease in Japan, 76.7% of Nintedanib users with Idiopathic Pulmonary Fibrosis were prescribed Nintedanib as monotherapy and 75.6% of Pirfenidone users were prescribed Pirfenidone as monotherapy. Among inpatients with Idiopathic Pulmonary Fibrosis, 75.2% were prescribed Nintedanib, and 76.1% were prescribed Pirfenidone, as first-line therapy. About half of the patients with Progressive Pulmonary Fibrosis were prescribed Nintedanib concomitantly with other glucocorticoids/immunosuppressant drugs, and after one or more glucocorticoids/immunosuppressant drugs. In patients with Idiopathic Pulmonary Fibrosis, 18.6% of Nintedanib users and 18.2% of Pirfenidone users were prescribed glucocorticoids concomitantly. This study showed that both Nintedanib and Pirfenidone are used in clinical practice as antifibrotic agents for the treatment of interstitial lung diseases including Idiopathic Pulmonary Fibrosis, Systemic sclerosis-associated interstitial lung disease and Progressive Pulmonary Fibrosis.[432]

530. Since all three major types of interstitial lung disease (Idiopathic Pulmonary Fibrosis, Systemic Sclerosis-associated Interstitial Lung Disease, and Progressive Pulmonary Fibrosis) have been reported to be significantly increased among workers who have been occupationally exposed to respirable crystalline silica, antifibrotics have been used in clinical practice for the treatment of silicosis even though few studies have evaluated the efficacy of antifibrotics among silicosis patients.

531. Antifibrotic pharmacologic agents that have proven effective in treating fibrotic lung disease and are likely effective for treating silicosis patients include Nintedanib and Pirfenidone, as well as the new drug Nerandomilast. Another antifibrotic agent, Treprostinil, is nearing completion of Phase 3 clinical trials. Poly-2-vinylpyridine-N-oxide (PVNO) has long been reported to have antifibrotic efficacy for silicosis, but has not yet been evaluated in clinical trials.

[432] Kondoh Y, et al., "Patient characteristics and pharmacologic treatment patterns in antifibrotic-treated patients with fibrosing interstitial lung diseases: real-world results from a claims database," *BMC Pulmonary Med.* 2025; 25:253.

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1. Nintedanib

532. Nintedanib is an oral multitarget tyrosine kinase inhibitor (TKI) approved for the treatment of patients with idiopathic pulmonary fibrosis (IPF). It works by blocking the active site of tyrosine kinases, preventing them from phosphorylating other proteins, thereby disrupting the signaling pathways that promote cell growth, proliferation, and survival.

533. A phase 2 double-blind, dose finding, placebo-controlled clinical trial (NCT00514683) and following phase 3 trials (NCT-1335464) demonstrated efficacy of nintedanib in reducing disease progression, leading to the approval of the drug for clinical use in idiopathic pulmonary fibrosis.[433]

534. In 2019, investigators of the INBUILD Trial published a multinational study of a Nintedanib trial in patients with progressive fibrotic lung diseases. In this double-blind, placebo-controlled, phase 3 trial conducted in 15 countries, patients with fibrosing lung disease affecting more than 10% of lung volume on high-resolution computed tomography (CT) were randomly assigned to receive nintedanib at a dose of 150 mg twice daily or placebo. All the patients met criteria for progression of interstitial lung disease in the past 24 months despite treatment and had a forced vital capacity (FVC) of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide ranging from 30 to less than 80% of the predicted value. Randomization was stratified according to the fibrotic pattern (a pattern of usual interstitial pneumonia [UIP] or other fibrotic patterns) on high-resolution CT. The primary end point was the annual rate of decline in the FVC, as assessed over a 52-week period. The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern. A total of 663 patients were treated. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib and −187.8 ml per year with placebo, for a between-group difference of 107.0 ml per year (95% confidence interval [CI], 65.4 to 148.5; P<0.001). In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in the FVC was −82.9 ml per year with

[433] Richeldi L, et al., "Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS®trials." *Respir. Med.* 2016; 113:74–79; Richeldi L, et al., "Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis." *N. Engl. J. Med.* 2014; 370:2071–2082.

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nintedanib and –211.1 ml per year with placebo, for a difference of 128.2 ml (95% CI, 70.8 to 185.6; P<0.001). Diarrhea was the most common adverse event, as reported in 66.9% and 23.9% of patients treated with nintedanib and placebo, respectively. Abnormalities on liver-function testing were more common in the nintedanib group than in the placebo group. The investigators concluded that in patients with progressive fibrosing interstitial lung diseases, the annual rate of decline in FVC was significantly lower among patients who received nintedanib than those who received placebo.[434] Although this study did not involve patients who had been diagnosed as having silicosis with progressive massive fibrosis, the study did show a significant benefit in interstitial lung diseases other than idiopathic pulmonary fibrosis who had progressive fibrosis and is therefore relevant to silicosis patients who have been diagnosed with progressive massive fibrosis.

535. "The subsequent open-label extension trials and large observational real-world studies substantially confirmed the effectiveness of nintedanib in reducing disease progression rate and the risk of acute exacerbation incidence in IPF."[435]

536. In light of these promising results, Italian researchers enrolled 197 interstitial lung disease patients treated with nintedanib at a referral center in Siena from 2014 to 2021. Pulmonary functional tests and survival data were collected throughout the observation period for the evaluation of mortality and disease progression outcomes. The investigators found that nintedanib treatment significantly reduced the FVC decline rate in IPF and PF-ILD subgroups, but not in familial

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[434] Flaherty KR, et al., "Nintedanib in Progressive Fibrosing Interstitial Lung Diseases," *New Engl. J. Med.* 2019; 381:1718-1727.

[435] Cameli P, et al., "The Effectiveness of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis, Familial Pulmonary Fibrosis and Progressive Fibrosing Interstitial Lung Diseases: A Real-World Study," *Biomedicines* 2022; 10:1973, citing Dobashi M, et al., "The efficacy of nintedanib in 158 patients with idiopathic pulmonary fibrosis in real-world settings: A multicenter retrospective study," *SAGE Open Med.* 2021; 9:20503121211023356; Rahaghi F, et al., "Delphi Consensus Recommendations on Management of Dosing, Adverse Events, and Comorbidities in the Treatment of Idiopathic Pulmonary Fibrosis with Nintedanib," *Clin. Med. Insights Circ. Respir. Pulm. Med.* 2021; 15:11795484211006050; Kato M, et al., "Clinical Significance of Continuable Treatment with Nintedanib Over 12 Months for Idiopathic Pulmonary Fibrosis in a Real-World Setting," *Drug Des. Dev. Ther.* 2021; 15:223–230; Antoniou K, et al., "Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: A retrospective, observational, cohort study," *ERJ Open Res.* 2020; 6:172–2019; Brunnemer E, et al., "Real-World Experience with Nintedanib in Patients with Idiopathic Pulmonary Fibrosis," *Respir. Int. Rev. Thorac. Dis.* 2018; 95:301-309; Tzouvelekis A, et al., "Safety and efficacy of nintedanib in idiopathic pulmonary fibrosis: A real-life observational study in Greece," *Pulm. Pharmacol. Ther.* 2018; 49:61–66; Hughes G, et al., "Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis," *J. Clin. Med.* 2016; 5:78.

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pulmonary fibrosis patients. The main findings of the study substantially confirmed the effectiveness of nintedanib in reducing the progression rate of fibrotic lung diseases, improving the life expectancy in patients with IPF and PF-ILD, as already reported by randomized controlled trials and real-life observational studies in FPF subjects.[436]

537. In 2025, Japanese investigators published the results of a 1-year interim analysis of a prospective, multicenter observational study in Kyushu and Okinawa, Japan. The study included 215 patients with early-stage IPF (stage I/II per the Japanese IPF severity system) who were followed up for 52 weeks. Changes in FVC and diffusion capacity of carbon monoxide (DLco); incidence of adverse events, acute exacerbations, and death; and factors associated with FVC decline and nintedanib discontinuation were evaluated. The percentage of predicted FVC (%FVC) remained stable, from 83.2% at baseline to 83.7% at 52 weeks, while %DLco decreased from 70.8% to 64.2%. Incidences of acute exacerbation and death were both 4.7%. Nintedanib was discontinued due to adverse events in 21.9% of the patients. Risk factors for FVC decline (>5%) included female sex, GAP stage II/III, low oxygen saturation (SpO2) in the 6-minute walk test (6 MWT), and elevated biomarkers (KL-6). Significant factors for nintedanib discontinuation were advanced age, modified Medical Research Council (mMRC) grade I or higher, GAP stage II/III, low %FVC, low SpO2 in the 6 MWT, short 6 MWT distance, and low albumin levels. The investigators concluded that the findings of this interim analysis indicate that nintedanib has good efficacy, safety, and tolerability for early-stage IPF in real-world settings, outside randomized control trials.[437]

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[436] Cameli P, et al., "The Effectiveness of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis, Familial Pulmonary Fibrosis and Progressive Fibrosing Interstitial Lung Diseases: A Real-World Study," *Biomedicines* 2022; 10:1973, citing Richeldi L, et al., "Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS®trials." *Respir. Med.* 2016; 113:74–79; Lancaster L, et al., "Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: Pooled data from six clinical trials," *BMJ Open Respir. Res.* 2019; 6:e000397; Flaherty KR, et al, "Nintedanib in Progressive Fibrosing Interstitial Lung Diseases." *N. Engl. J. Med.* 2019; 381:1718–1727; Cameli P, et al., "Long-Term Follow-Up of Patients with Idiopathic Pulmonary Fibrosis Treated With Pirfenidone or Nintedanib: A Real-Life Comparison Study," *Front. Mol. Biosci.* 2020; 7:581828.

[437] Sakamoto N, et al., "Efficacy and Safety of Nintedanib in Japanese Patients With Early-Stage Idiopathic Pulmonary Fibrosis: A One-Year Interim Analysis from a Multicenter Observational Study in Kyushu and Okinawa, Japan," *Clin. Ther.* 2025; S0149-2918(25)00171-7. Doi: 10.1016/j.clinthera.2025.05.007.

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2. Pirfenidone

538. Pirfenidone is an antifibrotic medication that inhibits the production and signaling of Transforming Growth Factor β, a key cytokine that promotes fibrosis, preventing excess collagen synthesis and extracellular matrix production, reducing the accumulation of scar tissue in the lungs.

539. In 2019, researchers Shandong, China studied the role of Pirfenidone in rats exposed to silica dust by intratracheal instillation of 50 mg/ml silica. From the first day after silica instillation rats were given pirfenidone (50, 100 mg/kg/day) and were sacrificed at 14 and 28 days to observe the histopathology of lungs, to analyze the level of TNF-α, IL-1β, IL-6 in lung tissues and to measure the expression of TGF-β1, Smad2/3, vimentin, and E-cadherin in lung tissues. Results showed that pirfenidone (50, 100 mg/kg/day) reduced silica-induced alveolar inflammation, damage of alveolar structure and blue areas of collagen fibers in the lungs of rats. At the same time, pirfenidone also reduced the level of TNF-α, IL-1β, IL-6 in lung tissues and the protein expression of collagen I. After pirfenidone intervention for 14 days and 28 days, protein expression of vimentin was down-regulated and protein expression of E-cadherin was up-regulated in lung tissues. In addition, the TGF-β1/smad2/3 pathway was activated at 14 days and 28 days after silica instillation, and pirfenidone reduced the expression of TGF-β1 and smad2/3 in the lungs. The investigators concluded that pirfenidone intervention inhibited epithelial-mesenchymal transition and pulmonary fibrosis in rat silicosis model, which effects may be related to the TGF-β1/smad pathway.[438]

540. In 2025, researchers from South Korea studied the therapeutic effects of Pirfenidone on particulate matter-induced pulmonary fibrosis. They induced pulmonary fibrosis by the intratracheal application of 100 μg/kg PM10 mixed with 200 μL saline. After 42 days of PM10 infusion, 0.2 mL of distilled water with pirfenidone was orally administered to the pirfenidone-treated groups (200 and 400 mg/kg) every other day for a total of 15 times over 30 days. The intratracheal administration of particulate matter resulted in lung injury and a significant decrease in the number of bronchoalveolar lavage fluid cells. Particulate matter administration increased the lung injury score, level of lung fibrosis, and production of pro-inflammatory cytokines. Pirfenidone

[438] Guo J, et al., "Pirfenidone inhibits epithelial-mesen-chymal transition and pulmonary fibrosis in the rat silicosis model," *Toxicol. Lett.* 2019; 300:59-66.

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treatment effectively suppressed transforming growth factor-β-activated kinase 1 in PM-induced pulmonary fibrosis. The present changes inhibited the expressions of mitogen-activated protein kinase kinase 3 and p38, which suppressed transforming growth factor-β, ultimately alleviating lung fibrosis. Particulate matter exposure upregulated the expressions of fibronectin and type 1 collagen. Particulate matter exposure enhanced connective tissue growth factor and hydroxyproline levels in the lung tissue. The levels of these fibrosis-related factors were inhibited by pirfenidone treatment. The researchers concluded that their results suggest that pirfenidone is therapeutically effective against particulate matter-induced pulmonary fibrosis.[439]

541. Also in 2025, researchers from Ningxia, China executed network pharmacology to replenish Pirfenidone's molecular mechanisms and potential therapeutic targets. They replicated a silicosis C57BL6/J mouse model and evaluated inflammation and fibrosis using HE, Masson, and Sirius Red staining assays. The expression of fibrotic markers α-SMA and Fibronectin were determined by immunofluorescence assay. Network pharmacology and molecular docking were used to predict potential therapeutic mechanisms and targets. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) and immunofluorescence experiments were verified as key predicted targets. Pirfenidone alleviated the level of inflammation and collagen deposition and fibrotic markers α-SMA and Fibronectin expression in silicosis lung. Network pharmacology analysis predicted 3 potential target proteins, including TNF, MMP9, and NF-κB1, and 10 possible signaling pathways. Molecular docking showed a good binding activity between Pirfenidone and hub genes. qRT-PCR and immunofluorescence confirmed that Pirfenidone inhibited TNF, MMP9, and NF-κB activation. Additionally, the investigators found increased expression of TLR2, a key upstream gene of NF-κB. They concluded that they had identified TNF, MMP9, NF-κB1 and TLR2, that contribute to the therapeutic effects of Pirfenidone in silicosis and that mechanistically, Pirfenidone appears to mitigate silicosis pathogenesis through suppression of epithelial TLR2/NF-κB pathway activation.[440]

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[439] Sung J-S, et al., "Pirfenidone Alleviates Against Fine Particulate Matter-Induced Pulmonary Fibrosis Modulating via TGF-ß1/TAK1/MKK3/p38 MAPK Signaling Pathway in Rats," *Biomedicines* 2025; 13:989.

[440] Chang S, et al., "The updated evidence of pirfenidone treated silicosis based on network pharmacology, molecular docking and experimental validation," *Front. Med.* 2025; 12:1573241.

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3. Combination Nintedanib and Pirfenidone Therapy

542. In a recent study nintedanib and pirfenidone were administered individually and combined in mice with advanced silicosis to evaluate lung function, inflammatory responses, and fibrotic status. Transcriptomic and metabolomic analyses were also done to ascertain the mechanisms underlying different therapeutic strategies. Both drugs were effective in treating advanced silicosis, with superior outcomes observed in combination therapy. Transcriptomic and metabolomic analyses revealed that pirfenidone and nintedanib primarily exerted their therapeutic effects by modulating immune responses, signalling cascades and metabolic processes involving lipids, nucleotides and carbohydrates. Furthermore, monotherapy and combined therapy yielded therapeutic benefits through two common signalling pathways (steroid biosynthesis and purine metabolism), thereby experimentally validating therapeutic benefits. Based on the results of their study the investigators concluded that pirfenidone and nintedanib, individually and in combination, demonstrated substantial potential in advanced silicosis. Combined therapy outperformed monotherapy, even at low doses, which the investigators attributed to their influence on diverse signaling pathways and metabolic processes.[441]

543. In 2018, two studies of Idiopathic Pulmonary Fibrosis patients who were administered Nintedanib and Pirfenidone in combination reported that the combined therapy was well tolerated by a majority of patients and that adverse effects of the combined therapy were similar to those of the individual drugs and were manageable.[442]

544. In a study by European investigators of 37 patients who received combined nintedanib and pirfenidone therapy, 29 subjects (78.4%) reported one or more adverse events, the most common being diarrhea, nausea, lower respiratory tract infections, vomiting, headache and dyspepsia. Diarrhea was the mot frequently reported adverse event. No serious adverse events were reported. The investigators concluded their study suggested there was no relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone administered as combination therapy in patients with

[441] Bai L, et al., "Combined therapy with pirfenidone and nintedanib counteracts fibrotic silicosis in mice," *Br. J. Pharmacol.* 2025; 182(5):1143-1163.

[442] Vancheri C., et al., "Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis: Results of the INJOURNEY Trial," *Am J. Respir. Crit. Care Med.* 2018; 197(3):356-363; Flaherty KR, et al., "Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis," *Eur. Respir. J.* 2018; 52:1800230.

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idiopathic pulmonary fibrosis and that the safety results of the trial were consistent with the known adverse event profiles of the individual drugs.[443]

545. In a multicenter retrospective cohort study of 46 patients with Idiopathic Pulmonary Fibrosis from 16 institutes in Japan who received combination therapy with nintedanib and pirfenidone, 33 patients (71%) had some adverse drug reactions and 14 patients (30.4%) permanently discontinued either drug or both drugs due to the development of adverse drug reactions during the observation period (mean 59 weeks). Decreased appetite and diarrhea were observed in 39.1% and 34.8% of patients, respectively, and two patients (4.3%) had serious adverse drug reactions (liver toxicity and pneumothorax). The investigators concluded that their real-world data indicated that combination therapy with pirfenidone and nintedanib for Idiopathic Pulmonary Fibrosis has a manageable safety/tolerability profile.[444]

546. In a multicenter retrospective cohort study of 45 patients with Idiopathic Pulmonary Fibrosis, the most common adverse events after combination therapy were diarrhea and anorexia. In patients with serial lung function data, the rate of decline in forced vital capacity was significantly reduced after the combination therapy. In the matched analysis, the combination group had a higher incidence of diarrhea than the monotherapy group without an increase in serious adverse events.[445]

547. In a systematic review and meta-analysis of 4 clinical trials involving 191 patients, the pooled proportions of serious and any adverse drug reactions were 10% and 82% respectively. During follow-up, gastrointestinal symptoms were the most frequent adverse drug reaction and acute exacerbation of Idiopathic Pulmonary Fibrosis was reported in 7% of patients.[446]

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[443] Richeldi L, et al., "No relevant pharmaco-kinetic drug-drug interaction between nintedanib and pirfenidone," *Eur. Respir. J.* 2019; 53:1801060.

[444] Hisata S, et al., "Safety and tolerability of combination therapy with pirfenidone and nintedanib for idiopathic pulmonary fibrosis: A multicenter observational study in Japan," *Respir. Investig.* 2021; 59(6):819-826.

[445] Huh, J-Y, et al, "Efficacy and safety of combination therapy with pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis," *Front. Pharmacol.* 2023; 14:1391923.

[446] Lee J, et al., "Safety and tolerability of combination treatment with pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis," *J. Thorac. Dis.* 2023; 15(11):5913-5921.

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4. Nerandomilast

548. Nerandomilast is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory properties. Recent studies have shown it to be an effective antifibrotic therapy for pulmonary fibrosis.

549. Nerandomilast was first proposed as a drug candidate for the oral treatment of idiopathic pulmonary fibrosis in 2022.[447] That year Phase I studies were done which found that BI 1015550 had an acceptable safety profile in healthy male subjects and male and female patients with idiopathic pulmonary fibrosis.[448] The same year a phase 2, double-blind, placebo-controlled trial demonstrated that treatment with BI 1015550, either alone or with background use of an antifibrotic agent, prevented a decrease in lung function in patients with idiopathic pulmonary fibrosis.[449]

550. In 2023, Phase III trials of BI 1015550 were designed for patients with idiopathic pulmonary fibrosis and progressive pulmonary fibrosis.[450]

551. In 2024, German researchers published a study in which they assessed the effects of nerandomilast on pulmonary fibrosis in rats and on biomarkers in human lung epithelial cells. They analyzed whole-lung homogenates from a therapeutic male Wistar rat model of pulmonary fibrosis by next-generation sequencing (NGS). Data were matched with public domain data derived from human Idiopathic Pulmonary Fibrosis (IPF) samples to investigate how well the rat model reflected human IPF. They scored the top counter-regulated genes following treatment with nerandomilast in human single cells and validated disease markers discovered in the rat model using a human disease-relevant in vitro assay of IPF. Nerandomilast improved the decline of lung function parameters in bleomycin-treated animals. In the NGS study, most transcripts deregulated by

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[447] Herrmann FE, et al., "BI 1015550 is a PDE4B Inhibitor and a Clinical Drug Candidate for the Oral Treatment of Idiopathic Pulmonary Fibrosis," *Frontiers Pharmacol.* 2022; 13:838449.

[448] Maher TM, et al., "Phase I studies of BI 101550, a preferential phosphodiesterase 4B inhibitor, in healthy males and patients with idiopathic pulmonary fibrosis," *European Respir. J. Open Res.* 2022; 8:00240-2022.

[449] Richeldi L, et al., "Trial of a Preferential Phosphodiesterase 4B Inhibitor for Idiopathic Pulmonary Fibrosis," *New Engl. J. Med.* 2022; 386:2178-2187.

[450] Richeldi L, et al., "Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with idiopathic pulmonary fibrosis (FIBRONEER-IPF)," *BMJ Open Respir. Res.* 2023; 10:e001563; Maher TM, et al., "Design of a phase III, double-blind, randomised, placebo-controlled trial of BI 1015550 in patients with progressive pulmonary fibrosis (FIBRONEER-ILD)," *BMJ Open Respir. Res.* 2023; 10:e001580.

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bleomycin treatment were normalized by nerandomilast treatment. Most notably, a significant number of deregulated transcripts that were identified in human IPF disease were also found in the animal model and reversed by nerandomilast. Mapping to single-cell data revealed the strongest effects on mesenchymal, epithelial and endothelial cell populations. In a primary human epithelial cell culture system, several disease-related biomarkers were inhibited by nerandomilast in a concentration-dependent manner. The investigators concluded that their study further supports the available knowledge about the anti-inflammatory/antifibrotic mechanisms of nerandomilast and provides novel insights into the mode of action and signaling pathways influenced by nerandomilast treatment of lung fibrosis.[451]

552. In 2024, a rationale for Nerandomilast as a treatment strategy for interstitial lung diseases associated with rheumatic diseases was proposed.[452] This rationale is relevant to the use of Nerandomilast as a treatment for silicosis, because crystalline silica is a cause of rheumatoid arthritis.

553. In 2025, American researchers published a review regarding phosphodiesterase 4B inhibitors in the treatment of interstitial lung disease associated with autoimmune diseases.[453] This study is relevant to the use of Nerandomilast as a treatment for silicosis, because crystalline silica is a known cause of multiple autoimmune diseases.

554. In 2025, the New England Journal of Medicine published two Phase III clinical trials of Nerandomilast – one in patients with Idiopathic Pulmonary Fibrosis patients, the other in patients with progressive pulmonary fibrosis. The results of both studies showed therapeutic benefit.

555. In a phase 3, double-blind trial, researchers randomly assigned patients with idiopathic pulmonary fibrosis in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo, with stratification according to background antifibrotic therapy (nintedanib or pirfenidone vs. none). The primary end point was the absolute

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[451] Reininger D, et al., "PDE4B inhibition by nerandomilast: Effects on lung fibrosis and transcriptome in fibrotic rats and on biomarkers in human lung epithelial cells," *Br. J. Pharmacol.* 2024; 181(23):4766-4781.

[452] Aringer M, et al., "Rationale for phosphodiesterase-4 inhibition as a treatment strategy for interstitial lung diseases associated with rheumatic diseases," *RMD Open* 2024; 10:e004704.

[453] Castelino FV, et al., "Potential of phosphodiesterase 4B inhibitors in the treatment of interstitial lung disease associated with autoimmune diseases," *Clin. Exp. Rheumatol.* 2025; 43(1):119-125.

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change from baseline in forced vital capacity (FVC), measured in milliliters, at week 52. A total of 1177 patients underwent randomization, of whom 77.7% were taking nintedanib or pirfenidone at enrollment. Adjusted mean changes in FVC at week 52 were −114.7 ml (95% confidence interval [CI], −141.8 to −87.5) in the nerandomilast 18-mg group, −138.6 ml (95% CI, −165.6 to −111.6) in the nerandomilast 9-mg group, and −183.5 ml (95% CI, −210.9 to −156.1) in the placebo group. The adjusted difference between the nerandomilast 18-mg group and the placebo group was 68.8 ml (95% CI, 30.3 to 107.4; P<0.001), and the adjusted difference between the nerandomilast 9-mg group and the placebo group was 44.9 ml (95% CI, 6.4 to 83.3; P = 0.02). The most frequent adverse event in the nerandomilast groups was diarrhea, reported in 41.3% of the 18-mg group and 31.1% of the 9-mg group, as compared with 16.0% in the placebo group. Serious adverse events were balanced across trial groups. The investigators concluded that in patients with idiopathic pulmonary fibrosis, treatment with nerandomilast resulted in a smaller decline in the FVC than placebo over a period of 52 weeks.[454]

556. In a phase 3, double-blind trial, patients with progressive pulmonary fibrosis were randomly assigned in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo, with stratification according to background therapy (nintedanib vs. none) and fibrotic pattern on high-resolution computed tomography (usual interstitial pneumonia-like pattern vs. other patterns). The primary end point was the absolute change from baseline in the forced vital capacity (FVC), measured in milliliters, at week 52. A total of 1176 patients received at least one dose of nerandomilast or placebo, of whom 43.5% were taking background nintedanib therapy at baseline. The adjusted mean change in the FVC at week 52 was −98.6 ml (95% confidence interval [CI], −123.7 to −73.4) in the nerandomilast 18-mg group, −84.6 ml (95% CI, −109.6 to −59.7) in the nerandomilast 9-mg group, and −165.8 ml (95% CI, −190.5 to −141.0) in the placebo group. The adjusted difference between the nerandomilast 18-mg group and the placebo group was 67.2 ml (95% CI, 31.9 to 102.5; P<0.001), and the adjusted difference between the nerandomilast 9-mg group and the placebo group was 81.1 ml (95% CI, 46.0 to 116.3; P<0.001). The most frequent adverse event was diarrhea, reported in 36.6% of the patients in the

[454] Richeldi L, et al., "Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis," *New Engl. J. Med.* (published online May 18, 2025).

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nerandomilast 18-mg group, 29.5% of those in the nerandomilast 9-mg group, and 24.7% of those in the placebo group. Serious adverse events occurred in similar percentages of patients in the trial groups. The investigators concluded that in patients with progressive pulmonary fibrosis, treatment with nerandomilast led to a smaller decline in the FVC than placebo over a period of 52 weeks. [455]

557. In 2025, Chinese researchers published a study in which the from Beijing Chao-Yang Hospital in Beijing, China published a study in which they synthesized BI 1015550 (Nerandomilast) autonomously and demonstrated that it could significantly improve lung fibrosis and inflammation in a silica-induced silicosis mouse model. They also found that it could alleviate lung inflammation in a Lipopolysaccharide (LPS)induced acute lung injury moue model. They noted that the mechanism of action may involve the regulation of cAMP-related signaling pathways.[456]

558. In 2025, researchers from Beijing Chao-Yang Hospital in Beijing, China published an abstract in which they evaluated the potential effects of Nerandomilast on silica-induced lung inflammation and fibrosis, and explored the underlying mechanisms. Silicosis mouse model Male C57BL/6N mice (8-10 weeks old) were used to model silicosis via a single intratracheal instillation of silica suspension (0.4 g/kg) or saline as control. Single-cell RNA sequencing Single-cell RNA sequencing (scRNA-seq) and weighted gene co-expression network analysis (WGCNA) were performed on lung tissue from both silicosis and saline control mice. The PDE4B inhibitor, Nerandomilast, was administered orally at two doses (2.5 mg/kg or 12.5 mg/kg, twice daily) during early (days 1-27) or late (days 14-41) treatment window. Lung tissue was collected on days 28 or 42. Bulk RNA sequencing was performed on lung tissues from control, silicosis, and treated mice. Cell culture and treatment THP-1 human monocytic cells were differentiated into macrophages, stimulated with silica, and treated with Nerandomilast. Pyroptosis and cell viability were assessed by microscopy and CCK-8 assay, while the cytokine levels and protein expressions were quantified by ELISA, qRT-PCR, and Western blot. Supernatants from silica-treated macrophages were collected to culture MRC-5 lung fibroblasts. Single-cell RNA sequencing and WGCNA analysis

[455] Maher TM, et al., "Nerandomilast in Patients with Progressive Pulmonary Fibrosis," *New Engl. J. Med.* (published only May 19, 2025).

[456] Liu Y, et al., "BI 1015550 Improves Silica-Induced Silicosis and LPS-Induced Acute Lung Injury in Mice," *Molecules* 2025; 30:1311.

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identified Pde4b as a key regulator of macrophage activity in the lungs of silicosis in mice. In early treatment, Nerandomilast (2.5 mg/kg or 12.5 mg/kg) reduced lung index and improved pulmonary function. Histology showed decreased inflammation and fibrosis in treated mice. Similar improvements were seen in the late treatment model. Bulk RNA sequencing revealed upregulation of NLR signaling, which was reduced after Nerandomilast treatment. ELISA, Western blot and qRT-PCR confirmed downregulation of inflammation and fibrosis-related proteins and genes. Silica exposure induced pyroptosis and reduced viability in THP-1 macrophages, but Nerandomilast restored cell viability and reduced pyroptosis markers. Fibronectin and collagen I expression in MRC-5 fibroblasts, cultured with silica-treated macrophage supernatants, were elevated but decreased following Nerandomilast treatment. The investigators concluded that Nerandomilast effectively suppressed silica-induced inflammation via the NLRP3 Inflammasome pathway and lung fibrosis through the TGF-β/Smad pathway, highlighting its therapeutic potential for silicosis.[457]

559. Recently, Japanese researchers published an article regarding autoimmune connective tissue disease associated with interstitial lung disease (CT-ILD), commenting that "there is a need for more efficacious and tolerable pharmacotherapies for CTD-ILD" and recommending Nerandomilast as one of three promising compounds in clinical trials for treating CTD-ILD.[458]

560. The therapeutic effects of Nerandomilast demonstrated in the Phase III clinical trials for idiopathic pulmonary fibrosis and progressive pulmonary fibrosis, the biological rationales for the use of Nerandomilast in treating interstitial lung diseases associated with rheumatologic diseases and autoimmune diseases, as well as the recent animal studies in silica-exposed mice and rats demonstrating therapeutic antifibrotic effects of Nerandomilast through known silicosis pathways all support the use of this phosphodiesterase 4B inhibitor in the treatment of silicosis.

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[457] Ye Q, et al., "A Phosphodiesterase-4b Inhibitor, Nerandomilast Amerliorates Silica-induced Lung Infalmmation and Fibrosis in Mice by Inhibiting NLRP3 Inflammasome Activation and the TGF-β/SMAD Pathway," *Am. J. Respir. Crit. Care Med.* 2025; 211:A4279.

[458] Kondoh Y, et al., "Unmet needs and emerging pharmacotherapies for autoimmune connective tissue disease-associated interstitial lung diseases," *Autoimmun. Rev.* 2025; 24(11):103900.

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5. Treprostinil

561. Treprostinil is a synthetic analog of prostacyclin that has been approved for the treatment of pulmonary arterial hypertension. It is a direct vasodilator of pulmonary and systemic vascular beds, thereby reducing pulmonary artery pressure and improving systemic oxygenation.[459]

562. Trepostinil inhibits proliferation and extraceullar matrix deposition by fibroblasts through cAMP activation.[460]

563. In 2021, American researchers published the results of the INCREASE clinical trial, a multicenter, randomized, double-blind, placebo-controlled 16-week trial of Treprostinil in patients with interstitial lung disease and pulmonary hypertension. This study showed that in patients with pulmonary hypertension due to interstitial lung disease, inhaled Treprostinil improved exercise capacity from baseline, assessed with the use of a 6-minute walk test, as compared with a placebo.[461]

564. In 2023, American researchers published the results of an Open-Label Extension (OLE) of the INCREASE trial that evaluated long-term effects of inhaled Treprostinil in pulmonary hypertension due to interstitial lung disease. Of 258 eligible patients, 242 enrolled in the INCREASE OLE and received inhaled Treprostinil. Assessments included 6 minute walk distance (6MWD), pulmonary function testing, N-terminal pro-brain natriuretic peptide (NtproBNP), quality of life and adverse events. Hospitalisations, exacerbations of underlying lung disease and death were recorded. At baseline, patients had a median age of 70 years and a mean 6MWD of 274.2 m; 52.1% were male. For the overall population, the mean 6MWD at week 52 was 279.1 m and the mean change from INCREASE RCT baseline was 3.5 m (22.1 m for the prior inhaled treprostinil arm and −19.5 m for the prior placebo arm); the median NT-proBNP decreased from 389 pg·mL−1 at RCT baseline to 359 pg·mL−1 at week 64; and the absolute (% predicted) mean forced vital capacity change from RCT baseline to week 64 was 51 mL (2.8%). Patients who received inhaled treprostinil versus placebo in the RCT had a 31% lower relative risk of exacerbation of underlying lung disease

[459] Zare P, et al., "Treprostinil," *StatPearls* 2023.

[460] Lambers C, et al., "Trepostinil inhibits proliferation and extraceullar matrix deposition by fibroblasts through cAMP activation," *Sci. Rep.* 2018; 8:1087.

[461] Waxman A, et al, "Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease," *New Engl. J. Med.* 2021; 384(4):325-334.

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in the OLE (hazard ratio 0.69 (95% CI 0.49–0.97); p=0.03). Adverse events leading to drug discontinuation occurred in 54 (22.3%) patients. The investigators concluded that these results support the long-term safety and efficacy of inhaled Treprostinil in patients with pulmonary hypertension due to interstitial lung disease and were consistent with the results observed in the INCREASE randomized clinical trial.[462]

565. The results of the INCREASE trial led to the approval by the US Food and Drug Administration of inhaled Treprostinil to treat pulmonary hypertension in interstitial lung disease.[463]

566. Since publication of the INCREASE trial and the Open-Label Extension, several *post hoc* analyses were published showing clinical improvement of interstitial lung disease patients treated with Treprostinil.[464]

567. One *post hoc* analysis of the INCREASE trial evaluated whether higher dosages of inhaled Treprostinil have greater benefits in preventing clinical worsening and achieving clinical improvement in interstitial lung disease patients with pulmonary hypertension. Four groups of patients from the INCREASE trial were identified based on the number of breaths per session (bps; < 9 and ≥ 9 bps) of active drug or placebo attained at 4 weeks. Patients were evaluated for clinical worsening (15% decrease in 6-min walk distance, cardiopulmonary hospitalization, lung transplantation, or death) or clinical improvement (15% increase in the six-minute walk distance with a concomitant 30% reduction in N-terminal prohormone of brain natriuretic peptide without any clinical worsening event). At 4 weeks, 70 patients were at a dose of ≥ 9 bps (high-dosage group) and 79 patients were at a dose of < 9 bps (low-dosage group) in the inhaled Treprostinil arm vs 86 patients in the high-dose group and 67 patients in the low-dose group in the placebo arm. Between weeks 4 and 16, 17.1% of patients in the high-dose Treprostinil group and 22.8% in the low-dose treatment group experienced a clinical worsening event vs 33.7% and 34.3% of patients in the two

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[462] Waxman A, et al., "Long-term inhaled treprostinil for pulmonary hypertension due to interstitial lung disease: INCREASE open-label extension study," *Eur. Respir. J.* 2023; 61:2202414.

[463] Cottin V, et al., "Inhaled treprostinil for interstitial lung disease-associated pulmonary hypertension: a silver lining on a very dark cloud," *Eur. Respir. J.* 2023; 61:2300944.

[464] Cottin V, et al., "Inhaled treprostinil for interstitial lung disease-associated pulmonary hypertension: a silver lining on a very dark cloud," *Eur. Respir. J.* 2023; 61:2300944.

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placebo arms, respectively (P = .006). By week 16, 15.7% and 12.7% of patients in the high- and low-dose iTre groups, respectively, demonstrated clinical improvement vs 7% and 1.5% patients in the placebo arms (P = .003). The investigators concluded higher dosages of inhaled Treprostinil overall showed greater benefit in terms of preventing clinical worsening and achieving clinical improvement. They also concluded that these data support the early initiation and uptitration of inhaled Treprostinil therapy to a dosage of at least 9 bps four times daily in patients with pulmonary hypertension resulting from interstitial lung disease.[465]

568. Another *post hoc* analysis evaluated the effect of continued treatment with inhaled Treprostinil on the frequency and impact of multiple disease progression events. In this study patients enrolled in INCREASE were analyzed for disease progression events, defined as at least 15% decline in 6-minute-walk distance, exacerbation of underlying lung disease, cardiopulmonary hospitalization, lung transplantation, at least 10% decline in forced vital capacity, or death during the duration of the 16-week study. In total, 147 disease progression events occurred in the inhaled treprostinil group (89/163 patients, 55%) compared with 215 events (109/163 patients, 67%) in the placebo group (P = 0.018). There was a lower incidence of each disease progression component in the inhaled treprostinil group: 6-minute-walk distance decline (45 vs. 64 events), lung disease exacerbation (48 vs. 72 events), FVC decline (19 vs. 33), cardiopulmonary hospitalization (23 vs. 33 events), and death (10 vs. 12). Fewer patients receiving inhaled Treprostinil had multiple progression events compared with those receiving the placebo (35 vs. 58, 22% vs. 36%; P = 0.005). The investigators of this *post hoc* study concluded that patients who received inhaled treprostinil were significantly less likely to experience further disease progression events after an initial event compared with patients receiving the placebo and that the results of their study supported the continuation of inhaled Treprostinil for interstitial lung disease patients in clinical practice.[466]

569. Yet another *post hoc* analysis of the INCREASE trial evaluated FVC changes in the

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[465] Nathan SD, et al., "Inhaled treprostinil dosage in pulmonary hypertension associated with interstitial lung disease and its effects on clinical outcomes," *Chest* 2023; 163(2):398-406.

[466] Nathan SD, et al., "Efficacy of Inhaled Treprostinil on Multiple Disease Progression Events in Patients with Pulmonary Hypertension due to Parenchymal Lung Disease in the INCREASE Trial," *Am. J. Respir. Crit. Care Med.* 2022; 205(2):198-207.

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overall study population and in various subgroups defined by cause of disease or baseline clinical parameters. Inhaled Treprostinil was associated with a placebo-corrected least squares mean improvement in FVC of 28·5 mL (SE 30·1; 95% CI -30·8 to 87·7; p=0·35) at week 8 and 44·4 mL (35·4; -25·2 to 114·0; p=0·21) at week 16, with associated percentage of predicted FVC improvements of 1·8% (0·7; 0·4 to 3·2; p=0·014) and 1·8% (0·8; 0·2 to 3·4; p=0·028). Subgroup analysis of patients with idiopathic interstitial pneumonia showed FVC differences of 46·5 mL (SE 39·9; 95% CI -32·5 to 125·5; p=0·25) at week 8 and 108·2 mL (46·9; 15·3 to 201·1; p=0·023) at week 16. Analysis of patients with idiopathic pulmonary fibrosis showed FVC differences of 84·5 mL (52·7; -20·4 to 189·5; p=0·11) at week 8 and 168·5 mL (64·5;40·1 to 297·0; p=0·011) at week 16. The investigators of this study concluded that in patients with interstitial lung disease and associated pulmonary hypertension, inhaled Treprostinil was associated with improvements in FVC versus placebo at 16 weeks, the difference being most evident inpatients with idiopathic interstitial pneumonia, particularly idiopathic pulmonary fibrosis.[467]

570. "This observation was of significant interest since previous experimental studies provided a rationale for investigating the potential benefit of potentiating the prostaglandin pathway in pulmonary fibrosis."[468]

571. Randomized clinical trials of Treprostinil for treating idiopathic pulmonary fibrosis (TETON-IPF) and progressive pulmonary fibrosis (TETON-PPF) are nearing completion.

572. Recently, Japanese researchers concluding that "there is a need for more efficacious and tolerable pharmacotherapies for CTD-ILD" [connective tissue disease-related interstitial lung disease] and recommending Treprostanil as one of three promising compounds for this condition.[469]

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[467] Nathan SD, et al., "Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study," *Lancet Respir. Med.* 2021; 9(11):1266-1274.

[468] Cottin V, et al., *supra,* citing Wilborn J, et al., "Cultured lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis have a diminished capacity to synthesize prostaglandin E2 and to express cyclo-oxygenase-2," *J. Clin. Invest.* 1995; 95:1861-1868; Kolodsick JE, et al., "Prostaglandin E2 inhibits fibroblast to myofibroblast transition via E. prostanoid receptor 2 signaling and cyclic adenosine monophosphate elevation," *Am. J. Respir. Cell. Mol. Biol.* 2003; 29:537–544; Huang SK, et al., "Prostaglandin E(2) induces fibroblast apoptosis by modulating multiple survival pathways," *FASEB J* 2009; 23:4317–4326.

[469] Kondoh Y, et al., "Unmet needs and emerging pharmacotherapies for autoimmune connective tissue disease-associated interstitial lung diseases," *Autoimmun. Rev.* 2025; 24(11):103900.

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6. Poly-2-vinylpyridine-N-oxide (PVNO)

573. Poly-2-vinylpyridine-N-oxide (PVNO) has long been known to prevent or reduce the toxic, fibrogenic and immunosuppressive effects of silica. See, Hasirci VN, et al., "Poly (2-vinylpyridine 1-oxide) in silicosis therapy: effective molecular weight," *Int. Arch. Occup. Environ. Health* 1977; 38(3):177-188.

574. In vivo and in vitro research has shown that PVNO can improve lung clearance after exposure to silica dust and prevent dust from invading the lung interstitium. Ernst H., et al., "Pulmonary inflammation in rats after intratracheal instillation of quartz, amorphous SiO2, carbon black, and coal dust and the influence of poly-2-vinylpyridine-N-oxide (PVNO)," *Exp. Toxicol. Pathology* 2002; 54(2):109–126.

575. PVNO may also eliminate the free radicals induced by SiO2 and protect macrophages, reducing the silicosis nodules and delaying the development of silicosis. PVNO has a protective effect on silica-induced pulmonary fibrosis and shows good effects in animal models. Yang B, et al., "silicosis: from pathogenesis to therapeutics," *Frontiers Pharmacol.* 2025; 16:1516200, citing Idec-Sadkowska I, et al., "Trials of ca[us]al treatment of silicosis," *Med Pr.* 2006; 57(3):271-280.

7. Immunosuppressive Drugs

576. Immunosuppressive drugs are promising candidates for the treatment of artificial-stone induced silicosis, because these drugs can reduce inflammation and hence improve lung function or at least retard loss of lung function as fibrosis progresses. Immunosuppressive agents such as Tocilizumab, Mycophenolate Mofetil, Cyclophosphamide, Methotrexate, Rituximab, and Azathioprine may be used to reduce inflammation and retard the progression of fibrosis.

577. Tocilizumab is a recombinant humanized monoclonal antibody of the immuno-globulin IgG1 subclass against the interleukin-6 receptor, a cytokine that plays an important role in immune response and is implicated in the pathogensis of autoimmune diseases. Tocilizumab was approved for medical use in the United States in January 2010 and is indicated for the treatment of

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rheumatoid arthritis and systemic sclerosis-associated interstitial lung disease, both of which are known to be caused by exposure to respirable crystalline silica. Tocilizumab is a prime candidate for treatment of artificial-stone induced silicosis, because this disease usually manifests with progressive massive fibrosis and has been associated with the development of connective tissue autoimmune diseases for which this drug has been shown to be effective.

578. In 2021, researchers published the results of a phase 3 randomized placebo-controlled trial of Tocilizumab in patients with systemic sclerosis and progressive skin disease. Participants had baseline and serial spirometry along with high resolution chest CT at baseline and week 48. Quantitative interstitial lung disease and fibrosis were derived using computer software. We divided quantitative interstitial lung disease in mild (5-10%), moderate (>10-20%), or severe (>20%) categories. Of 210 participants recruited in the trial, 136 [65%] had interstitial lung disease. The majority of these participants had moderate-to-severe involvement defined by >10% lung involvement (77%). The tocilizumab arm demonstrated preservation of forced vital capacity over 48 weeks (least squared mean change in %predicted = −0.1) compared to placebo (−6.3%). For mild, moderate, and severe QILD, the mean decline in the %pFVC in the tocilizumab arm at 48 weeks were −4.1, 0.7, and 2.1, and in the placebo group were −10.0, −5.7, and −6.7, respectively. Similar treatment-related preservation findings were seen independent of fibrosis severity. The investigators concluded that Tocilizumab in early Systemic Sclerosis- associated interstitial lung disease with progressive skin disease stabilized forced vital capacity over 48 weeks, independent of the extent of quantitative radiographic interstitial lung disease or fibrosis.[470]

579. In 2022, the same researcher group assessed long-term safety and efficacy of Tocilizumab. Adults with diffuse cutaneous Systemic Sclerosis for <60 months and elevated acute-phase reactants, including those with Interstitial Lung Disease, received weekly placebo or tocilizumab 162 mg subcutaneously in the 48-week, double-blind period and then open-label tocilizumab from Weeks 48 to 96 (placebo-tocilizumab; continuous-tocilizumab). Eighty-two of 107 patients in the placebo-tocilizumab group and 85 of 105 patients in the continuous-tocilizumab

[470] Roofeh D, et al., "Tocilizumab Prevents Progression of Early Systemic Sclerosis Associated Interstitial Lung Disease," *Arthritis Rheumatol.* 2021; 73(7):1301-1310.

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group completed 96 weeks. Mean age and disease duration were 48 years and 23 months; high-resolution computed tomography revealed ILD in 61%. Mean (95% confidence interval [CI]) change in modified Rodnan skin score from baseline to week 96 was 28.4 (210.0 to 26.8) for placebotocilizumab and 29.6 (210.9 to 28.4) for continuoustocilizumab. Mean (95% CI) change in FVC (percent predicted) from baseline to week 96 was 23.3 (25.1 to 21.5) for placebotocilizumab and 20.5 (22.4 to 1.3) for continuous-tocilizumab among completers and, in a post hoc analysis, 24.1 (26.7 to 21.6) and 20.6 (23.1 to 2.0), respectively, among completers with Interstitial Lung Disease (mean [95% CI] change from Weeks 48 to 96: 0.9 [20.8 to 2.7] and 20.4 [22.3 to 1.5], respectively). Rates per 100 patient-years of serious adverse events from Weeks 48 to 96 were 14.8 for placebo-tocilizumab and 15.8 for continuous-tocilizumab. The investigators concluded that Tocilizumab preserved lung function, slowing decline in FVC, in patients with Systemic Sclerosis, including those with Interstitial Lung Disease and that long-term safety was consistent with the known safety profile of tocilizumab.[471] Khanna D, et al., "Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis-Interstitial Lung Disease: Open-Label Extension of a Phase 3 Randomized Controlled Trial," *Am. J. Respir. Crit. Care Med.* 2022; 205(6):674-684.

580. In 2024, two systematic reviews and meta-analyses found that Tocilizumab use in patients with systemic sclerosis associated interstitial lung disease resulted in less lung function decline that in patients given a placebo.[472] Elrosasy A, et al., "Efficacy and Safety of Tocilizumab in Systemic Sclerosis and associated Interstitial Lung Disease: a systematic review and meta-analysis of randomized controlled trials," *Cureus* 2024; 16(7):a1280; Ghazpiura M, et al., "Toxilizumab in Patients with Systemic Sclerosis-associated Interstitial Lung Disease: A Systematic Review and Meta-Analysis," *Ann. Am. Thorac. Soc.* 2024; 21(2):328-337.

[471] Khanna D, et al., "Long-Term Safety and Efficacy of Tocilizumab in Early Systemic Sclerosis-Interstitial Lung Disease: Open-Label Extension of a Phase 3 Randomized Controlled Trial," *Am. J. Respir. Crit. Care Med.* 2022; 205(6):674-684.

[472] Elrosasy A, et al., "Efficacy and Safety of Tocilizumab in Systemic Sclerosis and associated Interstitial Lung Disease: a systematic review and meta-analysis of randomized controlled trials," *Cureus* 2024; 16(7):a1280; Ghazpiura M, et al., "Toxilizumab in Patients with Systemic Sclerosis-associated Interstitial Lung Disease: A Systematic Review and Meta-Analysis," *Ann. Am. Thorac. Soc.* 2024; 21(2):328-337.

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8. Combined Antifibrotic and Immunosuppressive Therapy

581. A few studies have evaluated the combined administration of antifibrotics and immunosuppressive medications in patients with progressive interstitial lung disease.

582. In 2024, Greek researchers published a study in which they observed patients diagnosed with systemic sclerosis (one of autoimmune conditions caused by crystalline silica) who had progressive interstitial lung disease. Consecutive patients who received off-label Tocilizumab for Systemic Sclerosis plus Nintedanib for progressive Interstitial Lung Disease were retrospectively studied. Adverse events, and changes in Forced Vital Capacity (FVC), Diffusing Capacity for Carbon Monoxide (DLCO) and high resolution chest tomography (HRCT) between baseline and 6 and 12 months were assessed. Tocilizumab/Nintedanib combination was well tolerated by all 20 patients [aged 52 ± 13 years (mean ± SD), 14 women, 15 diffuse SSc, disease duration of 5.7 ± 4.9 years]; 7 of 20 patients received concomitant mycophenolate mofetil safely. No serious adverse events or laboratory abnormalities were noted. Five patients developed persistent diarrhea and 2 of them reduced dosage of Nintedanib. Baseline FVC (74%±12%) and DLCO (45%±10%) remained overall stable both at 6 months (73.5%±13% and 46%±11%, respectively) and 12 months (73%±14% and 45%±11%, respectively), regardless of disease duration. The extent of fibrotic reticular pattern in available pairs of HRCTs (n = 12) remained also stable at 12 months, whereas the proportion (%) of ground glass opacities decreased from 29%±16 to 21%±14% (p = 0.048); improvement in HRCTs by almost 75% was noted in 2 of these12 patients. Tocilizumab/Nintedanib combination for one year was safe and stabilized lung function in real-world Systemic Sclerosis patients with progressive Interstitial Lung Disease.[473]

[473] Panopoulos S, et al., "Tocilizumab plus Nintedanib for progressive interstitial lung disease in systemic sclerosis: a one-year observational study," *Rheumatology Int.* 2024; 44:1959-1966.

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9. Molgramostim

583. Molgramostim is a synthetic protein that acts as a recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). It stimulates the growth and function of immune cells, particularly white blood cells that are essential for the body's defense against infections and for restoring immunity. It has been used to aid in the recovery of white blood cell counts after chemotherapy and to help with the mobilization of stem cells for bone marrow transplants.

584. In recent years, Molgramostim has been studied as a treatment for autoimmune pulmonary alveolar proteinosis. The efficacy of Molgramostim in treating pulmonary alveolar proteinosis is especially relevant to the treatment of artificial stone-induced silicosis, because occupational exposure to artificial stone dust has been reported to cause pulmonary alveolar proteinosis as an acute form of silicosis that is sometimes referred to as silicoproteinosis.[474] Indeed, examination of explanted lungs of transplanted artificial stone fabricators, as well as lungs of deceased California artificial stone fabricators, have consistently evidenced alveolar proteinosis.[475]

585. In 2000, German researchers examined leukocyte counts and ex vivo cytokine response of whole blood to lipopolysaccharide (LPS) or lipoteichoic acid (LTA) in patients given low-dose molgramostim therapy. Patients were injected subcutaneously daily for ten days with 1 µg/kg *(n* = 9) or 2 µg/kg (*n* =14) molgramostim. Leukocytosis was observed in all patients, but only the eosinophil fraction was significantly increased in relation to other leukocyte populations. Ex vivo IFN-y release was decreased and IL-IO and IL-lra secretion were increased in response to LPS or LTA. The investigators observed that in non-neutropenic patients, leukocytosis can already be initiated by low doses of molgramostim. They concluded that the ex vivo cytokine data suggest that

[474] Requena-Mullor M, et al., "Association between Crystalline Silica Dust Exposure and Silicosis Development in Artificial Stone Workers," *Int. J. Environ. Res. Public Health* 2021; 18:5625 ["The most frequent clinical form of the disease was acute silicosis (42.2%)."]; Cena AC, et al., "Silicosis: No longer exclusively a chronic disease," *J. Am. Acad. Physicians' Assistants* 2024; 37(9):14-20; Barnes H, et al., "Silica-associated lung disease: an old-world exposure in modern industries," *Respirology* 2019; 24(12):1165-1175; Manglani R, et al., "A 44-year-old stone worker with progressive dyspnea: lessons from a new twist on an old foe," *Monaldi Arch. Chest Dis.* 2023; 93:2345; Khan SNS, et al., "Gm-CSF antibodies in artificial stone associated silicoproteinosis: A case report and literature review," *Respirology Case Reports* 2022; 10: e01021; Fazio JC, et al., "A review of silicosis and other silica-related diseases in the engineered stone countertop processing industry," *J. Occup. Med. Toxicol.* 2025; 20:9.

[475] Pulmonary pathology reports and photoelectronmicrogaphs showing pulmonary alveolar proteinosis of multiple California artificial stone countertop fabricators prepared by Dr. Jerrold Abraham.

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these doses prime blood towards a systemic anti-inflammatory response.[476]

586. In 2016, Danish researchers published a study in which they administered Molgramostim by inhalation to 42 healthy adults to determine its efficacy, tolerability and safety. Inhaled molgramostim resulted in dose-dependent, temporary increases from baseline in WBC (1.3 - 1.8 times), neutrophils (1.2 - 3.5 times), monocytes (1.1 - 2.4 times), and eosinophils (2.0 - 3.7 times) 6 hours post-dose. No antibodies to GM-CSF were detected. No clinically relevant changes in spirometry, ECGs, clinical laboratory results or vital signs were observed. The investigators concluded that inhaled molgramostim is well-tolerated in healthy subjects, is absorbed systemically at picogram levels, and showed a clear effect on WBC differentials. They concluded that inhaled molgramostim may be a promising new treatment for pulmonary conditions with high unmet need.[477]

587. In 2020, American researchers published a randomized clinical trial of inhaled Molgramostim in autoimmune pulmonary alveolar proteinosis (aPAP). In a double-blind, placebo-controlled, three-group trial, they randomly assigned patients with aPAP to receive the recombinant GM-CSF molgramostim (300 μg once daily by inhalation), either continuously or intermittently (every other week), or matching placebo. The 24-week intervention period was followed by an open-label treatment-extension period. The primary end point was the change from baseline in the alveolar–arterial difference in oxygen concentration (A-aDo2) at week 24. In total, 138 patients underwent randomization; 46 were assigned to receive continuous molgramostim, 45 to receive intermittent molgramostim, and 47 to receive placebo. Invalid A-aDo2 data for 4 patients (1 in each molgramostim group and 2 in the placebo group) who received nasal oxygen therapy during arterial blood gas measurement were replaced by means of imputation. For the primary end point — the change from baseline in the A-aDo2 at week 24 — improvement was greater among patients receiving continuous molgramostim than among those receiving placebo (−12.8 mm Hg vs. −6.6 mm Hg; estimated treatment difference, −6.2 mm Hg; P = 0.03 by comparison of least-squares

[476] Hartung T, et al., "Blood Cytokine Response of Low-Dose Molgramostim (rh(GM-CSF)-Treated Patients," *Cytokine* 2000; 12(10):1570-1574.

[477] Tarnow I, et al., "A Randomized, Double-Blind, Placebo-Controlled, Single-Centre, Single Ascending Dose and Multiple Ascending Dose Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Molgramostim (rhgm-Csf) Administered by Inhalation to Healthy Adult Subjects," *Am. J. Respir. Crit. Care Med.* 2016; 193:A1856 [poster presentation].

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means). Patients receiving continuous molgramostim also had greater improvement than those receiving placebo for secondary end points, including the change from baseline in the St. George's Respiratory Questionnaire total score at week 24 (−12.4 points vs. −5.1 points; estimated treatment difference, −7.4 points; P = 0.01 by comparison of least-squares means). For multiple end points, improvement was greater with continuous molgramostim than with intermittent molgramostim. The percentages of patients with adverse events and serious adverse events were similar in the three groups, except for the percentage of patients with chest pain, which was higher in the continuous-molgramostim group. The investigators concluded that in patients with aPAP, daily administration of inhaled molgramostim resulted in greater improvements in pulmonary gas transfer and functional health status than placebo, with similar rates of adverse events.[478]

588. A Phase 3 trial (IMPALA-2) evaluated efficacy of Molgramostim treatment of autoimmune Pulmonary Alveolar Proteinosis in a 48-week double-blind treatment period. A total of 164 patients received molgramostim (n=81) or placebo (n=83). Molgramostim significantly improved DLco% compared with placebo at week 24 (difference in least squares mean change 6.0%, p=0.0007) and at week 48 (6.9%, 95% CI 2.9, 10.9). Molgramostim treated patients had greater mean improvements than placebo patients at Week 24 and at Week 48 in SGRQ total score (difference in least squaresmean change at Week 24: -6.59 points, 95% CI -11.4, -1,79; Week 48: -4.87 points, 95% CI -10.76, 1.01) and EC (Week 24: 0.41 METs, 95% CI-0.06, 0.89; Week 48: 0.55 METs, 95% CI 0.07, 1.03). SGRQ Activity was also improved at Week 24. Molgramostim was well tolerated; most adverse events were mild or moderate in severity. All patients who completed double-blind treatment continued in the open-label period.[479]

589. Another study reported health-related quality of life, as measured by Saint George's Respiratory Questionnaire. This study showed improvements from baseline with greater effects for Molgramostim versus placebo at week 48 than at week 24. More aPAP patients on Molgramostim

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[478] Trapnell BC, et al., "Inhaled Molgramostim Therapy in Autoimmune Pulmonary Alveolar Proteinosis," *New Engl. J. Med.* 2020; 383:1635-1644.

[479] McCarthy C, et al., "Molgramostim improves pulmonary gas exchange in patients with autoimmune pulmonary alveolar proteinosis (aPAP): results from the IMPALA-2 phase 3 clinical trial," *Thorax* 2024; 79(Suppl. 2) Abstract 112.

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than on placebo reported improvements in mobility, self-care, usual activities, and pain/discomfort, as well as improvements in breathing problems and physical activity level.[480]

590. Subsequent publications of the Phase 3 clinical trial reported favorable results for gas exchange, exercise capacity and quality of life,[481] long-term outcomes,[482] and reduction of surfactant burden and number of necessary whole lung lavages.[483]

591. On August 20, 2025, the researchers published the final results of the Phase 3 trial. A total of 164 patients underwent randomization: 81 were assigned to receive molgramostim and 83 to receive placebo. The least-squares mean change in DLCO from baseline to week 24 was 9.8 percentage points (95% confidence interval [CI], 7.3 to 12.3) with molgramostim and 3.8 percentage points (95% CI, 1.4 to 6.3) with placebo (estimated treatment difference, 6.0 percentage points; 95% CI, 2.5 to 9.4; P<0.001). The least-squares mean change in DLCO from baseline to week 48 was 11.6 percentage points (95% CI, 8.7 to 14.5) with molgramostim and 4.7 percentage points (95% CI, 1.8 to 7.6) with placebo (P<0.001), and the least-squares mean change in the SGRQ-T score at week 24 was −11.5 points (95% CI, −15.0 to −8.0) and −4.9 points (95% CI, −8.3 to −1.5), respectively (P=0.007). No significant between-group difference in the change in SGRQ-A score was observed at 24 weeks, so no statistical inference was drawn with respect to subsequent secondary end points. The percentage of patients with at least one adverse event and the percentage with at least one serious adverse event were similar in the two groups. Once-daily inhaled molgramostim led to a greater increase in pulmonary gas transfer than placebo in patients with aPAP.[484]

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[480] Ataya A, et al., "The Effects of Molgramostim on Respiratory Health-related Quality of Life and Patient-reported outcomes in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP)," *Am. J. Respir. Crit. Care Med.* 2025; 211:A1811 [abstract].

[481] Bonella F, et al., "Inhaled molgramostim improves pulmonary gas exchange, exercise capacity, and quality of life in patients with autoimmune pulmonary alveolar proteinosis (aPAP)," *Pneumologie* 2025; 79(s01:S31-S32)

[482] Montano C, et al., "Long-term outcomes in five patients with autoimmune pulmonary alveolar proteinosis treated with molgramostim inhalation solutions," *ERJ Open Res.* 2025; 11:00567-2024.

[483] Wang TS et al., "Molgramostim Reduces Surfactant Burden and Number of Whole Lung Lavage Procedures in Patients with Autoimmune Pulmonary Alveolar Proteinosis (aPAP): Results from the IMPALA-2 Phase 3 Clinical Trial," *Am. J. Respir. Crit. Care. Med.* 2025; 211: Abstract 1129.

[484] Trapnell BC, et al., "Phase 3 Trial of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis," *New Engl. J. Med.* 2025; 393:764-773.

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D. Alkaloid Treatments

592. "Alkaloids are a group of naturally occurring chemical compounds that contains mostly basic nitrogen atoms." "They rank among the most diverse, efficient and therapeutically significant plant substances." "On the basis of their biosynthetic precursor and heterocyclic ring system, the compounds have been classified into various categories which include indole, piperidine, tropane, purine, pyrrolizidine, imidazole, quinolozidine, isoquinoline and pyrrolidine alkaloids."[485]

593. "In recent years, the anti-pulmonary fibrotic potential of natural products has garnered increasing attention, with alkaloids showing particularly promising prospects. Alkaloids can intervene [in] pulmonary fibrosis through multiple signaling pathways. Alkaloids exert anti-inflammatory, antioxidant, and antiapoptotic effects, which contribute to the inhibition of extracellular matrix (ECM) deposition, the protection of alveolar epithelial cells, and the suppression of lung fibroblast activation and proliferation involved in pulmonary fibrosis."[486]

594. In 2021, Indian reviewed bioactive compounds of medicinal plants, specially emphasizing the importance of isoquinoline alkaloids in treating pulmonary fibrosis.[487]

595. In 2025, Chinese researchers reviewed the mechanisms by which alkaloids prevent and treat pulmonary fibrosis, including experimental methodologies and clinical findings. They also discussed challenges and outlined potential directions for future research, with the goal of providing insight to development of therapeutic agents for pulmonary fibrosis prevention and treatment.[488]

596. Alkaloids that are candidates for treating silicosis and other silica-related diseases include Anisodamine, Berberine and Demethyleneberberine, Chelerythrine, Eviodiamine, Homoharringtonine, Neverine, Piperine, Tetrandrine, Vincamine, and Vinpocetine.

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[485] Roy A, "A Review on the Alkaloids an Important Therapeutic Compound from Plants," *Int. J. Plant Biotech.* 2017; 3(2):1-9.

[486] Wang Y, et al., "Alkaloids as Emerging Therapeutics against Pulmonary Fibrosis: Classification, Mechanisms, and Translational Potential," *Chemistry & Biodiversity* 2025 Aug 20: e01495 [online ahead of print].

[487] Dudala SS, et al., "A review on importance of bioactive compounds of medicinal plants in treating idiopathic pulmonary fibrosis (special emphasis on isoquinoline alkaloids)," *Future J. Pharm. Sci.* 2021; 7:156.

[488] Wang Y, et al., "Alkaloids as Emerging Therapeutics against Pulmonary Fibrosis: Classification, Mechanisms, and Translational Potential," *Chem. Biodivers.* 2025 Aug. 20: e01495.

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1. Anisodamine

597. "Anisodamine . . . is an alkaloid extracted from the roots of the *Anisodus tanguticus* Maxim." "[A] prominent constituent of the tropine alkaloid family . . . , [it] is less toxic than atropine and scopolamine." "Anisodamine . . . exhibits anti-inflammatory, antiviral, anti-hypoxia, antioxidant, inhibition of cellular senescence, and microcirculation improvement properties."[489]

598. In 2021, two studies by Chinese researchers investigated the effect of Anisodamine on rats administered bleomycin, a fibrotic agent. The study by researchers from Chengdu showed that Anisodamine inhibits TGF-ß-induced pulmonary fibrosis and protects lung tissue structure and dysfunction by inhibiting JAK2/STAT3 phosphorylation.[490] The study by researchers from Changchun showed that Anisodamine protects bleomycin-induced acute lung injury by modulating oxidative stress, inflammation and cell apoptosis, also by inhibiting the JAK2/STAT3 pathway.[491]

599. In 2022, researchers from Xi'an China showed that Anisodamine reduced lung damage, myeloperoxidase activity, lung wet/dry ratio, total cell number, and protein concentrations in bronchoalveolar lavage fluid, that it decreased interleukin (IL)-6 level and the levels of M1 phenotypic markers, and that it increased IL-10 level and the levels of M2 phenotypic markers in mice via nasal instillation of lipopolysaccharide. They concluded that Anisodamine treatment attenuated acute lung injury and pulmonary edema caused by lipopolysaccharide (LPS) stimulation, and that Anisodamine reversed the LPS-induced alterations of M1 and M2 polarization by inhibiting G9a-mediated methylation and expression suppression of interferon regulatory factor 4.[492]

600. In 2024, Chinese researchers evaluated the protective effect and mechanism of Anisodamine on radiation-induced lung injury. They divided mice into control, model, medication

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[489] Xia Q, et al., "A Review on the Chemical Properties, Plant Sources, Anti-shock Effects, Pharmaco-kinetics, Toxicity, and Clinical Applications of Anisodamine," *Chem. Biodiversity* 2024; 21: 3202301477.

[490] Luo J-L, et al., "Anisodamine alleviating bleomycin-induced pulmonary fibrosis and pathological damage in rats by inhibiting JAK2/STATE3 phosphorylation," *Chinese J. Immunol.* 2021; 37(5):529-534.

[491] Zhao X, et al., "Protective effect of anisodamine on bleomycin-induced acute lung injury in immature rats via modulating oxidative stress, inflammation and cell apoptosis by inhibiting the JAK2/STAT3 pathway," *Ann. Transl. Med.* 2021; 9(10):859.

[492] Zhang Y, et al., "Anisodamine enhances macrophage M2 polarization through suppressing G9a-mediated interferon regulatory factor 4 silencing to alleviate lipopolysaccharide-induced acute lung injury," *J. Pharmacol. Exp. Ther.* 2022; 381(3):247–256.

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(control + Anisodamine), and treatment (model + Anisodamine) groups. Mice in medication and treatment groups were intraperitoneally injected with 5 mg/kg Anisoadmine every other day until sacrifice at week 6. *In vitro* experiments used MLE-12 cells irradiated with 16 Gy, divided into control, model, and model + Anisodamine 2 μM and 10 μM groups. Anisodamine mitigated pulmonary pathological damage, inflammation, DNA damage, cellular senescence, and apoptosis in mice with radiation-induced lung injury and MLE-12 cells. Anisodamine also restored epithelial cell proliferation ability and enhanced antioxidant capacity. Finally, Anisodamine activated the Nrf2/ARE pathway, increased Nrf2 phosphorylation, and upregulated antioxidant gene expression. Inhibition of Nrf2 reversed the effects of Anisodamine on reactive oxygen species production, antioxidant capacity, and cell senescence. The researchers concluded that Anisodamine can activate the Nrf2/ARE pathway, enhance cellular antioxidant capacity, and inhibit cellular senescence, thereby exerting a protective effect against radiation-induced lung injury.[493]

601. In 2025, researchers from Taiyuan China published a study in which they examined the effects of Anisodamine on pulmonary inflammation and fibrosis in silicotic mice. They showed that Anisodamine significantly reduced alveolar structure damage and the formation of silicotic nodules in mice by inhibiting pulmonary inflammation and fibrosis through modulation of the JAK2/STAT3 signaling pathway. The investigators concluded that based on the results of their study coal workers could utilize Anisodamine early on to treat and prevent silicosis.[494]

602. Collectively, the studies show that Anisodamine exerts protective effects against various forms of lung injury, including LPS-induced inflammation, radiation-induced lung damage, and bleomycin-induced fibrosis and silicosis, by modulating key inflammatory and oxidative stress pathways, including α7nAChR/JAK2/STAT3, Nrf2/ARE, and G9a/IRF4, thereby reducing inflammation, oxidative stress, apoptosis, and fibrosis in lung tissue.

[493] Guo H, et al., "Activation of Nrf2/ARE pathway by Anisodamine (654-2) for inhibition of cellular aging and alleviation of radiation-induced lung injury," *Biomed. Pharmacother*. 2024; 174:114071.

[494] Liu M, et al., "Anisodamine ameliorates crystalline silica-exposed pulmonary inflammation and fibrosis via the α7nAChR/JAK2/STAT3 signaling pathway," *Ecotoxicol. Environ. Safety* 2025; 289:117534.

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2. Protoberberine Alkaloids

603. "The protoberberine alkaloids are comprised of a tetracyclic ring system, which is based on the dibenzo[a,g]quinolizidine system. These tetracyclic alkaloids are derived from benzyl-isoquinolines through phenolic oxidation and coupling with the isoquinoline N-methyl group."[495]

604. "Berberine, berberrubine, thalifendine, demethyleneberberine, jatrorrhizine, and columbamine are six natural protoberberine alkaloid compounds that display extensive pharmacological properties and share the same protoberberine molecular skeleton with only slight substitution differences. The oral delivery of most protoberberine alkaloids is hindered by their poor bioavailability, which is largely caused by P-glycoprotein-mediated drug efflux. Meanwhile, P-glycoprotein undergoes large-scale conformational changes . . . when transporting substrates, and these changes might strongly affect the P-glycoprotein-binding specificity. To confirm whether these six compounds are substrates of P-glycoprotein, to investigate the differences in efflux capacity caused by their trivial structural differences and to reveal the key to increasing their binding affinity to P-glycoprotein, [Chinese researchers] conducted a series of in vivo, in vitro, and in silico assays. [They] confirmed that all six compounds were substrates of P-glycoprotein by comparing the drug concentrations in wild-type and P-glycoprotein-knockout mice in vivo. The efflux capacity (net efflux) ranked as berberrubine > berberine > columbamine ~ jatrorrhizine > thalifendine > demethyleneberberine based on in vitro transport studies in Caco-2 monolayers. Using molecular dynamics simulation and molecular docking techniques, [the researchers] determined the transport pathways of the six compounds and their binding affinities to P-glycoprotein. The results suggested that at the early binding stage, different hydrophobic and electrostatic interactions collectively differentiate the binding affinities of the compounds to P-glycoprotein, whereas electrostatic interactions are the main determinant at the late release stage. In addition to hydrophobic interactions, hydrogen bonds play an important role in discriminating the binding affinities."[496]

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[495] da-Cunha, EVL, et al., "Proroberberine Alkaloids," in *The Alkaloids: Chemistry and Biology* 2005; 62:1-75.

[496] Zhang Y-T, et al., "Different structures of berberine and five other proroberberine alkaloids that affect P-glycoprotein-mediated efflux capacity," *Acta Pharmacologica Sinica* 2019; 40:133-142.

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3. Berberine

605. "Berberine is a naturally occurring yellow plant extract with a long history of medicinal uses in Ayurvedic and Chinese medicines. It is an alkaloid present in root, stem, bark, leaves and rhizomes of *Berberis vulgaris, Tinospora cordifolia* and many other plants. Berberine activates the enzyme called AMPK, which regulates biological activities that normalize lipid, glucose and energy imbalances. Studies have shown that berberine has various pharmacological functions such as anti-diabetic, anti-bacterial, anti-viral, anti-cancer, anti-inflammatory effects."[497]

606. The first studies regarding the antifibrotic effects of berberine were published by researchers from India.[498]

607. In 2013, the Indian researchers showed the Berberine attenuates bleomycin-induced pulmonary fibrosis by suppressing NF-κB dependent TGF-β activation.[499]

608. Two years later, the Indian researchers showed that Berberine inhibits signaling and enhances autophagy against pulmonary fibrosis.[500]

609. In 2015, Italian researchers investigated the effects of the berberine, dihydroberberine, canadine, stylopine, and coptisine in an in vitro model of fibrosis using human dermal fibroblasts. All of the alkaloids except coptisine inhibited TGF-β1-induced collagen production.[501]

610. In 2016, Iranian researchers published a study which showed that *Berberis vulgaris*

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[497] Prajwala B, et al., "Berberine and its Pharmacology Potential: A Review," *Eur. J. Biomed. Pharm. Sci.* 2020; 7(5):115-123.

[498] Chitra P, et al., "Berberine attenuates bleomycin induced pulmonary toxicity and fibrosis via suppressing NF-κB dependant TGF-β activation: A biphasic experimental study," *Toxicol. Lett.* 2013; 219(2):178-193; Chitra P, et al., "Berberine inhibits Smad and non-Smad signaling cascades and enhances autophagy against pulmonary fibrosis," *J. Mol Med. (Berl.)* 2015; 93(9):1015-1031.

[499] Chitra P, et al., "Berberine attenuates bleomycin induced pulmonary toxicity and fibrosis via suppressing NF-κB dependant TGF-β activation: A biphasic experimental study," *Toxicol. Lett.* 2013; 219(2):178-193.

[500] Chitra P, et al., "Berberine inhibits Smad and non-Smad signaling cascades and enhances autophagy against pulmonary fibrosis," *J. Mol Med. (Berl.)* 2015; 93(9):1015-1031.

[501] Pietra D, et al., "In vitro studies of antifibrotic and cytoprotective effects elicited by proto-berberine alkaloids in human dermal fibroblasts," *Pharmacol. Rep.* 2015; 67(6):1081-1089.

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fruit extract reduced Paraquat-induced pulmonary fibrosis in rats in a dose-dependent manner.[502]

611. In 2018, researchers from Nanjing, China published a study in which they showed that orally administered Berberine ameliorates bleomycin-induced pulmonary fibrosis in mice.[503]

612. In 2019, Chinese researchers evaluated the therapeutic effect of Berberine and Dexamethasone in bleomycin-induced pulmonary fibrosis. They divided bleomycin-treated rats into groups administered Berberine, Dexamethasone and both compounds. On days 3, 7 and 14, blood samples were collected from the rats. CXC chemokine ligand 14 (CXCL14), collagen I, collagen III, matrix metalloproteinase (MMP)2 and MMP9 serum levels were measured by ELISA. On day 14, all rats were sacrificed, tissues were stained, and hydroxyproline assessment was performed to observe histopathological changes and collagen deposition. mRNAand protein levels of CXCL14, CXC chemokine receptor 4 (CXCR4), collagen I/III, α-smooth muscle actin, MMP2/9 and phosphorylated-Smad 2/3 in lung tissue were evaluated. Similar effects in preventing lung damage were observed histopathologically for Dexamethasone and Berberine compared with the bleomycin group. The treatments reduced levels of Hydroxyproline, CXCL14, CXCR4, collagen I/III, MMP2/9, α-SMA and p-Smad 2/3. The combined treatment exhibited increased effectiveness compared with the single treatments. The results suggested that antifibrotic mechanisms were involved in inhibiting CXCL14 and MMP2/MMP9 expression, and preventing the activation of Smad2/3 and hedgehog signaling pathways. The researchers concluded that the combined use of Dexamethasone and Berberine is a potential therapeutic approach for pulmonary fibrosis.[504]

613. In 2023, two studies by different research groups were published demonstrating that the use of Berberine-loaded nanoparticles can overcome poor permeability and bronchial remodeling,

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[502] Javad-Mousavi SA, et al., "Protective effect of *Berberis vulgaris* fruit extract against Paraquat-induced pulmonary fibrosis in rats," *Biomed. Pharmacother.* 2016; 81:329-336.

[503] Guan C, et al., "Orally administered berberine ameliorates bleomycin-induced pulmonary fibrosis in mice through promoting activation of PPAR-γ and subsequent expression of HGF in colons," *Toxicol. Appl. Pharmacol.* 2018; 343:1-15.

[504] Li L, et al., "Dexamethasone combined with berberine is an effective therapy for bleomycin-induced pulmonary fibrosis in rats," *Exper. Ther. Med.* 2019; 18:2385-2392.

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thereby enhancing the antifibrotic effect of Berberine as a treatment for pulmonary fibrosis.[505]

614. In 2024, Chinese researchers published a review of the mechanisms of Berberine in the treatment of fibrosis. They summarized the anti-fibrotic effects of Berberine to hepatic fibrosis, myocardial fibrosis, pulmonary fibrosis, renal fibrosis, pancreatic fibrosis, adipose tissue fibrosis, and epidural fibrosis, and the multiple pathways that Berberine inhibits these fibrotic effects. They also described 5 pathways by which Berberine ameliorates pulmonary fibrosis: (1) the Transforming Growth Factor-β (TGF-β) pathway, (2) the anti-inflammatory pathway, (3) the Stromal cell-derived factor-1/CSCR4 pathway, (4) the PPAR-γ pathway, and (5) the Nuclear factor-κB pathway.[506]

615. The same year Chinese investigators from Chengdu published a systematic review of the effective role of Berberine in fibrosis-related diseases, concluding that the scientific evidence supports the use of Berberine in the treatment of fibrotic diseases including pulmonary fibrosis.[507]

616. In 2024, Egyptian researchers also published a review of the pharmacological activities and medicinal uses of Berberine,[508] summarizing Berberine's antifibrotic effects as follows: "Several studies have demonstrated the efficacy of BBR against fibrotic diseases in vivo, including pulmonary fibrosis,[509] myocardial fibrosis,[510] renal fibrosis,[511] and adipose tissue fibrosis,[512] and

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[505] Chakraborty A, et al., "Anti-Inflammatory and Anti-Fibrotic Effects of Berberine-Loaded Liquid Crystalline Nanoparticles," *EXCLI J.* 2023; 22:1104-1108; De Rubis G, et al., "Berberine-loaded engineered nanoparticles attenuate TGF-β-induced remodelling in human bronchial epithelial cells," *Toxicol. In Vitro* 2023; 92:105660.

[506] Liu X, et al., "Advances in the pharmacological mechanisms of berberine in the treatment of fibrosis," *Front. Pharmacol.* 2024; 15:1455058.

[507] Gao R, et al., "The Application of Berberine in Fibrosis and the Related Diseases," *Am. J. Chin. Med.* 2024; 52(3):753-773.

[508] Shams G, et al., "Pharmacological activities and medicinal uses of berberine: A review," *J. Advanced Veterinary Res.* 2024; 14(2):330-334.

[509] Chitra P, et al., "Berberine Inhibits Smad and Non-smad Signaling Cascades and Enhances Autophagy against Pulmonary Fibrosis," *J. Mol. Med.* 2015; 93:1015-1031.

[510] Zhang YJ, et al., "Berberine Attenuates Adverse Left Ventricular Remodeling and Cardiac Dysfunction after Acute Myocardial Infarction in Rats: Role of Autophagy," *Clin. Exp. Pharmacol. Physiol.* 2014; 41:995-1002.

[511] Wang N, et al., "Berberine Inhibition of Fibrogenesis in a Rat Model of Liver Fibrosis and in Hepatic Stellate Cells," *Evid. Based Complement. Alternat. Med.* 2016; 8762345.

[512] Xu X, et al., "Therapeutic Effect of Berberine on Metabolic Diseases: Both Pharmacological Data and Clinical Evidence," *Biomed. Pharmacother.* 2021; 133: 110984.

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multifaceted causal relationships illustrate the efficacy of BBR against liver fibrosis."[513]

617. In 2025, Chinese researchers investigated the mechanism by which Berberine ameliorates pulmonary fibrosis. They analyzed mRNA expression of thrombospondin 2 (THBS2) by quantitative real-time polymerase chain reaction. Protein expression level was detected by western blotting assay or immunohistochemistry assay. Cell function was analyzed using cell counting kit-8 assay, 5Ethynyl-2'-deoxyuridine assay, transwell invasion assay, wound-healing assay, enzyme-linked immunosorbent assays, and colorimetric assay. The pulmonary fibrosis mouse model used bleomycin to analyze the effect of berberine on pulmonary fibrosis. THBS2 expression was upregulated in the lung tissues of bleomycin-induced pulmonary fibrosis mice and transforming growth factor-β1 (TGF-β1)-induced HLF cells. Berberine ameliorated bleomycin-induced pulmonary fibrosis in vivo. TGF-β1 treatment induced HLF cell proliferation, invasion, migration, inflammation response, and oxidative stress, accompanied by increases in collagen I, fibronectin, and α-SMA protein expression, but these effects were attenuated after THBS2 silencing. Berberine also attenuated TGF-β1-induced pro-fibrotic phenotypes of HLF cells and bleomycin-induced pulmonary fibrosis through the inactivation of the THBS2/Smad2/3 pathway. The Chinese investigators concluded that Berberine inhibited bleomycin-induced pulmonary fibrosis by inactivating the THBS2/Smad2/3 pathway, providing a theoretical basis for treating pulmonary fibrosis treatment with Berberine.[514]

[513] Wang N, et al., "Berberine Inhibition of Fibrogenesis in a Rat Model of Liver Fibrosis and in Hepatic Stellate Cells," *Evid. Based Complement. Alternat. Med.* 2016; 8762345; Bansod S, et al., "Molecular Updates on Berberine in Liver Diseases: Bench to Bedside," *Phytother. Res.* 2021; 35:5459-5476..

[514] Zhang L, et al., "Berberine Ameliorates Pulmonary Fibrosis by Inactivating the Thrombospondin 2/Smad Homolog 2/3 Pathway," *Chem. Biol. Drug Des.* 2025; 105(4): e70111.

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4. Demethyleneberberine

618. "Demethyleneberberine is an active component extracted from the Chinese herbal drug Cortex Phellodendri. It is also a metabolite of berberine in animals and humans. . . . [I]ts bioavailability [i]s comparable, ranging from 4.47% to 5.94%, higher than that of berberine."[515]

619. In 2024, Chinese researchers investigated the therapeutic potential of Demethyleneberberine in alleviating pulmonary fibrosis. They showed that Demethyleneberberine alleviates bleomycin-induced pulmonary fibrosis and inhibits epithelial-mesenchymal transition (EMT) and fibroblast-myofibroblast transition (FMT). They also showed that GREM1, a highly upregulated profibrotic mediator in Idiopathic Pulmonary Fibrosis and bleomycin-induced pulmonary fibrosis, was significantly downregulated by Demethyleneberberine. The investigators concluded that Demethyleneberberine can promote GREM1 degradation, thus alleviating pulmonary fibrosis.[516]

620. In 2025, Chinese researchers further investigated the therapeutic potential of Demethyleneberberine in pulmonary fibrosis and elucidated its underlying mechanisms of action. They showed that DMBtreatment significantly alleviated histopathological alterations and reduced collagen deposition in lung tissues, that it inhibited activation of both canonical and non-canonical NLRP3 inflammasomes, and that it reversed epithelial-mesenchymal transiation-related marker expression in both in vivo and in vitro models. The investigators observed that Demethyleneberberine ameliorates pulmonary fibrosis by inhibiting NLRP3 inflammasome activation and suppressing the EMT. They concluded that inhibition of NLRP3 appears to play a critical role in mediating the antifibrotic effects of Demethyleneberberine and that the findings of their study imply that Demethyleneberberine may represent a promising therapeutic candidate for clinical management of idiopathic pulmonary fibrosis.[517]

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[515] Li J, et al., "Pharmacokinetics, Tissue Distribution and Excretion of Demethyleneberberine, a Metabolite of Berberine, in Rats and Mice," *Molecules* 2023; 28:7725.

[516] Ge C, et al., "Demethyleneberberine Alleviates Pulmonary Fibrosis through Disruption of USP11 Deubiquitinating GREM1," *Pharmaceuticals* 2024; 17:279.

[517] Wang X, et al., "Demethyleneberberine ameliorates pulmonary fibrosis by inhibiting the NLRP3 inflammasome and the epithelial-mesenchymal transition," *Int. Immunopharmacol.* 2025; 161:15003.

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5. Chelerythrine

621. Chelerythrine is a type of benzo[c]phenanthridine alkaloid isolated from plants such as Chelidonium, which has recognized antitumor, antibiotic and anti-inflammation pharmacological properties.[518]

622. Chelerythrine (CHE) consists mainly of extracted and isolated alkaloid components from four plants of the families Papaveraceae (e.g., *Chelidonium majus* L., *Macleaya cordata* (Willd.) R.Br., and *Sanguinaria canadensis* L.) and Rutaceae (e.g., *Zanthoxylum asiaticum* (L.)." "[S]cientific studies have proven that the[se] four plants have antitumor medicinal values."[519]

623. In 2018, Chinese researchers investigated the effect of Chelerythrine against lipopolysaccharide (LPS)-induced acute lung injury. They showed that treatment with Chelerythrine significantly ameliorated LPS-induced pathological changes in the lung. CH also markedly suppressed LPS-induced Tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 1b (IL-1b) production, and oxidative stress. Western blot showed that Chelerythrine suppressed LPS-stimulated inflammation of RAW264.7 cells through activation of the nuclear factor kappa-B (NF-kB) pathway. Knocking down of nuclear factor erythroid 2-related factor 2 (Nrf2) led to the reduction of nuclear translocation of the NF-kB p65, which triggered inflammation. The investigators concluded that their experimental results provided evidence that Chelerythrine could be a potential therapeutic candidate for the intervention of acute lung injury caused by LPS.[520]

624. In 2021, Chinese researchers, noting that Chelerythrine had shown anti-fibrotic effects in the kidney and liver, investigated whether Chelerythrine exerts like effects in lung tissue. Pulmonary fibrosis mouse models were established through intratracheal injection of bleomycin, after which the mice were intraperitoneally injected with Chelerythrine (0.375 or 0.75 mg/kg/d)

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[518] Fan L, et al., "Chelerythrine Attenuates the Inflammation of Lipopolysaccharide-Induced Acute Lung Inflammation Through NF-κB Signaling Pathway mediated by Nrf2," *Front. Pharmacol.* 2018; 9:1047.

[519] Chen N, et al., "Rediscovery of Traditional Plant Medicine: An Underestimated Anticancer Drug of Chelerythrine," *Front. Pharmacol.* 2022; 13:906301.

[520] Fan L, et al., "Chelerythrine Attenuates the Inflammation of Lipopolysaccharide-Induced Acute Lung Inflammation Through NF-κB Signaling Pathway mediated by Nrf2," *Front. Pharmacol.* 2018; 9:1047.

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every other day. The mice were sacrificed at the 28th day to collect blood serum, bronchoalveolar lavage fluid (BALF), and pulmonary tissues. At both concentrations Chelerythrine attenuated pulmonary fibrosis. Chelerythrine injection reduced the expression levels of fibronectin, α-SMA, and TGF-β, upregulated the levels of SOD and GSH and decreased the levels of 4-HNE and HP. Also, CHE increased the expressions ofNrf2, HO-1, and NQO1. Treatment of Nrf2/antioxidant response element (ARE) inhibitor blocked the Nrf2/ARE signaling pathway, thus perturbing the inhibition of Chelerythrine on Bleomycin-induced pulmonary fibrosis in mice. The investigators concluded that the results of their study showed the Chelerythrnie alleviates pulmonary fibrosis in mice through activating theNrf2/ARE pathway to increase the activity of antioxidant enzymes.[521]

625. In 2024, researchers from Guiyang China conducted an integrative approach of network pharmacology and experimental validation study to elucidate the underlying mechanisms of Chelerythrine in treating fibrotic diseases. They analyzed 27 common targets of Chelerythrine against fibrotic disease. The results of GO and KEGG enrichment analyses (two types of bioinformatics analyses) suggested that Chelerythrine exerted pharmacological effects on fibrotic disease by regulating mTOR, AKT-PI3K, and apoptosis signaling pathways. Finally, molecular docking confirmed a strong binding affinity between Chelerythrine and the core target proteins. The researchers observed that Chelerythrine has inhibitory effects on the proliferation and migration of L929 cells, promotes cell apoptosis, decreases levels of Bcl-2, p-AKT/AKT, p-mTOR/mTOR and p-PI3K/PI3K, while increasing levels of the Bax. The investigators concluded that the results of their study indicate that Chelerythrine may be a potential drug for anti-fibrotic disease therapy.[522]

626. Collectively, the published studies indicate that Chelerythrine holds much promise as a treatment for fibrotic lung disease, including silicosis.

[521] Peng L, et al., "Chelerythrine Ameliorates Pulmonary Fibrosis via Activating the Nrf2/ARE Signaling Pathway," *Cell. Biochem. Biophys.* 2021; 79(2):337-347.

[522] Han W, et al., "Elucidation of the anti-fibrotic diseases mechanism of chelerythrine by integrative approach of network pharmacology and experimental verification," *Nat. Prod. Res.* 2024;

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6. Eviodiamine

627. "Evodiamine (EVO) is a tryptamine indole alkaloid and the main active ingredient in *Evodia rutaecarpa*. In recent years, the antitumor, cardioprotective, anti-inflammatory, and anti-Alzheimer's disease effects of EVO have been reported.[523]

628. In 2017, Chinese researchers published a study in which they showed that evodiamine prevents activation of cardiac fibroblasts into myofibroblasts and protects umbilical vein endothelial cells against endothelial to mesenchymal transition. They concluded that these effects may be mediated by inhibition of the Transforming Growth Factor Beta 1 (TGF-β1) pathway.[524]

629. In 2018, researchers from Changzhou China published evaluated the effect of Evodiamine on severe pneumonia induced by methicillin-susceptible *Staphylococcus aureus* (MSSA) following cytomeglovirus reactivation. The results of this study The results showed that Evodiamine dose dependently reduced the protein and mRNA expression levels of tumor necrosis factor (TNF) α, interleukin (IL) 6 and IL 1β, and inhibited the levels of phosphorylated (p) inhibitor of NF κBα, p extracellular signal regulated kinase, p c Jun N terminal kinase and p p38, and decreased the nuclear translocation of NF κB/p65 in BEAS 2B cells infected with MSSA. Furthermore, Evodiamine markedly improved survival rate, decreased body weight loss and bacterial count, and attenuated lung histological alterations and the levels of inflammatory factors. The NF κB and MAPK signaling pathways were also significantly inhibited. The researchers concluded that collectively the results of their study showed that Evodiamine effectively alleviated pneumonia via the NF κB and MAPK pathways and may be a therapeutic agent for treating severe pneumonia.[525]

630. In 2021, Chinese researchers studied the effects of evodiamine in lipopoly-saccharide-induced lung inflammation and fibrosis in BALB/c mice and RAW264.7 macrophages. They conducted in vitro and in vivo experiments to assess evodiamine's anti-inflammatory and

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[523] Lin L, et al., "Evodiamine: A Extremely Potential Drug Development Candidate of Alkaloids from *Evodia rutaecarpa," Int. J. Nanomedicine* 2024; 19:9843-9870.

[524] Wu Q-Q, et al., "Evodiamine attenuates TGF-β1-induced fibroblast activation and endothelial to mesenchymal transition," *Mol. Cell Biochem.* 2017; 430(1-2):81-90.

[525] Chen X, et al., "Evodiamine alleviates severe pneumonia induced by methicillin-susceptible *Staphylococcus aureus* following cytomeglovirus reactivation through suppressing NF-κB and MAPKs," *Int. J. Mol. Med.* 2018; 42:3247-3255.

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anti-fibrotic actions, focusing on the apelin signaling pathway and cytokine regulation. They showed that evodiamine alleviates pulmonary inflammation and fibrosis by inhibiting inflammatory cytokines and activating the apelin pathway, supporting evodiamine's therapeutic potential.[526]

631. In 2021, Chinese researchers investigated the anti-inflammatory role of Evodiamine in H5N1 and Streptococcus pneumoniae D39 co-infected human bronchial epithelial BEAS-2B cells. They evaluated inflammatory cytokine levels and signaling pathways affected by Evodiamine using qPCR, ELISA, and Western blot analysis. Their results showed that Evodiamine significantly enhanced the anti-inflammatory effect of clindamycin by reducing pro-inflammatory cytokines and inhibiting the CREB-C/EBPβ signaling pathway in BEAS-2B cells.[527]

632. In 2022, Chinese researchers reviewed natural indole alkaloids, including evodiamine, and their therapeutic effects on organ fibrosis, particularly in the lungs. They synthesized data on the pharmacological effects of indole-based small molecules in modulating fibrosis-related pathways such as TGF-β/Smad and NF-κB in various organ models. They concluded that evodiamine and related indole alkaloids exhibit anti-fibrotic effects across multiple organ systems, including the lungs, by suppressing inflammation, oxidative stress, and extracellular matrix accumulation.[528]

633. In 2023, researchers from Tianjin China investigated the mechanism by which Evodiamine alleviates blood transfusion related acute lung injury (TRALI) in rats by regulating high mobility group protein Bl (HMGB1)/ toll like receptor 4 (TLR4)/nuclear transcription factor-κB (NF-κB) signaling pathway. A total of 72 rats were randomly divided into the model group, low-dose evodiamine group, high-dose evodiamine group, no load group, high-dose evodiamine+HMGB1 overexpression group, and control group with 12 rats in each. Except for the control group, the TRALI model was prepared by intraperitoneal injection of lipopolysaccharide (LPS) combined with infusion of human plasma. Compared with the model group, the pulmonary function indexes MV

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[526] Ye C, et al., "Evodiamine alleviates lipopolysaccharide-induced pulmonary inflammation and fibrosis by activating apelin pathway," *Phytother. Res*. 2021;35:3406–3417.

[527] Liu X, et al., "Evodiamine Enhanced the Anti-Inflammation Effect of Clindamycin in the BEAS-2B Cells Infected with H5N1 and Pneumoniae D39 Through CREB-C/EBPb Signaling Pathway," *Viral Immunol*. 2021;34(6):410–415.

[528] Qin R, et al., "Indole-Based Small Molecules as Potential Therapeutic Agents for the Treatment of Fibrosis," *Front. Pharmacol*. 2022;13:845892.

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and PEF in low-dose evodiamine group and high-dose evodiamine group were increased ($P < 0.05$), while Ri, lung wet-dry ratio, lung histopathological score, platelet-neutrophil optical density in lung tissue, total number of cells in BALF, percentage of neutrophils, levels of pro-inflammatory factors TNF-α and IL-1β in BALF and serum, HMGB and TLR4 protein expression in lung tissue and p-NF-κB p5/NF-κB p5 were all decreased ($P<0.05$). Overexpression of HMGB1 attenuated improvement of lung function by Evodiamine in TRALI rats. The investigators concluded that Evodiamine may inhibit the inflammation in TRALI rats by inhibiting the activation of HMGB1/TLR4/NF-κB signaling, thereby reducing its acute lung injury, and repairing its lung function.[529]

634. In 2025, Chinese researchers systematically investigated Evodiamine's therapeutic effects and mechanisms against silicosis. The identified potential targets of Evodiamine and silicosis through mining of public databases. A Protein-Protein Interaction (PPI) network was created using Cytoscape, followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Molecular docking and molecular dynamics simulations were conducted to validate the binding ability of Evodiamine with putative targets. An *in vivo* silicotic mouse model was established to evaluate the anti-fibrotic effects and mechanism of Evodiamine against silicosis. In total, 265 Evodiamine targets and 270 silicosis-associated targets were identified. Integrative analysis of molecular docking, dynamics simulations, and KEGG pathways revealed key targets including AKT1, MAPK3, IL6, SRC, VEGFA, PTGS2, and STAT3, with thePI3K/AKT signaling pathway emerging as a critical mediator of Evodiamine's anti-fibrotic effects. The efficacy of Evodiamine was further validated using lung tissues from silicotic mice treated with Evodiamine. The researchers concluded that their study provided compelling evidence for Evodiamine's therapeutic potential in mitigating silica-induced pulmonary fibrosis, primarily through modulation of the PI3K/AKT signaling pathway, opening new avenues for innovative silicosis treatments.[530]

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[529] Qiao J, et al., "Evodiamine Alleviates Blood Transfusion Related Acute Lung Injury in Rats by Regulating HMBG1/TLR4/NF-κB Signaling pathway," J. Clin. Trnasfusion Lab. Med. 2023; 25(5): 599-606.

[530] Qin Y, et al., "Evodiamine Attenuates Silica-Induced Pulmonary Fibrosis via PI3K/AKT Pathway Suppression: Integrated Computational and Experimental Validation," *Biochem. Biophys. Res. Comm.* 2025; 782:152567.

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7. Homoharringtonine

635. "Homoharringtonine is a natural alkaloid with significant pharmacological potential that has demonstrated promising efficacy in the treatment of hematological malignancies in recent years. . . . Additionally, Homoharringtonine exhibits multiple biological activities, including immunomodulation, antiviral effects, and anti-fibrotic properties, with recent studies also revealing its potential neuroprotective functions."[531]

636. In 2021, Chinese researchers showed that Homoharringtonine inhibits fibroblast proliferation and extracellular matrix production, reducing fibrosis via PI3K/AKT/mTOR pathway-mediated apoptosis.[532]

637. In 2021, Chinese researchers studied the CCL2/CCR2 signaling axis and its role in fibrosis in multiple organs, including the lung. They reviewed preclinical and clinical data to assess the therapeutic relevance of targeting this pathway in fibrosis and showed that blocking CCL2/CCR2 reduced monocyte recruitment, inflammation, and fibrotic remodeling in lung and other organs.[533]

638. In 2022, Chinese researchers studied human precision-cut lung slices exposed to SARS-CoV-2 to test Homoharringtonine's effects on cytokine production and viral replication. They treated ex vivo lung tissues with Homoharringtonine and analyzed immune response, inflammation, and tissue integrity. Their results showed that Homoharringtonine suppressed inflammatory cytokine release and protected lung tissue from viral-induced fibrosis-like injury.[534]

639. In a 2023 study of natural products with anti-fibrotic potential, "homoharringtonine exhibited the strongest antifibrotic properties leading to a nearly complete inhibition of ECM

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[531] Wang W, et al., "Homoharringtonine: mechanisms, clinical applications and research progress," *Front. Oncol.* 15:1522273.

[532] Sun Y, et al., "Homorharringtonine inhibits fibroblasts proliferation, extracellular matrix production and reduces surgery-induced knee arthrofibrosis via PI3K/AKT/mTOR pathway-mediated apoptosis," *J. Orhopaedic Surg. Res.* 2021; 16:9.

[533] Liu L, et al., "Targeting the CCL2/CCR2 signaling axis in fibrotic diseases," *Front. Pharmacol*. 2021; 12:688469.

[534] Zhang Y, et al., "Homoharringtonine is a broad-spectrum inhibitor that suppresses SARS-CoV-2 and multiple cytokines induced in human precision-cut lung slices," *Phytomedicine*. 2022;104:154237.

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production at concentrations 100-fold lower than lycorine" without inducing cellular toxicity.[535]

640. In 2025, Chinese researchers constructed a mouse model of silica-induced pulmonary fibrosis and evaluated the preventive and therapeutic capacity of Homoharringtonine, which attenuated the progression of silica-induced pulmonary fibrosis in mice. They then used MRC-5, a human lung fibroblast cell line to explore the mechanisms underlying Homorharringtonine's inhibitory effects *in vitro.* Homoharringtonine significantly inhibited the activation and migratory capacity of MRC-5 cells. Mechanistically, the effects were mediated by enhanced ubiquitination and degradation of the CCR1 protein. Furthermore, Homoharringtonine exhibited favorable bio-compatibility *in vivo*, and its preventive and therapeutic effects were validated in silica-treated mice. The researchers concluded that their study demonstrates that Homoharringtonine holds significant potential as a therapeutic agent for silicosis by targeting CCR1 and the PI3K/AKT/mTOR signaling pathway, rendering it a promising candidate for clinical development in silicosis treatment.[536]

8. Neferine

641. "Neferine is a bisbenzylisoquinoline alkaloid, obtained from seed embryo of *N. Nucifera* which is reported to have anti-cancerous, antidepressant, antioxidant, and anti-inflammatory properties. It is a small sized molecule which acts as an autophagy inducer and has neuro-protective potential as well."[537]

642. In 2010, researchers from Wuhan China published a study in which they evaluated the anti-fibrotic potential of neferine in Kunming mice. Hydroxyproline was significantly suppressed by neferine administration. The attenuated-fibrosis condition was also validated by

[535] Nicolini G, et al., "Activated fibroblasts in cardiac and cancer fibrosis: An overview of analog[u]es and new potential therapeutic options," *Life Sci.* 2023: 321:121575, citing Kreutzer FP, et al., "Development and characterization of anti-fibrotic natural compound similars with improved effectivity," *Basic Res. Cardiol.* 2022; 117:9.

[536] Jia X, et al., "Homoharringtonine exerts anti-silicosis potential by inhibiting the CCR1 and PI3K/AKT signaling pathways in lung fibroblasts," *J. Biomed. Res.* 2025 May 25:1-16 [online ahead of print].

[537] Shibu MA, et al., "Pharmacological benefits of neferine - A comprehensive review," *Life Sci.* 2018; 199:60-70.

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histological observations. Biochemical measurements showed that bleomycin caused a significant decrease in lung superoxidae dismutase (SOD) activity and a significant increase in malondialdehyde (MDA) levels and myeloperoxidase (MPO) activity on the 7th and 14th days. Neferine reversed the decrease the in SOD activity as well as the increase in MDA and MPO activity. Enzyme-linked immunosorbent assay and radio-immunity assay showed that treatment with neferine alleviated bleomycin-induced increase of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6 and endothelin-1 in plasma or in tissue. Additionally, neferine blocked bleomycin-induced increases of NF-κB in nuclear extracts and TGF-β1 in total protein extracts of murine RAW264.7 macrophages. The investigators found that neferine attenuates bleomycin-induced pulmonary fibrosis in vitro and in vivo and concluded that the beneficial effect of neferine is associated with its anti-inflammation, antioxidation, cytokine and NF-κB inhibition effects.[538]

643. In 2013, researchers from Wuhan assessed effects of neferine on amiodarone-induced pulmonary fibrosis in mice. Neferine significantly restored reductions in body weight, increased levels of lung index and hydroxyproline, abnormal histological findings, serum SP-D increase, Th1/Th2 imbalance and increases in the population of CD4+CD25+ Tregs associated with amiodarone instillation in mice. The researchers concluded that the results of their study showed neferine possessed a significant inhibitory effect on amiodarone-induced pulmonary fibrosis, probably due to its properties of anti-inflammation, SP-D inhibition and restoring increased CD4+CD25+ Tregs which may modulate Th1/Th2 imbalance by suppressing Th2 response.[539]

644. In 2016, researchers from Shandong published a study showing that neferine inhibits proliferation and collagen synthesis in cardiac fibroblasts and reduces cardiac fibrosis in mice.[540]

645. In 2022, researchers from Tianjin investigated the inhibitory effects of lotus plumule extracts (LPEs) on bleomycin-induced pulmonary fibrosis in mice. Histopathological examination

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[538] Zhao L, et al., "Neferine, a gixbenzylisoquinline alkaloid attenuates bleomycin-induced pulmonary fibrosis," *Eur. J. Pharmacol.* 2010; 627: 304-312.

[539] Niu C-H, et al., "Protective effects of neferine on amiodarone-induced pulmonary fibrosis in mice," *Eur. J. Pharmacol.* 2013; 714(1-3):112-119.

[540] Liu X, et al., "Neferine inhibits proliferation and collagen synthesis induced by high glucose in cardiac fibroblasts and reduces cardiac fibrosis in diabetic mice," *Oncotarget* 2016; 7(38):61703-61715.

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demonstrated that LPEs decreased the degree of alveolitis, deposition of extracellular matrix and the production of collagen I (Col-I) in the pulmonary interstitium. In addition, the results showed that LPEs markedly alleviated the expression of interleukin(IL)-6, IL-17, transforming growth factor (TGF)-β, and α-smooth muscle actin (α-SMA). The content of Col-I and hydroxyproline (HYP) was also attenuated. The investigators concluded that LPEs can ameliorate the lung fibrosis, suggesting that LPEs could serve as a potential therapeutic approach for pulmonary fibrosis.[541]

646. In 2022, Taiwanese researchers evaluated the protective effect of neferine on Doxorubicin- mediated fibrosis. Doxorubicin-induced fibrosis involves activation of transforming growth factor β1 (TGF β1), matrix metalloproteinase 2 (MMP 2), and MMP 9 with concomitant downregulation of tissue inhibitors of MMPs (TIMP) 1 and TIMP 2 expressions in H9c2 cardio-myoblasts. Doxorubicin also resulted in hypertrophy with increased cell volume and overexpression of hypertrophy markers calcineurin, brain natriuretic peptide, and atrial natriuretic peptide. Finally, Doxorubicin treatment resulted in apoptosis through activation of p53. Pretreatment with neferine markedly activated SIRT1 expression and modulated expression levels of TGF β1 and p53, significantly reducing Doxorubicin-induced fibrosis, hypertrophy and apoptosis in H9c2 cardiomyoblasts.[542]

647. In 2025, researchers from Chongqing China reviewed the mechanisms by which neferine ameliorates inflammatory-related diseases. They observed that research indicates that neferine exhibits significant pharmacological activities, including anti-tumor, anti-inflammatory, anti-fibrosis, anti-oxidative stress, anti-platelet aggregation, and anti-arrhythmic effects. They concluded that numerous studies highlight the anti-inflammatory properties of neferine across various signaling pathways, establishing a foundational framework for its development as a therapeutic agent for inflammatory conditions.[543]

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[541] Guo P, et al., "Protective effects of lotus plumule ethanol extracts on bleomycin-induced pulmonary fibrosis in mice," *Drug Chem. Toxicol.* 2022; 4593):1432-1441.

[542] Lonanathan BP, et al., "Neferine attenuates doxorubicin-induced fibrosis and hypertrophy in H9c2 cells," *J. Biochem. Mol. Toxicol.* 2022; 36: e23054.

[543] Zhang Q, et al., "Action and mechanisms of neferine in inflammatory diseases (Review)," *Mol. Med. Rep.* 2025; 32:174.

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9. Piperine

648. "Piperine is a natural amide alkaloid from *Piper nigrum* and displays an inhibitory effect toward sEH [soluble epoxide hydrolase]." "Compound 11h attenuated the pathological course of LPS-mediated acute lung injury *in vivo*. Furthermore, levels of cytokines TNF-α, IL-6, myeloperoxidase (MPO), and lactate dehydrogenase (LDH) were decreased after administration of 11h. The LPS-mediated inflammation and redox unbalance, including expressions of COX-2, HO-1, ICAM-1, VCAM-1, p-p65/p65, GCLM, and Nrf2, were ameliorated through NF-κB and Nrf2 pathways *via* enhancing levels of epoxy-eicosatrienoic acids (EETs) in LPS-exposed ALI mice after compound 11h treatment. These findings demonstrated that compound 11h may serve as a lead compound for developing soluble exposide hydrolase inhibitors and treating inflammation related to diseases, such as ALI [acute lung injury.]"[544]

649. "Piperine [exerts] various bioactive effects, such as antibacterial activity, in addition to several physiological benefits that could help overall human health, such as immunomodulatory, hepatoprotective, antioxidant, antimetastatic, anticancer, and many more properties that have been established. Clinical trials revealed that this phytochemical has exceptional antioxidant, anticancer, and drug availability-enhancing properties, as well as immunomodulatory potential."[545]

650. In 2018, Egyptian researchers examined the anti-inflammatory effects of piperine in a rat model of gamma-ray–induced lung injury. They administered piperine orally for 6 weeks prior to a single 12 Gy whole-body gamma irradiation and measured antioxidant enzyme activities, inflammatory cytokines, and lung histopathology. They showed that piperine restored antioxidant levels, reduced pro-inflammatory cytokines, and minimized structural lung damage compared to controls.[546]

651. In 2019, Iranian researchers studied renal ischemia-reperfusion–induced acute kidney injury in rats to investigate whether piperine pretreatment could prevent subsequent liver injury.

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[544] Zhang J, et al., "Discovery of soluble epoxide hydrolase inhibitors based on the skeleton of piperine: synthesis, properties, molecular dynamics simulation, and their potentials in acute lung injury." *Acupuncture and Herbal Med*. 2025; 5(2):193-204.

[545] Umapathy VR, et al. "Anticancer Potential of the Principal Constituent of Piper nigrum, Piperine: A Comprehensive Review," *Cureus*. 2024; 16(2): e54425.

[546] Elkady AA, et al., "Anti-inflammatory role of piperine against rat lung tissue damage induced by gamma-rays," *Int. J. Radiation Res*. 2018; 16(1):75-84.

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They induced AKI by 30 minutes of bilateral renal ischemia followed by 24 hours of reperfusion, administered piperine at 10 or 20 mg/kg before injury, and assessed plasma liver enzyme levels, oxidative stress markers, inflammatory gene expression, leukocyte infiltration, and histopathology. They showed that piperine reduced liver enzyme elevations, oxidative stress, ICAM-1 expression, inflammatory cell infiltration, and tissue damage, with the 20 mg/kg dose being more effective.[547]

652. In 2019, Iranian researchers conducted a randomized controlled trial on adults with ultrasound-diagnosed nonalcoholic fatty liver disease to test whether curcuminoids coadministered with piperine could improve disease severity and biochemical parameters. They assigned 70 patients to receive either 500 mg curcuminoids plus 5 mg piperine daily or placebo for 12 weeks and measured liver enzymes, lipid profile, glycemic indices, hematologic markers, and NAFLD severity by sonography. They showed that curcuminoids plus piperine significantly reduced ALT, AST, ALP, cholesterol, LDL-C, ESR, and NAFLD severity, with greater improvement compared to placebo.[548]

653. In 2020, Brazilian researchers studied TGF-β1-induced epithelial-mesenchymal transition in human lung adenocarcinoma (A549) cells to evaluate the inhibitory effects of piperine. They treated A549 cells with sublethal concentrations of piperine prior to TGF-β1 stimulation and assessed EMT marker expression, SMAD2 and ERK1/2 phosphorylation, metalloproteinase activity, and cell motility. The results of this study showed that piperine disrupted EMT-related events, reduced mesenchymal marker expression, and inhibited SMAD2 and ERK1/2 phosphorylation, suggesting potential therapeutic use in EMT-associated disorders such as fibrosis.[549]

654. In 2021, Egyptian researchers studied thioacetamide-induced liver fibrosis in mice to evaluate therapeutic effects of piperine. They induced fibrosis for six weeks, administered piperine daily during the last 21 days, and measured miR-17 expression, Smad-7 levels, TGF-β/Smad signaling activity, hepatic stellate cell activation, and collagen deposition. They showed that piperine

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[547] Mohammadi M, et al., "Piperine pretreatment attenuates renal ischemia-reperfusion induced liver injury," *Heliyon* 2019; 5: e02180.

[548] Panahi Y, et al., "Curcuminoids plus piperine improve nonalcoholic fatty liver disease: A clinical trial," *J. Cell Biochem*. 2019; 120:15989-15996.

[549] da Fonseca LM, et al., "Piperine Inhibits TGF-β Signaling Pathways and Disrupts EMT-Related Events in Human Lung Adenocarcinoma Cells," *Medicines*. 2020;7(4):19.

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downregulated miR-17, restored Smad-7, inhibited TGF-β/Smad signaling, suppressed hepatic stellate cell activation, and reduced collagen deposition, indicating strong anti-fibrotic potential.[550]

655. In 2021, Indian researchers conducted a clinical trial on patients with oral submucous fibrosis to evaluate curcumin and piperine as an antioxidant adjuvant to intralesional dexamethasone therapy. Fifty patients were randomized into two groups. Both received intralesional dexamethasone twice weekly for 12 weeks, but the test group also took oral Turmix® tablets (curcumin 300 mg + piperine 5 mg) three times daily for three months. The combination therapy group showed significantly greater improvement in burning sensation, mouth opening, and reduction in fibrotic band thickness on ultrasonography compared to the steroid-only group.[551]

656. In 2021, Indian researchers published a study in which they used C57BL/6 mice to evaluate the therapeutic effects of galangin and piperine, individually and in combination, in bleomycin-induced pulmonary toxicity and oxidative stress. Fifty male mice were divided into seven groups, including controls, bleomycin-only, and treatment groups receiving galangin, piperine, or their combination, and were monitored for 21 days for body weight and hematological changes. The combination of galangin and piperine significantly improved body weight, increased hemoglobin and total erythrocyte counts, and reduced leukocyte counts compared to bleomycin-only mice, with combination therapy showing greater ameliorative effects than either treatment alone.[552]

657. In 2022, Indian researchers studied piperine's therapeutic spectrum for clinical practice. They reviewed traditional, preclinical, and clinical evidence on piperine's pharmacological actions, including its anti-inflammatory, antioxidant, immunomodulatory, antiviral and bioenhancing effects. They showed that piperine has therapeutic potential in respiratory diseases, metabolic disorders, cancer, neurological conditions, and infectious diseases, with bioavailability enhancement

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[550] Abdelhamid AM, Selim A, Zaafan MA, "The Hepatoprotective Effect of Piperine Against Thioacetamide-Induced Liver Fibrosis in Mice: The Involvement of miR-17 and TGF-β/Smads Pathways," *Front Mol Biosci*. 2021;8:754098.

[551] Sharma N, et al., "Efficacy of Curcumin and Piperine as Antioxidant Adjuvant to Intralesional Dexamethasone Injection for Management of Oral Submucous Fibrosis: A Clinical Trial," *J. Orofacial Sci*. 2021; 13:129-135.

[552] Vanitha Sree K, et al., "Therapeutic efficacy of galangin and piperine individually and in combination with the bleomycin on body weights and hematology alterations in c57bl/6 mice," *The Pharma Innovation Journal*. 2021;10(12):3254-3261.

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as a key mechanism.[553]

658. In 2022, Indian and American researchers studied cigarette smoke-induced lung pathology in cell and mouse models to investigate piperine's protective effects. They exposed BEAS-2B and A549 cells to cigarette smoke extract and BALB/c mice to cigarette smoke and treated them with piperine intranasally to assess oxidative stress, inflammation, epithelial–mesenchymal transition (EMT), and related molecular pathways. The results of their study showed that piperine restored epithelial markers, reduced mesenchymal and inflammatory markers, improved lung function, and modulated the SIRT1/Nrf2 axis to inhibit EMT and oxidative stress.[554]

659. In 2023, Iranian, American, and British researchers utilized preclinical and clinical models to review the effects of curcumin-piperine co-supplementation on human health. They searched Scopus, PubMed, Web of Science, and Google Scholar for relevant studies, analyzing both preclinical and clinical data on curcumin-piperine use. Th results of this study showed that curcumin-piperine improved glycemic indices, lipid profile, antioxidant status, inflammatory markers, respiratory conditions, and neurological disorders.[555]

660. In 2023, Iranian researchers reviewed antioxidant therapy targeting the TGF-β/Smad pathway in organ fibrosis, including pulmonary fibrosis. They summarized evidence from in vitro and in vivo studies on vitamins, natural compounds, and synthetic antioxidants that inhibit or modulate TGF-β/Smad signaling and related processes such as epithelial–mesenchymal transition, fibroblast proliferation, and extracellular matrix deposition. Their findings showed that antioxidants can counteract oxidative stress, downregulate TGF-β signaling, and attenuate fibrosis progression in multiple organs, supporting their potential as therapeutic agents in pulmonary fibrosis.[556]

661. In 2024, Iranian researchers studied paraquat-induced lung damage in male Wistar

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[553] Yadav SS, et al., "Therapeutic spectrum of piperine for clinical practice: a scoping review," *Crit. Rev. Food Sci. Nutrition*. 2022; 62(36):9816-9838.

[554] Saha P, et al., "Piperine Attenuates Cigarette Smoke-Induced Oxidative Stress, Lung Inflammation, and Epithelial–Mesenchymal Transition by Modulating the SIRT1/Nrf2 Axis," *Int. J. Mol. Sci.* 2022; 23:14722.

[555] Heidari H, et al., "Curcumin-piperine co-supplementation and human health: A comprehensive review of preclinical and clinical studies," *Phytotherapy Res.* 2023; 37(4):1462-1487.

[556] Ghafouri-Fard S, et al., "Antioxidant therapy against TGF-β/SMAD pathway involved in organ fibrosis," *J. Cellular Mol. Med*. 2023; 27(24):3584-3604.

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rats and the effects of piperine with or without aerobic exercise. They assessed oxidative stress, inflammatory markers and lung histopathology after 7 weeks of treatments, including piperine, exercise, their combination, and vitamin E. They showed that piperine and piperine plus exercise significantly reduced oxidative and inflammatory damage, improved antioxidant and anti-inflammatory markers, and protected lung tissue more effectively than exercise alone.[557]

662. In 2025, Chinese and American researchers studied LPS-induced acute lung injury (ALI) in mice to evaluate the anti-inflammatory effects of piperine-derived soluble epoxide hydrolase (sEH) inhibitors. They designed and synthesized a library of urea-type piperine analogues, identified potent sEH inhibitors, and tested their therapeutic activity in vivo, focusing on cytokine release, oxidative stress, and NF-κB/Nrf2 pathway modulation. Their findings showed that lead compound 11h reduced inflammatory cytokines, improved redox balance, suppressed NF-κB activation, enhanced Nrf2 signaling, and alleviated lung injury.[558]

663. These studies show that piperine and its derivatives possess significant therapeutic potential in lung injury and fibrosis by modulating key inflammatory and oxidative stress pathways. They demonstrate that piperine can attenuate lung damage by reducing pro-inflammatory cytokines, inhibiting epithelial–mesenchymal transition, and restoring redox balance. Structural optimization of piperine has yielded potent soluble epoxide hydrolase inhibitors that further suppress NF-κB activation and enhance Nrf2 signaling, resulting in improved lung function and tissue repair. Both natural piperine and its synthetic analogues exhibit strong antioxidant, anti-inflammatory, and bioavailability-enhancing properties, making them promising candidates for adjunctive therapy. Overall, the evidence supports piperine-based compounds as versatile agents for treating inflammation-driven lung diseases such as acute lung injury and pulmonary fibrosis.

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[557] Ariyanasab R, et al., "The interactive effect of seven weeks aerobic exercise training and piperine against paraquat-induced lung damage in male Wistar rats: Investigating role of oxidative and inflammatory indices," *Heliyon* 2024; 10(6):e33241.

[558] Zhang J, et al., "Discovery of soluble epoxide hydrolase inhibitors based on the skeleton of piperine: synthesis, properties, molecular dynamics simulation, and their potentials in acute lung injury." *Acupuncture and Herbal Med*. 2025; 5(2):193-204.

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10. Tetrandrine

664. "Tetrandrine is a bisbenzylisoquinoline alkaloid isolated from the root of Stephania tetrandra."[559] "Tetrandrine . . . has been approved to treat silicosis in China."[560]

665. "Tetrandrine . . . can inhibit lung inflammation and lung fibrosis to improve pulmonary function."[561]

666. "Clinical trials have shown that patients' lung function, quality of life, and exercise ability have significantly improved after treatment with traditional Chinese medicines."[562]

667. In a study by researchers from a hospital in Jiangsu Province, 96 patients with silicosis were randomly divided into treatment group (49 cases) and control group (47 cases). Both groups were given routine therapy including anti-inflammatory, antitussive, and antiasthmatic drugs, and the patients in treatment group were given tetrandrine combined with acetylcysteine effervescent tablets at the same time. Tetrandrine (100 mg) was orally administrated twice a day, and there was a one-day interval between every 6 days' continuous administration; totally, there were four courses of treatment, with 3 months for each course, and there was a one-month break between each course. Acetylcysteine effervescent tablets (600 mg) were taken twice a day; each course of treatment was 12 days, and there were four courses; for the first two months, there was one course per month, and then one course every other two months for the rest of time. Clinical symptoms, pulmonary ventilation function, serum superoxide dismutase (SOD) and changes in X-ray findings were observed. After treatment, the treatment group had significantly increased rates of improvements

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[559] Wu W-H, et al., "Clinical efficacy of tetrandrine in artificial stone-associated silicosis: A retrospective cohort study," *Front. Med.* 2023; 10:1107967, citing, Bhagya N, et al., "Tetrandrine–a molecule of wide bioactivity," *Phytochemistry* 2016; 125:5–13.

[560] Li T, et al., "Early Identification, Accurate Diagnosis, and Treatment of Silicosis," *Can. Resp. J.* 2022:3769134, citing, Zhang J, et al., "Effects of tetrandrine combined with acetylcysteine on exercise tolerance, pulmonary function and serum TNF-beta1 and MMP-7 in silicosis patients," *Exp. Ther. Med.* 2020; 19(3): 2195–2201.

[561] Li T, *supra,* citing, Liu Y, et al., "Tetrandrine modulates Rheb-mTOR signaling-mediated selective autophagy and protects pulmonary fibrosis," *Front. Pharmacol.* 2021; 12:739220.

[562] Li T, et al., "Early Identification, Accurate Diagnosis, and Treatment of Silicosis," *Canadian Respir. J.* 2022: 3769134, citing, Tang WYN, et al., "Efficacy and safety of dahuang zhechong pill in silicosis: a randomized controlled trial," *Evidence-Based Complementary Alt. Med.* 2021, Article ID 4354054.

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in cough, expectoration, chest congestion and pain, and dyspnea compared with the control group ($P < 0.05$). Compared with the control group (serum SOD level: 70.466±20.261 U/ml) and the treatment group before therapy (serum SOD level: 68.182±21.414 U/ml), the treatment group after therapy had significantly increased serum SOD level (77.389±21.315 U/ml), forced vital capacity, and forced expiratory volume in one second ($P < 0.05$). Eight patients in the treatment group showed improvement in chest X-ray findings of silicosis. The investigators concluded that the combination of tetrandrine and acetylcysteine effervescent tablets show some effect in the treatment of silicosis and can be an effective option for treating silicosis as there are no other specific remedies.[563]

668. In 2023, researchers from Guangzhou and Changsha conducted a retrospective study exploring clinical effects of Tetrandrine on progressive massive fibrosis (PMF) of pneumoconiosis. They collected 344 pneumoconiosis patients with Progressive Massive Fibrosis (PMF), of whom 127 were eligible for the final analysis, including 67 patients in the Tetandrine group and 70 patients in the control group. The progress of imaging and lung function were compared between the two groups. After 13 months of treatment, the size of PMF was smaller in the Tetrandrine group than that in the control group (1526 vs. 2306, p=0.001), and the size was stable in the Tetrandrine group (1568 vs. 1526, p= 0.381), while it progressed significantly in the control group (2055 vs. 2306, p=0.000). Small nodule profusion and emphysema were also milder than that in the control group (6.0 vs. 7.5, p=0.046 and 8.0 vs. 12, p=0.016 respectively). Pulmonary function parameters FVC and FEV1 improved in the Tetrandrine group (3222 vs. 3301, p=0.021; 2202 vs. 2259, p=0.025 respectively) and decreased in the control group (3272 vs. 3185, p= 0.00; 2094 vs. 1981, p=0.00 respectively). FEV1/FVC was also significantly higher in the Tetrandrine group than in the control group (68.45vs. 60.74, p=0.001). However, DLco% showed a significant decrease in both groups. The investigators concluded that Tetrandrine has shown great potential in the treatment of PMF by slowing the progression of pulmonary fibrosis and the decline of lung function.[564]

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[563] Miao R-M, et al., [Clinical efficacy of tetrandrine combined with acetylcysteine effervescent tablets in treatment of silicosis], *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2013; 31(11):857-858.

[564] Tang M, et al., "Tetrandrine slows the radiographic progression of progressive massive fibrosis in pneumoconiosis: a retrospective cohort study," *BMC Pulmonary Med.* 2023; 23:290.

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669. In a retrospective study published in 2023, Shanghai physicians evaluated clinical data of 89 artificial stone-associated silicosis patients treated in Shanghai Pulmonary Hospital, Patients who agreed to be administered tetrandrine entered the observation group and those who disagreed entered the control group. Changes in chest HRCT, pulmonary function, and clinical symptoms of patients in two groups were compared pre- and post-treatment. After treatment for 3-12 months, 56.5% - 65.4% of patients in the observation group showed improvements in HRCT imaging, while there was no improvement in the control group ($p < 0.05$). Disease progression occurred in 0% - 17.4% of patients in the observation group after 3-12 months of treatment compared with 44.4% - 92.0% of patients in the control group ($p < 0.05$). After 3 months of treatment, the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and diffusing capacity of the lung for carbon monoxide (DLco) in the observation group increased by 136.7 ± 189.2 mL ($p < 0.05$), 124.2 ± 169.9 mL ($p < 0.05$), and 1.4 ± 2.3 mL/min/mmHg ($p > 0.05$), respectively, while those in the control group decreased (145.8 ± 356.5; 107.5 ± 272.1; 1.9 ± 3.8). After 6 months of treatment, FVC, FEV1, and DLco in the observation group increased by 207.8 ± 372.2 mL ($p > 0.05$), 107.8 ± 295.2 mL ($p > 0.05$) and 0.7 ± 6.0 mL/min/mmHg ($p > 0.05$), respectively, while those of the control group decreased (383.3 ± 536.7; 215.6 ± 228.9; 1.4 ± 1.7). The incidences of clinical symptoms such as cough, expectoration, dyspnea, chest tightness, and chest pain in the observation group were decreased-after treatment (all $p < 0.05$), while the incidences of these symptoms increased in the control group, although the change was not statistically significant (all $p > 0.05$). The investigators concluded that tetrandrine can control and delay the progression of artificial-stone induced silicosis, with improved chest HRCT imaging and pulmonary function.[565]

670. In a study from Shandong, lung function parameters of patients showed significant improvement compared to the control group after pneumoconiosis patients were treated with

[565] Wu W-H, et al., "Clinical efficacy of tetrandrine in artificial stone-associated silicosis: A retrospective cohort study," *Front. Med.* 2023; 10:1107967.

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Tetrandrine for 10 months.[566]

671. In May 2025, the American Thoracic Society held its annual conference in San Francisco. Abstracts of this international conference were thereupon published in the American Journal of Respiratory and Critical Care Medicine. One of the abstracts published in this journal, by Shanghai investigators, was titled "Artificial Stone-related Silicosis in China." Demographic information, lung function, chest CT scans, and follow-up data were collected for 865 patients with artificial stone-related silicosis in Shanghai Pulmonary Hospital between January 2014 and October 2024. Additionally, a comparative analysis was conducted on the chest CT and lung function changes observed in 189 silicosis patients before and after undergoing antifibrotic therapy. Among the 424 patients who underwent CT reexamination within 24 months, a remarkable 90% (381/424) demonstrated significant progression. This progression was evident in at least one of the following: an increase in small nodules, enlarged masses, and exacerbation of emphysema or bullae. Additionally, the average yearly decrease in FVC was 725.6 ± 77.24 ml. Among all patients, 14.6% (125/865) were complicated with pneumothorax, of which 16.0% (20/125) were recurrent or refractory pneumothorax. Among 189 patients who underwent antifibrotic treatment with tetrandrine, there was an average decrease in FVC of 75.6 ± 17.46 ml per year over a two-year period. Additionally, CT scans indicated progression in 40.2% (76 out of 189) of these patients. In comparison, patients who received standard treatment for six years had a CT progression rate of 61.3% (28 out of 46), with an average FVC decrease of 54.4 ± 12.24 ml per year. The investigators concluded that artificial stone-related silicosis is an accelerated silicosis with a poor prognosis, often complicated by pneumothorax and mycobacterial infection, but that anti-fibrotic treatment with tetrandrine can effectively slow down the progression of fibrosis in this condition.[567]

672. In July 2025, Chinese researchers published a retrospective cohort study in which they evaluated the efficacy of tetrandrine in slowing the progression of artificial stone-associated silicosis.

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[566] Zhang G, "A Prospective Observational Study on the Effect of Tetrandrine on the Progression of Pneumoconiosis Fibrosis," *MEDS Clin. Med.* 2024; 5(3):136-144.

[567] Mao L, et al.,"Artificial Stone-related Silicosis in China," A16 Beyond the Dust: Advancing Exposure Assessment, Metabolomics, and Treatment in Occupational Lung Diseases / Mini Symposium / May 18, 2025 09:15-11:15 AM, Room 2010202 (South Building, Level 2), Moscone Center, "Artificial Stone-related Silicosis in China," https://www.atsjournals.org/doi/epdf/10.1164/ajrccm.2025.211.Abstracts.A1024?role=tab.

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They divided patients into an observation group of 53 patients who received tetrandrine (60 mg, 3 times daily for 6 consecutive days, followed by a 1-day break, with each cycle lasting 3 months), and a control group of 26 patients who received only symptomatic treatment. High-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) were performed at baseline and after 12 months of treatment. Progression, stability, or improvement in HRCT findings and changes in PFT parameters were analyzed. Continuous variables and categorical variables were analyzed using the t-test and chi-square test, respectively, for statistical comparisons. After 12 months, 49.1% of patients in the observation group exhibited improvement in HRCT findings, compared to none in the control group, in which 84.6% of individuals exhibited progression. PFT findings improved in the observation group, whereas they significantly declined in the control group ($p < 0.001$). Patients treated with tetrandrine for more than 6 months experienced greater improvements in HRCT findings and pulmonary function than those in the control group. Adverse reactions to tetrandrine, including facial pigmentation and liver function abnormalities, were mild. The investigators concluded that tetrandrine significantly mitigated HRCT-detected disease progression and lung function decline in patients with artificial stone-associated silicosis, particularly after prolonged treatment. They further concluded that their findings suggested that tetrandrine may serve as a viable therapeutic option for managing artificial stone-associated silicosis.[568]

673. Collectively, the studies regarding Tetrandrine, especially the most recent studies by Chinese investigators of stone countertop fabricators diagnosed with engineered stone silicosis, show a substantial benefit of treating these workers with Tetrandrine.

[568] Zhou S, et al., "Tetrandrine slows disease progression on high-resolution computed tomography and lung function decline in artificial stone-associated silicosis: a retrospective cohort study," *BMC Pulmonary Med.* 2025; 25:343.

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11. Vincamine

674. "Vincamine is an indole alkaloid extracted from the leaves of periwinkle plant (*Vinca rosea*), studied widely since 1950's and has been shown to possess numerous medicinal properties such as antioxidant, anti-apoptotic, hepatoprotective, nephroprotective and neuroprotective."[569]

675. In 2022, researchers from India studied the protective effect of vincamine *in vitro* and *in vivo* against lipopolysaccharide (LPS) induced ALI [acute lung injury] in Swiss albino mice. Vincamine significantly reduced nitrite and TNF-α release from the LPS stimulated macrophages and increased the levels of IL-10, indicating potent anti-inflammatory effects. At the 40 mg/kg dose Vincamine significantly reduced LPS induced inflammatory cell count in blood and in broncho-alveolar lavage (BAL) fluid. Further, Vincamine exerted potent suppression of inflammation by reducing the expression of proinflammatory cytokines, while significantly increased ($p < 0.001$) the expression of anti-inflammatory cytokine (IL-10 and IL-22). Histological changes were reversed in Vincamine treated groups in a dose-dependent manner. Immunohistochemical analysis revealed significantly enhanced expression of NF-κB, TNF- α and COX-2 while reduced expression of Nrf-2 in disease control group, which were significantly ($p < 0.001$) ameliorated by Vincamine. The investigators concluded that Vincamine possesses protective potential against LPS-induced inflammation and oxidative stress, possibly by inhibiting the NF-κB cascade, while positively regulating the Nrf-2 pathway. Vincamine significantly reduced nitrite and TNF-α release from LPS-stimulated macrophages and increased the IL-10 levels, indicating potent anti-inflammatory effects.[570]

676. In 2023, Indian researchers studied the anti-inflammatory and antioxidant effects of vincamine in a lipopolysaccharide-induced acute lung injury model using Swiss albino mice. They administered vincamine and evaluated its effects on inflammatory markers, cytokine levels, and histopathological changes in the lungs. Their results showed that vincamine significantly alleviated

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[569] Renushe AP, et al., "Vincamine, an active constituent of *Vinca rosea* ameliorates experimentally induced acute lung injury in Swiss albino mice through modulation of Nrf-2/NF-κB signaling cascade," *Int. Immunopharmacol.* 2022; 108:108773.

[570] Renushe AP, et al., "Vincamine, an active constituent of *Vinca rosea* ameliorates experimentally induced acute lung injury in Swiss albino mice through modulation of Nrf-2/NF-κB signaling cascade," *Int. Immunopharmacol.* 2022; 108:108773.

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lung injury by reducing inflammation and oxidative stress through modulation of the NF-κB and Nrf-2 pathways.[571]

677. In 2023, Egyptian and Japanese researchers investigated the protective effects of vincamine in a rat model of bleomycin-induced pulmonary fibrosis. They assessed markers of epithelial-mesenchymal transition (EMT), oxidative stress, and fibrosis signaling pathways including TGF-β1/MAPK/Snai1. Their findings revealed that vincamine suppressed EMT and fibrosis progression by regulating apoptotic and fibrotic pathways, restoring antioxidant balance and improving lung histology.[572]

678. In 2023, Chinese researchers examined the therapeutic role of vincamine as a GPR40 agonist in a mouse model of bleomycin-induced pulmonary fibrosis. They investigated pulmonary GPR40 expression in both human patients and mice, and tested vincamine's effects using GPR40 knockout mice and siRNA-transfected cells. Their findings demonstrated that vincamine alleviated pulmonary fibrosis by activating GPR40 and modulating associated inflammatory and fibrotic signaling pathways including NF-κB/NLRP3 and β-arrestin2/SMAD3.[573]

679. In 2023, American researchers conducted a review examining the pathological and molecular links between idiopathic pulmonary fibrosis and diabetes mellitus. They analyzed how shared mechanisms such as oxidative stress, mitochondrial dysfunction, and glycated protein signaling contribute to disease progression in both conditions. Their findings highlighted common molecular targets and emphasized the need for therapies that address multiple pathways to effectively treat lung fibrosis.[574]

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[571] Renushe AP, et al., "Vincamine, an active constituent of Vinca rosea ameliorates experimentally induced acute lung injury in Swiss albino mice through modulation of Nrf-2/NF-κB signaling cascade," *J Ethnopharmacol.* 2023.

[572] Alaaeldin R, et al., "Vincamine Ameliorates Epithelial-Mesenchymal Transition in Bleomycin-Induced Pulmonary Fibrosis in Rats; Targeting TGF-β/MAPK/Snai1 Pathway," *Pharmaceuticals*.

[573] Zhao T, et al., "Vincamine as an agonist of G protein-coupled receptor 40 effectively ameliorates pulmonary fibrosis in mice," *Phytomedicine.* 2023.

[574] Mendoza Mari Y, et al., "Pulmonary Fibrosis and Diabetes Mellitus: Two coins with the same face," *Transl Res*. 2023.

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12. Vinpocetine

680. "Vinpocetine is an alkaloid extracted from the periwinkle plant and has been tested as a neuronal plasticity enhancer and marketed as a "memory booster. . . . The cognitive enhancement function of vinpocetine comes from its inhibition of PDE type 1, which leads to an increase in cAMP and cGMP levels. These cyclic nucleotides can in turn activate a series of kinases that phosphorylate the transcription factors cAMP response element binding protein (CREB) and serum response factor (SRF), leading to the expression of plasticity-related genes."[575]

681. In 2010, researchers from showed that vinpocetine acts as an anti-inflammatory agent in vitro and in vivo. In particular, vinpocetine inhibits TNF-α–induced NF-κB activation and the subsequent induction of proinflammatory mediators in multiple cell types, including vascular smooth muscle cells, endothelial cells, macrophages, and epithelial cells. These researchers also showed that vinpocetine inhibits monocyte adhesion and chemotaxis, which are critical processes during inflammation. Moreover, they showed that vinpocetine potently inhibits TNF-α- or LPS-induced up-regulation of proinflammatory mediators, including TNF-α, IL-1β, and macrophage inflammatory protein-2, and decreases interstitial infiltration of polymorphonuclear leukocytes in a mouse model of TNF-α- or LPS-induced lung inflammation. These studies thus identified vinpocetine as a unique anti-inflammatory agent that may be repositioned for the treatment of many inflammatory diseases.[576]

682. In 2021, Korean researchers investigated the association between phosphodiesterase (PDE), specifically PDE1, and asthma using 3-isobutyl-1-methylxanthine (IBMX; a non-specific PDE inhibitor) and vinpocetine (Vinp; a PDE1 inhibitor). Balb/c mice were randomized to five treatment groups: control, ovalbumin (OVA), OVA + IBMX, OVA + Vinp, and OVA + dexamethasone (Dex). All mice were sensitized and challenged with OVA, except for the control group. IBMX, Vinp, or Dex was intraperitoneally administered 1 hour before the challenge. Vinp treatment significantly inhibited the increase in airway hyper-responsiveness ($P<0.001$) and reduced the number of inflammatory cells, particularly eosinophils, in the lungs ($P<0.01$). It also ameliorated

[575] Medina AE, "Vinpocetine as a potent antiinflammatory agent," *PNAS* 2010; 107(22):9921-9922.

[576] Jeon K-I, et al., "Vinpocetine inhibits NF-κB-dependent inflammation via an IKK-dependent but PDE-independent mechanism," *PNAS* 2010; 107(21):9795-9800.

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the damage to the bronchi and alveoli and decreased the OVA-specific IgE levels in serum, an indicator of allergic inflammation increased by OVA (P<0.05). Furthermore, the increase in interleukin-13, a known Th2 cytokine, was significantly decreased by Vinp (P<0.05), and Vinp regulated the release and mRNA expression of macrophage inflammatory protein-1β(MIP-1β) increased by OVA (P0.05). The investigators concluded that taken together, these results suggested that PDE1 is associated with allergic lung inflammation induced by OVA and that PDE1 inhibitors can be a promising therapeutic target for the treatment of asthma.[577]

683. In 2023, researchers from Saudi Arabia and Egypt administered vinpocetine to treat Wistar rats in which pulmonary fibrosis was induced by intratracheal instillation of bleomycin. They administered oral vinpocetine at doses of 5, 10, or 20 mg/kg to treat pulmonary fibrosis for 21 days immediately after bleomycin instillation. Vinpocetine dose-dependently ameliorated pulmonary fibrosis induced by bleomycin administration, effectively restoring normal body weight gain rates, pulmonary architecture, and collagen fiber distribution and suppressing the elevated BALF cell count, lymphocytes and neutrophils percentage, BALF, IL-6, TNF-α, and TGF-β1 levels and LDH activity, lung tissue MDA level, PDE activity, hydroxyproline content, immunohistochemical expression of α-SMA and CD68 positive macrophage, and fibrosis score. Vinpocetine also efficiently augmented the reduced BALF macrophage percentage, IL-10 level, lung tissue GSH level, CAT, and SOD activities. The investigators therefore concluded that Vinpocetine may be a promising new agent for the management of pulmonary fibrosis.[578]

684. In 2024, Iraqi researchers investigated the potential anti-fibrotic activity of Vinpocetine an bleomycin-induced pulmonary fibrosis and in the MRC-5 cell line. They showed that Vinpocetine alleviated the fibrotic endpoints by significantly improving the weight index, histopathological score, reduced expression of fibrotic-related proteins in immune-stained lung sections, as well as fibrotic markers measured in serum samples. Vinpocetine also alleviated tissue levels of oxidative stress and inflammatory and pro-fibrotic mediators significantly elevated in

[577] Choi WS, et al., "Vinpocetine alleviates lung inflammation via macrophage inflammatory protein-1β inhibition in an ovalbumin-induced allergic asthma model," *PloS ONE 2021;* 16(4): d0251012.

[578] Balaha M, et al., "Vinpocetine's immunomodulating, anti-oxidant, anti-inflammatory, anti-fibrotic, and PDE inhibiting potencies ameliorate bleomycin-induced pulmonary fibrosis," *Iran J. Basic Med. Sci.* 2023;26:13-22.

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bleomycin-only induced animals. The investigators concluded that Vinpocetine expressed a remarkable attenuating effect in pulmonary fibrosis both *in vivo* and *in vitro* either directly by interfering with the classical TGF-β/Smad2/3 signaling pathway or indirectly by upregulating the expression of Nrf2 enhancing the antioxidant system, activating PPAR-γ and downregulating the NLRP3/NF-κ pathway. The investigators concluded that these results render Vinpocetine a candidate for clinical investigation in cases of pulmonary fibrosis.[579]

685. In 2025, Egyptian researchers investigated the efficacy of Vinpocetine in reducing cyclophosphamide-induced lung injury. Rats were given oral Vinpocetine (10 and 20 mg/kg) daily for 14 days. On day 7, a single intraperitoneal injection of 200 mg/kg cyclophosphamide) was also given. Twenty-four hours after the last Vinpocetine dose, severity of lung injury, oxidative stress, antioxidant status markers, and pro-inflammatory and apoptotic markers were evaluated. The increased lung/body weight ratio and the infiltration of inflammatory cells in the lung tissues, in addition to a rise in the total content of protein and lactate dehydrogenase (LDH) activity in bronchoalveolar lavage fluid (BALF), were indicative of injury to the lung. The biochemical analysis was validated by histopathological investigation. In cyclophosphamide-intoxicated animals, the lungs showed increased oxidative stress, indicated by elevated levels of malondialdehyde (MDA) and total nitrate/nitrite (NOx), coupled with reduced antioxidant levels of glutathione (GSH). Cyclophosphamide initiated NLRP3 inflammasome activation, subsequently activating procaspase-1, which led to NF-κB activation and an increase in inflammatory cytokines (IL-1β, TNF-α, IL-6). This process was associated with the induction of apoptosis, as indicated by elevated caspase-3 levels and decreased Bcl-2 expression. Conversely, improvements in the biochemical and histological markers indicated that Vinpocetine effectively preserved lung function. The investigators concluded that their findings indicate that Vinpocetine alleviated cyclophosphamide-induced pulmonary damage by inhibiting the ROS/NLRP3/NF-κB pathway and suppressing apoptotic pathways.[580]

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[579] Hussein ZA, et al., "Vinpocetine alleviated alveolar epithelial cells injury in experimental pulmonary fibrosis by targeting PPAR γ/NLRP3/NF κB and TGF β1/Smad2/3 pathways," *Sci Rep.* 2024;14:1763.

[580] Salah R, et al., "Vinpocetine alleviated lung injury induced by cyclophosphamide in rats via modulation of NLRP3 inflammasome, NF-κB, and apoptotic pathways," *Biochem. Biophys. Res. Commun.* 2025; 778:152345.

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E. Anti-Cytokine Treatments

686. "Cytokines are proteins involved in cell signaling and function as immunomodulating agents. Cytokines are produced by immune cells (e.g. macrophages, B and T lymphocytes, mast cells, neutrophils, natural killer cells), endothelial cells, fibroblasts, and stromal cells."[581]

687. "Pro-inflammatory cytokines released during inflammation by macrophages and, potentially, also neutrophils, mast cells, and lymphocytes, promote the exaggerated development of silicosis."[582]

688. "Cytokine neutralization is successfully used for treatment of various autoimmune diseases and chronic inflammatory conditions."[583]

689. Several anti-cytokine therapies may have utility for treating silicosis. These include monocolonal antibodies against pro-inflammatory cytokines or antagonists of cytokine receptors.[584]

690. Anti-cytokine therapies include Anakinra (IL-1ra), Anti-IL-17 antibody, Anti-IL-9 antibody, Il-13 immunotoxin, Recombinant soluble TNF receptor, Infliximab, and AntiCD-11 antibodies.[585]

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[581] Gryczan TJ, "Etymologia: Cytokines," *Emerging Infectious Diseases* 2018; 24(7):1227.

[582] Liu T-T, et al., "The role of inflammation in silicosis," *Front. Pharmacol.* 2024; 15:1362509.

[583] Drutskaya MS, et al., "Can we design a better anticytokine therapy?" *J. Leukocyte Biol.* 2017; 102:783-790.

[584] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162.

[585] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Piguet PF, et al., "Interleukin 1 receptor antagonist (IL-1ra) prevents or cures pulmonary fibrosis elicited in mice by bleomycin or silica," *Cytokine* 1993; 5:57–61; Song L, et al., "Th17 can regulate silica-induced lung inflammation through an IL-1beta-dependent mechanism," *J. Cell. Mol. Med.* 2014; 18:1773-1784; Chen Y, et al., "Neutralization of interleukein-17A delays progression of silica-induced lung inflammation and fibrosis in C57BL/6 mice," *Toxicol. Appl. Pharmacol.* 2014; 275:62-72; Sugimoto N, et al., "IL-9 blockade suppresses silica-induced lung inflammation and fibrosis in mice," *Am. J. Respir. Cell. Mol. Biol.* 2019; 60:232-243; Rojas-Quintero J, et al., "Dusting off IL-9 as a new therapeutic target for pulmonary fibrosis," *Am. J. Respir. Cell. Mol. Biol.* 2019; 60:141-143; Ferreira TP, et al., "IL-13 immunotoxin accelerates resolution of lung pathological changes triggered by silica particles in mice," *J. Immunol.* 2013; 191:5220-5229; Piguet PF, et al., "Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice," *Eur. Respir. J.* 1994; 7:515-518; Altintas N, et al., "Protective effect of infliximab, a tumor necrosis factor-alfa inhibitor, on bleomycin-induced lung fibrosis in rats," *Inflammation* 2016; 39:65-78; Zhang H, et al., "Subcutaneous administration of infliximab-attenuated silica-induced lung fibrosis," *Int. J. Occup. Med. Environ. Health* 2018; 31:503-515; Piguet PF, et al., "Effective treatment of the pulmonary fibrosis elicited in mice by bleomycin or silica with anti-CD-11 antibodies," *Am. Rev. Respir. Dis.* 1993; 147:435-441.

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1. Anakinra

691. "Interleukin-1 (IL-1) is the prototypical inflammatory cytokine: two distinct ligands (IL-1α and IL-1β) bind the IL-1 type 1 receptor (IL-1R1) and induce a myriad of secondary inflammatory mediators, including prostaglandins, cytokines, and chemokines. IL-1α is constitutively present in endothelial and epithelial cells, whereas IL-1β is inducible in myeloid cells and released following cleavage by caspase-1. "Over the past 30 years, IL-1-mediated inflammation has been established in a broad spectrum of diseases, ranging from rare autoinflammatory diseases to common conditions such as gout and rheumatoid arthritis (RA), type 2 diabetes, atherosclerosis, and acute myocardial infarction. Blocking IL-1 entered the clinical arena with anakinra, the recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra); IL-1Ra prevents the binding of IL-1α as well as IL-1β to IL-1R1. Quenching IL-1-mediated inflammation prevents the detrimental consequences of tissue damage and organ dysfunction. Although anakinra is presently approved for the treatment of RA and cryopyrin-associated periodic syndromes, off-label use of anakinra far exceeds its approved indications. Dosing of 100 mg of anakinra subcutaneously provides clinically evident benefits within days and for some diseases, anakinra has been used daily for over 12 years. Compared to other biologics, anakinra has an unparalleled record of safety: opportunistic infections, particularly Mycobacterium tuberculosis, are rare even in populations at risk for reactivation of latent infections. Because of this excellent safety profile and relative short duration of action, anakinra can also be used as a diagnostic tool for undefined diseases mediated by IL-1."[586]

692. In 2014, Chinese researchers sought to elucidate the underlying mechanisms of IL-1β and IL-17 in silicosis by using anakinra and an anti-IL-17 monoclonal antibody (mAb) to block the receptor of IL-1β and IL-17, respectively, in a mouse model of silicosis. They observed increased IL-1β expression and an enhanced Th17 response after silica instillation. Treatment with anakinra substantially decreased silica-induced lung inflammation and the Th17 response. Lung inflammation and accumulation of inflammatory cells were attenuated in the IL-17-neutralized silicosis group.[587]

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[586] Cavalli G, et al., "Anakinra Therapy for Non-cancer Inflammatory Diseases," *Front. Pharmacol.* 2018; 9:1157.

[587] Song L, et al., "Th17 can regulate silica-induced lung inflammation through an IL-1β-dependent mechanism," *J. Cell. Mol. Med.* 2014; 18(9):1773-1784.

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693. In 2016, Spanish researchers reported a case of a man with Still's disease who developed acute pneumonitis after treatment with methotrexate and corticosteroids, but who showed clinical, analytical and radiologic improvement within days after being given Anakinra at 100 mg/day.[588]

694. In 2016, Italian researchers showed that Anakinra reduces inflammasome-driven inflammation in both murine models of cystic fibrosis and cystic fibrosis patients.[589]

695. In 2021, Spanish researchers reported on five Covid-19 patients with pulmonary fibrosis and persistent hypoxemia who received delayed treatment with Anakinra. They observed clinical improvement, suggesting that IL-1 blockade might benefit patients with post-Covid pulmonary fibrosis and ongoing respiratory impairment.[590]

696. In 2021, Chinese researchers reported that combined anakinra and MCC950 therapy significantly protected mice against acute lung injury by inhibiting the NF-κB-mediated MAPK and NLRP3 inflammasome pathways, reducing lung inflammation and injury.[591]

697. In 2022, French researchers demonstrated that anakinra administration reduces lung inflammation in experimental models of acute lung injury. Their study indicated that IL-1 blockade can mitigate inflammatory responses and potentially improve outcomes in acute lung damage.[592]

698. In 2022, Australian researchers reviewed the role of the NLRP3 inflammasome in silicosis pathogenesis and discussed therapeutic strategies targeting this inflammasome to reduce lung fibrosis and inflammation caused by silica exposure.[593]

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[588] Gomez CS, et al., "Acute Pneumonitis in a Patient With Adult-Onset Disease After Toclizumab Treatment With Good Response to Anakinra," *Reumatol. Clin.* 2016; 12(6):345-357.

[589] Iannitti RG, et al., "IL-1 Receptor Antagonist Ameliorates Inflammasome-Dependent Inflammation in Murine and Human Cystic Fibrosis," *Nature Comm.* 2016; 7:10791.

[590] Nan D, et al., "Delayed Use of the Recombinant Human IL-1 Receptor Antagonist Anakinra in Five COVID-19 Patients with Pulmonary Fibrosis and Persistent Hypoxaemia," *Eur. J. Case rep. Intern. Med.* 2021; 8.

[591] Wang X, et al., "Protective effect of combination of anakinra and MCC950 against acute lung injury is achieved through suppression of the NF-κB-mediated-MAPK and NLRP3-caspase pathways," *Int. Immunopharmacol.* (2021) 97:107506

[592] Engeroff P, et al., "Anakinra reduces lung inflammation in experimental acute lung injury," *Immun. Inflamm. Dis.* 2022; 10:123–129.

[593] Lam M, et al.,"Another One Fights the Dust: Targeting the NLRP3 Inflammasome for the Treatment of Silicosis," *Am. J. Respir. Cell. Mol. Biol.* 2022; 66(6):601-611.

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699. In 2025, American researchers found that IL-1 signaling and CD4+ T cells are critical for recruiting B cells to the lungs in chronic beryllium disease. Their study enhanced understanding of immune cell interactions driving lung inflammation in this occupational lung disease.[594]

700. In 2025, Greek researchers studied 992 Covid-19 patients who received 100 mg anakinra subcutaneously daily for 10 days. The incidence of severe respiratory failure was 18.8%, similar to the results of the phase III SAVE-MORE trial. Overall 30-day mortality was 9.5%. The most common adverse event was increased liver function tests. Post hoc comparison with the pivotal phase III trial showed similar anakinra outcomes among patient subgroups by levels of inflammatory mediators and D-dimers. The researchers concluded that the results of the study support the efficacy of anakinra as being similar to that of the pivotal registrational trial for Covid-19 pneumonia.[595] However, in a study of 2,274 critically ill Covid-19 patients, also published in 2025, found Tocilzumab and Sarilumab, but not Anakinra, to be effective, in treating Covid-19 patients.[596]

701. In a recent article, Chinese researchers noted that "the TNF-α inhibitor infliximab and the IL-1 receptor antagonist anakinra, have been used to treat chronic granulomatous disease-related inflammation with some success."[597]

702. These studies show that IL-1 signaling plays a central role in lung inflammation and fibrosis across various pulmonary conditions, including silicosis, pulmonary fibrosis, cystic fibrosis, acute lung injury, COVID-19-related lung damage, and chronic beryllium disease. They highlight the therapeutic potential of IL-1 blockade, particularly using agents like anakinra, to reduce inflammation, modulate immune responses, and improve lung function in these diseases.

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[594] Gaballa JM, et al., "Interleukin-1 signaling and CD4+ T cells control B cell recruitment to the lungs in chronic beryllium disease," *Front. Immunol.* 2025; 16:1479348.

[595] Kyriazopoulou E, et al., "Anakinra efficacy in COVID-19 pneumonia guided by soluble urokinase plasminogen activator receptor: Association with the inflammatory burden of the host," *Int. J. Microbial Agents* 2025; 65:107405.

[596] Derde L, et al., "Tocilizumab, sarilumab and anakinra in critically ill patients with COVID-19: a randomised, controlled, open-label, adaptive platform trial," *Thorax* 2025; 80(8): e222488.

[597] Yu H, et al., "Single-cell and spatial transcriptomics reveal the pathogenesis of chronic granulomatous disease in a natural model," *Cell Rep.* 2025; 44:115612, citing de Luca A, et al., "IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans," *Proc. Natl. Acad. Sci. USA* 2014; 111:3526-3531 and Conrad A., et al., "Infections in Patients with Chronic Granulomatous Disease Treated with Tumor Necrosis Factor Alpha blockers for Inflammatory Complications," *J. Clin. Immunol.* 2021; 41:185-193.

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2. IL-9 Antibody

703. In 2019, researchers from Tokyo sought to elucidate the mediator(s) responsible for the pathogenesis of lung fibrosis, through the use of a mouse model of silica-induced lung fibrosis. With a single nasal administration of 16 mg of silica, lung inflammation (assessed by elevated cellular components in the BAL fluids [BALFs]) and lung fibrosis (assessed by lung histology and lung hydroxyproline levels) were induced and sustained for as long as 24 weeks. Of the mediators measured in the BALFs, IL-9 was characteristically elevated gradually, and peaked at 24 weeks after silica administration. Treatment of silica-challenged mice with anti–IL-9–neutralizing antibody inhibited lung fibrosis, as assessed by lung hydroxyproline level, and suppressed the levels of major mediators, including IL-1b, IL-6, IL-12, CCL2, CXCL1, and TNF-a in BALFs. Moreover, human lung specimens from patients with IPF have shown high expression of IL-9 in alveolar macrophages, CD4-positive cells, and receptors for IL-9 in airway epithelial cells. The researchers concluded that collectively, these data suggest that IL-9 plays an important role in the pathogenesis of lung fibrosis in diseases such as Idiopathic Pulmonary Fibrosis (IPF) and that anti-IL-9 antibody inhibits IPF.[598]

704. In 2020, researchers from Hefei China investigated the role of IL-9 by using a Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia animal model. BALB/c mice underwent nasal inhalation with an ST239 MRSA strain to establish the mouse model of MRSA pneumonia, and a subset of mice were intravenously injected with IL-9 neutralizing antibody or immunoglobulin (Ig) G. At 3 and 8 days postinfection, the peripheral blood, bronchioalveolar lavage fluid (BALF), and lung tissues were collected. The frequencies of Th9 cells and levels of cytokines in peripheral blood, BALF, and lung tissues were determined by flow cytometry and enzyme-linked immunosorbent assay (ELISA), respectively. The colony counts of MRSA in BALF and lung tissue were determined. Data from flow cytometry, qRT-PCR, and ELISA showed that MRSA-infected mice exhibited higher frequency of Th9 cells and higher IL-9 mRNA and protein levels in the peripheral blood, BALF, and lung tissues of mice. In contrast, neutralization of IL-9 abrogated

[598] Sugimoto N, et al., "IL-9 Blockade Suppresses Silica-induced Lung Inflammation and Fibrosis in Mice," *Am. J. Respir. Cell Mol. Biol.* 2019; 60(2):232-243.

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MRSA inoculation-induced Th9 cell generation and IL-9 production in BALF and lung tissues. Bacterial counting and histological examination showed that the numbers of bacteria in BALF and lungs and the lung pathological scores induced by MRSA inoculation were attenuated by the neutralization of IL-9. Moreover, cell counting and ELISA results demonstrated that IL-9 neutralization diminished the MRSA inoculation-induced count of neutrophils and macrophages and levels of pro-inflammatory cytokines in BALF. The investigators concluded that collectively, IL-9 neutralization attenuated inflammation of MRSA pneumonia by regulating Th9/IL-9 expression.[599]

705. In 2022, researchers from Henan China investigated whether blocking IL-9 could alleviate ventilation-induced lung injury (VILI). Lung injury was induced by mechanical ventilation (MV) in C57BL/6 mice. Changes in inflammatory factors and NLRP3-related proteins were assessed using quantitative reverse transcription-polymerase chain reaction, western blotting, and enzyme-linked immunosorbent assay. Subsequently, Nlrp3$^{-/-}$ mice were used to elucidate the underlying mechanism. The percentage of Th9 cells in the peripheral blood, bronchoalveolar lavage fluid (BALF), and lung tissues of MV mice was increased compared to those of control mice. Treatment with anti-IL-9mAb significantly alleviated the changes in lung histopathology, wet/dry lung proportion, total protein content, and neutrophil content in BALF induced by VILI. Additionally, administering anti-IL-9mAb significantly downregulated the expression levels of inflammatory factors in BALF and lung tissues of mice with VILI. Administering anti-IL-9 mAb inhibited NLRP3 inflammasome activation, as evidenced by the observed downregulation of NLRP3, ASC, cleaved caspase-1, and GSDMD-N. NLRP3-deficient mice had lower lung injury induced by VILI than wild-type mice. The anti-IL-9 mAb only partially inhibited VILI in Nlrp3 mice. The researchers concluded that in MV mice, the anti-IL-9 mAb alleviated lung injury and reduced the secretion and expression of inflammatory factors partly by inhibiting the NLRP3 inflammasome pathway.[600]

[599] Xu W, et al., "IL-9 blockade attenuates inflammation in a murine model of methicillin-resistant *Staphylococcus aureus* pneumonia," *Acta Biochim. Biophys. Sin.* 2020; 5292):133-140.

[600] Wang T, et al., "IL-9 blockade attenuates inflammation in a murine model of mechanical ventilation-induced lung injury by inhibiting the NLRP3 inflammasome pathway," *Inflammopharmacol.* 2022;30(4):1395-1406.

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3. Anti-Il-17 Antibody

706. In 2010, European researchers studied the involvement of IL-17-producing T lymphocytes in a mouse model of lung inflammation and fibrosis induced by silica particles. Upregulation of IL-17A was associated with the development of experimental silicosis, but this response was markedly reduced in athymic, γδ T cell-deficient or CD4+ T cell-depleted mice. In addition, γδ T lymphocytes and CD4+T cells, but not macrophages, neutrophils, NK cells or CD8 T cells, purified from the lungs of silicotic mice markedly expressed IL-17A. Depletion of alveolar macrophages or neutralization of IL-23 reduced upregulation of IL-17A in the lung of silicotic mice. IL-17R–deficient animals (IL-17R$^{-/-}$) or IL-17A Ab neutralization, but not IL-22$^{-/-}$ mice, developed reduced neutrophil influx and injury during early lung response to silica, but chronic inflammation, fibrosis, and TGF-β expression induced by silica were not attenuated in the absence of IL-17R or -22 or after IL-17A Ab blockade. The researchers concluded that a rapid lung recruitment of IL-17A–producing T cells, mediated by macrophage-derived IL-23, is associated with experimental silicosis and although acute alveolitis induced by silica is IL-17A dependent, this cytokine appears dispensable for the development of the late inflammatory and fibrotic lung responses to silica.[601]

707. In 2014, Chinese researchers sought to elucidate the underlying mechanisms of IL-1β and IL-17 in silicosis by using anakinra and an anti-IL-17 monoclonal antibody (mAb) to block the receptor of IL-1β and IL-17, respectively, in a mouse model of silicosis. They observed increased IL-1β expression and an enhanced Th17 response after silica instillation. Lung inflammation and accumulation of inflammatory cells were attenuated in the IL-17-neutralized silicosis group.[602]

708. In 2014, Chinese researchers explored the effects of IL-17A on silica-induced inflammation and fibrosis. They showed that IL-17A neutralization delayed neutrophil accumulation and progression of silica-induced lung inflammation and fibrosis. IL-17A neutralization reduced the percentage of Th17 in CD4+ T cells, decreased IL-6 and IL-1β expression, and increased Tregs at an early phase of silica-induced inflammation. Neutralization of IL-17A delayed silica-induced

[601] Lo Re S, et al., "IL-17 and Th17 Lymphocytes Mediate Lung Inflammation but Not Fibrosis in Experimental Silicosis," *J. Immunol.* 2010; 184:6367-6377.

[602] Song L, et al., "Th17 can regulate silica-induced lung inflammation through an IL-1β-dependent mechanism," *J. Cell. Mol. Med.* 2014; 18(9):1773-1784.

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Th1/Th2 immune and autoimmune responses. The investigators concluded that the results of their study suggest that IL-17A neutralization alleviates early stage silica-induced lung inflammation and delays progression of silica-induced lung inflammation and fibrosis. Neutralization of IL-17A suppressed Th17 cell development by decreasing IL-6 and/or IL-1β and increased Tregs at an early phase of silica-induced inflammation. Neutralization of IL-17A also delayed the Th1/Th2 immune response during silica-induced lung inflammation and fibrosis.[603]

709. In 2018, Brazilian researchers investigated the mechanisms involved in the effect of anti-IL17 in a model of lipopolysaccharide (LPS)-induced acute lung injury in mice. Mice were pre-treated with anti-IL17, 1hour before saline/LPS intratracheal administration alongside non-treated controls and levels of exhaled nitric oxide (eNO), cytokine expression, extracellular matrix remodeling and oxidative stress, as well as immune cell counts in bronchoalveolar lavage fluid (BALF), and respiratory mechanics were assessed in lung tissue. LPS instillation led to an increase in multiple cytokines, proteases, nuclear factor-kB, and Forkhead box P3 (FOXP3), eNO and regulators of the actomyosin cytoskeleton, the number of CD4+ and iNOS-positive cells as well as the number of neutrophils and macrophages in BALF, resistance and elastance of the respiratory system, ARG-1 gene expression, collagen fibers, and actin and 8-iso-PGF2a volume fractions. Pre-treatment with anti-IL17 led to a significant reduction in the level of all assessed factors. The researchers concluded that Anti-IL17 can protect the lungs from the inflammatory effects of LPS-induced acute lung injury, primarily mediated by the reduced expression of cytokines and oxidative stress. They recommended studies using anti-IL17 in a treatment regime as highly worthwhile.[604]

710. In 2021, Brazilian researchers published a study in which they evaluated preventive and therapeutic effect of anti-interleukin (IL)-17 in a model of lung injury induced by elastase in male C57Bl6 mice. Treatment with anti-IL-17 decreased respiratory resistance and elastance, airway resistance, elastance of pulmonary parenchyma, exhaled nitric oxide, and linear mean intercept compared with controls. Treatment also decreased nuclear factor-rB, inducible nitric oxide synthase,

[603] Chen Y, et al., "Neutralization of interleukin-17A delays progression of silica-induced lung inflammation and fibrosis in C57BL/6 mice," *Toxicol. Appl. Pharmacol.* 2014; 275(1):62-72.

[604] Righetti RF, et al., "Protective Effects of Anti-IL17 on Acute Lung Injury Induced by LPS in Mice," *Front. Pharmacol.* 2018; 9:1021.

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matrix metalloproteinase-9, matrix metalloproteinase-12, transforming growth factor-β, tumor necrosis factor-α, neutrophils, IL-1β, isoprostane, and IL-17 in airways and alveolar septa; collagen fibers, decorin and lumican in airways; and elastic fibers and fibronectin in alveolar septa. The investigators concluded that anti-IL-17 treatment improved most parameters evaluated in inflammation and extracellular matrix remodeling in this model of lung injury.[605]

711. In 2023, Brazilian researchers evaluated the response of the airways and alveolar septa to anti-IL-17 treatment in an asthma-COPD overlap model. Fifty-six male BALB/c mice were sensitized with ovalbumin (OVA group), received porcine pancreatic elastase (PPE group), or both (ACO group). Mice were then treated with either anti-IL-17 monoclonal antibody or saline. The investigators evaluated hyperresponsiveness, bronchoalveolar lavage fluid (BALF) cell counts, and mean alveolar diameter. They also quantified inflammatory, response, extracellular matrix remodeling, oxidative stress markers, and signaling pathway markers. Anti-IL-17 treatment in the ACO anti-IL-17 group reduced the maximum response of respiratory system compared to the ACO group ($p<0.05$). There was a reduction in the total number of inflammatory cells, neutrophils, and macrophages in the BALF in the ACO anti-IL-17 group compared to the ACO group ($p<0.05$). There was also attenuation of dendritic cells, CD4+, CD8+, FOXP3, IL-1b, IL-2, IL-6, IL-13, IL-17, IL-33 in ACO anti-IL-17 group in airway and alveolar septum compared to the ACO group ($p<0.05$). The investigators observed a reduction of MMP-9, MMP-12, TIMP-1, TGF-b, collagen type I in ACO anti-IL-17 group in airway and alveolar septum compared to the ACO group ($p < 0.05$), as well as a reduction of iNOS and 8-iso-PGF2a in the airways and in the alveolar septum was reduced in the ACO anti-IL-17group compared to the ACO group ($p < 0.05$). Regarding the signaling pathways, NF-kB, ROCK-1, and ROCK-2 in the airway and alveolar septum were attenuated in the ACO anti-IL-17 group when compared to the ACO group ($p<0.05$). The researchers concluded that their results suggest that inhibiting IL-17 modulates cell-associated cytokine production in lung tissue, extra-cellular matrix remodeling, and oxidative stress through the modulation of NF-kB and FOXP3.[606]

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[605] Fukuzaki S, et al., "Preventive and therapeutic effect of anti-IL-17 in an experimental model of elastase-induced lung injury in C57BI6 mice," *Am. J. Physiol. Cell Psyciol.* 2021; 320:C341-C354.

[606] Camargo LdN, et al., "Modulating asthma-COPD overlap responses with IL-17 inhibition," *Front. Immunol.* 2023; 14:1271342.

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712. In 2025, Brazilian researchers evaluated the effect of an IL-17 inhibitor in a cigarette smoke-induced COPD in C57BL/6 mice. The mice were exposed to cigarette smoke for 6 months, and treatment with IL-17 inhibitor was initiated in the fifth month. Four experimental groups were constituted: a control group of animals housed in a vivarium, receiving filtered room air; a control anti-IL-17 group of animals housed in a vivarium, receiving filtered room air and treatment with an anti-IL-17-neutralizing antibody; a COPD group of animals exposed to cigarette smoke; and a COPD anti-IL-17 group of animals exposed to cigarette smoke and treated with an anti-IL-17-neutralizing antibody. In the COPD groups, an increase in mean linear intercept was observed, along with a decrease in tissue elastance and tissue damping, confirming COPD development. Administration of the IL-17-neutralizing antibody reversed these structural and functional alterations. Additionally, the COPD group exhibited an inflammatory response characterized by increased infiltration of polymorphonuclear and mononuclear cells and elevated numbers of IL-17- and IL-6-positive cells. These findings were consistent with the increased expression of IL-17 and IL-6 in lung homogenates, as assessed by ELISA. Treatment with the IL-17-neutralizing antibody effectively reversed this inflammatory response by reducing the expression of these inflammatory markers. These results were supported by the evaluation of RORγτ gene expression, which was significantly upregulated in the COPD group. Treatment with the IL-17-neutralizing antibody alleviated this upregulation. The investigators concluded that their study demonstrated the effectiveness of IL-17-neutralizing antibody treatment in a cigarette smoke-induced model of COPD, even after lung damage had been established, suggesting the therapeutic potential of IL-17-neutralizing antibodies in COPD.[607]

713. In a review of silicosis therapies, Australian researchers acknowledged the efficacy of IL-17 blockers and inhibitors, commenting that "[t]he potential benefits of downregulating or blocking IL-17 should be weighed against the potential risks of increased susceptibility to infections. They noted that common bacterial pathogens are increased in IL-17$^{-/-}$ mice and that silicosis patients have reduced functional parenchyma and may not tolerate recurrent or serious lung infections.[608]

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[607] Moreira AR, et al., "IL-17-neutralizing antibody mitigates functional and structural changes in cigarette smoke-induced COPD model," *Front. Immunol.* 2025; 16:1641300.

[608] Barnes H, et al., "Toward targeted treatments for silicosis," *Curr. Opin. Pulm. Med.* 2024; 30:185-194.

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4. IL-13 Immunotoxin

714. Interleukin-13 (IL-13) is a key mediator of tissue fibrosis caused by inflammation. Secreted by type 2 (Th2) T helper cells, it plays a key role in various inflammatory and pathogenic processes, such as granuloma formation, and has been studied for potential associations with several conditions, such as neoplastic diseases and non-alcoholic fatty liver disease.[609]

715. In 2003, American researchers investigated whether targeting of lung cells responsive to IL-4 and IL-13 exerts a therapeutic effect in the bleomycin-induced model of pulmonary fibrosis. IL-4, IL-13, and their corresponding receptor subunits, IL-4Rα, IL-13Rα1, and IL-13Rα2, were maximally expressed at the mRNA and protein levels in whole lung samples on day 21 or 28 after an intratracheal bleomycin challenge. The intranasal administration of an IL-13 immunotoxin chimeric molecule (IL13-PE) from days 21–28, but not for 1-wk periods at earlier times, after bleomycin challenge had a significant therapeutic effect on histological and biochemical parameters of bleomycin-induced pulmonary fibrosis compared with the control group. The intranasal IL13-PE therapy significantly reduced the numbers of IL-4 and IL-13 receptor-positive mononuclear cells and macrophages and the levels of profibrotic cytokine and chemokine in the lungs of bleomycin-challenged mice on day 28. The researchers concluded that their study showed that IL-4- and/or IL-13-binding cells are required for maintenance of pulmonary fibrosis induced by bleomycin.[610]

716. In 2010, Brazilian researchers investigated whether an immune response to *P. aeruginosa* and/or its exotoxin A would diminish the antifibrotic properties of IL13-PE. Fourteen days after P. aeruginosa infection, C57BL/6 mice were injected with bleomycin via the intratracheal route. Other groups of mice received 4 doses of saline or IL13-PE and were challenged intratracheally with bleomycin 28 days later. At day 21 after bleomycin, all mice received either saline vehicle or IL13-PE by the intranasal route and histopathological analyses of whole lung samples were performed at day 28. Intrapulmonary *P. aeruginosa* infection promoted a neutralizing

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[609] Ribeiro PC, et al., "Inflammatory biomarkers in workers exposed to silica dust: integrative review," *Rev. Bras. Med. Trab.* 2024; 22(3): e20231224, citing Shimamura T, et al., "Novel role of IL_13 in fibrosis induced by nonalchoholic steatohepatitis and its amelioration by IL-13$-directed cytotoxin in a rat model," *J. Immunol.* 2008; 181(7):4656-4665.

[610] Jakubzick C, et al., "Therapeutic Attenuation of Pulmonary Fibrosis Via Targeting of Il-4- and IL-13-Responsive Cells," *J. Immunol.* 2003; 171:2684-2693.

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IgG2A and IgA antibody response in BALF and serum. Surprisingly, histological analysis showed that a prior *P. aeruginosa* infection attenuated the development of bleomycin-induced pulmonary fibrosis, which was modestly further attenuated by the intranasal administration of IL13-PE. Although prior intranasal administration of IL13-PE failed to elicit an antibody response, the systemic administration of IL13-PE induced a strong neutralizing antibody response. However, the prior systemic sensitization of mice with IL13-PE did not inhibit the anti-fibrotic effect of IL13-PE in fibrotic mice. The researchers concluded that IL13-PE therapy in pulmonary fibrosis is effective regardless of the presence of a humoral immune response to Pseudomonas exotoxin A.[611]

717. In 2013, Brazilian researchers examined whether a recombinant immunotoxin comprised of human IL-13 and IL-13-PE might affect pathological features of experimental silicosis. Mice were administered silica particles intransally and were treated with intranasal IL-13–PE every other day from days 21 to 27 post-silica. Upregulation of IL-13, its receptor subunits IL-13Rα1 and IL-13Rα2, and shared receptor IL-4Rα were associated with development of granulomatous lung inflammation triggered by silica. IL-13–PE inhibited silica-induced granuloma and fibrotic responses noted at 24 h and 15 d after the last treatment. Upregulation of TNF-α, TGF-β, and chemokines, as well as increased collagen deposition and airway hyperreactivity to methacholine were all clearly sensitive to IL-13–PE. IL-13–PE also inhibited both IL-13–induced proliferation of cultured lung fibroblasts from silicotic mice and silica-induced IL-8 generation from A549 cells. The researchers concluded that their findings showed that therapeutic treatment with IL-13–PE can reverse important pathological features caused by inhalation of silica particles, suggesting that this recombinant immunotoxin is a promising molecular template in drug discovery for silicosis.[612]

718. The authors of a recent review of inflammatory biomarkers in workers exposed to silica dust observed that "preliminary findings suggest that [IL-13-PE] may be a way to reduce the pulmonary inflammation induced by silica dust exposure."[613]

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[611] Rosada RS, et al., "Therapeutic Efficacy of Cintredekin Besudotox (IL13-PE38QQR) in Murine Lung Fibrosis Is Unaffected by Immunity to *Pseudomonas aeruginosa* Exotoxin A," *PLoS One* 2010; 5(1): e8721.

[612] Ferreira TPT, et al., "IL-13 Immunotoxin Accelerates Resolution of Lung Pathological Changes Triggered by Silica particles in Mice," *J. Immunol.* 2013; 191:5220-5229.

[613] Ribeiro PC, et al., "Inflammatory biomarkers in workers exposed to silica dust: integrative review," *Rev. Bras. Med. Trab.* 2024; 22(3): e20231224.

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5. Recombinant Soluble TNF Receptor

719. Recombinant soluble Tumor Necrosis Factor (TNF) Receptor is a bioengineered protein that mimics the natural tumor necrosis factor (TNF) receptor found on cell surfaces, but is instead a soluble, non-membrane-bound version of the natural receptor. Produced using recombinant DNA technology, this protein acts as a decoy by binding to excess TNF-α, a pro-inflammatory cytokine, thus neutralizing its harmful effects and treating inflammatory conditions.

720. In 1994, Swiss researchers, noting that Tumor Necrosis Factor (TNF) seemed to be an important mediator in pulmonary fibrosis, investigated whether fibrosis might be prevented by a new TNF antagonist. They noted that two types of TNF receptors had been described in either mouse or human, a 55 and a 75 kD receptor (also called TNFR-β and TNFR-α respectively), which are capable of binding TNF-α and of blocking the effects of TNF-α *in vitro*. hey injected bleomycin in mice intratracheally for 15 days and injected about 2 mg silica in other mice intratracheally. Following instillation of bleomycin or silica, the lung collagen content increased between day 5-10 and, subsequently remained stable at a higher level for several weeks. They then explored whether a TNF antagonist not only prevented the accumulation of collagen but also influenced established fibrosis. They infused a 55 kD human recombinant soluble TNF receptor rsTNFR-β, at a rate of 20 µg per day in the mice. This treatment decreased lung collagen content when given 25 or more days after instillation. Their data showed that rsTNFR-β can effectively prevent silica or bleomycin-induced pulmonary fibrosis. The researchers concluded that rsTNFR-β, being of human origin and, therefore, non-immunogenic, may provide a new and promising therapy for pulmonary fibrosis.[614]

721. In 1999, Belgian researchers reported that they had found reduced activity of tumor necrosis factor (TNF)-α accompanying resolving and fibrosing alveolitis induced in NMRI mice by mineral particles (MnO_2 and SiO_2, respectively), in apparent contradiction to the well-recognized proinflammatory and profibrotic activities of this cytokine. They therefore examined the mechanisms involved in this paradoxical response in NMRI mice. Downregulation of the TNF-α

[614] Piguet TF, et al., "Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice," *Eur. Respir. J.* 1994; 7:515-518.

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protein was concurrent with the accumulation of recruited polymorphonuclear neutrophils (PMNs) in alveoli, and coculture experiments showed that PMN explanted from the lungs of mice treated with silica particles were able to downregulate the expression of TNF-α protein by naive alveolar macrophages. In addition, PMN depletion prevented the downregulation of TNF-α induced by silica, further establishing the role of PMNs in the downregulation of TNF-α. Marked increases in soluble p55 and p75 TNF receptors (sTNF-R), as well as in interleukin (IL)-10, paralleled the downregulation of TNF-α protein. The role of these mediators in the observed reduction of TNF-α activity was confirmed by immunoneutralizing the activity of p55 and p75 sTNF-R and by using IL-10–deficient animals. These investigators concluded that because IL-10 also exerts profibrotic activity in addition to its anti-inflammatory activity, the protracted overproduction of IL-10 observed in fibrosing alveolitis may help the understanding of why, in NMRI mice treated with silica particles, lung fibrosis develops in association with a downregulation of TNF-α.[615]

722. In 2002, Chinese researchers investigated whether systemic tumor necrosis factor alpha (TNF-a), soluble TNF-α receptors (p55, p75), interleukin 6(IL-6), and soluble IL-6 receptor could be markers of biological activities of coal workers' pneumoconiosis (CWP). The study population was composed of 182 Chinese retired coal miners who had similar dust exposure histories. Among them, 71were cases with CWP and 111were controls. Chest radiographs were classified according to International Labour Organization Criteria (ILO,1980). Individual dust exposure variables were estimated from work histories, and smoking information was obtained from interviews. Serum concentrations of TNF-α, TNF-α receptors (p55, p75), IL-6, and IL-6 receptor were measured by ELISA techniques. Mean serum levels of p55, p75 and IL-6 were significantly higher in cases than in controls ($P \leq 0.01$ for each comparison by crude analyses). Results from logistic regression models, adjusted for age, dust exposure variables, and smoking habits, found similar associations between soluble p55 and p75 levels and the presence of CWP. Linear regression analysis revealed that CWP radiographic stage (by ILO criteria) was significantly correlated with the

[615] Huaux F, et al., "Soluble tumor necrosis factor (TNF) receptors p55 and p75 and interleukin-10 downregulate TNF-α activity during the lung response to silica particles in NMRI Mice," *Am. J. Respir. Cell Mol. Biol.* 1999; 21:17-145.

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individual serum concentrations of p55, p75 and IL-6. Serum concentrations of all measured cytokines were not correlated to age, dust exposure, or smoking, but there were correlations between soluble p75 and p55 levels, and between p75 and IL-6 levels. The researchers concluded that the results of their study suggest that serum levels of TNF receptors and IL-6a re associated with the fibrotic process of CWP and serum cytokine levels may be correlated with the severity of CWP.[616]

723. In 2011, Chinese researchers investigated cross-talk of the related bioactivity mediators in silica-induced pulmonary inflammation and fibrosis in rats, which contributes to the preventive and therapeutic effect of soluble TNF-α receptor. Wistar rats were administered saline or 50 mg of quartz by intratracheal instillation. Rats in treated groups were given soluble tumor necrosis factor-α (TNF-α) receptor (500 μg) by hypodermic injection on days 1, 5 and 8 after operation. At 7 days or 14 days after instillation, rats were killed to observe the degree of injury and expression of the related bioactivity mediators including nuclear factor KB (NF-KB), nitric oxide, interleukin-1β, interleukin-10, transforming growth factor beta 1 (TGF-β1), TNF-α, interferon-Y (IFN-Y) and granulocyte macrophage colony-stimulating factor (GM-CSF). The area percentages of type I and III collagens in intervention group were lower than those in silica group. The expression of NF-κB, TGF-β1, and COL I were lower in intervention group than in silica group ($p < 0.05$) and GM-CSF was significantly higher ($p < 0.05$) at 7 days after instillation, however, NF-κB, TGF-β1, and COL I were identically lower in intervention group than in silica group, and TNF-α, IFN-γ, and GM-CSF were higher at 14 days after instillation. The investigators concluded that soluble TNF-α receptor upregulating or downregulating the expression of the related bioactivity mediators results in decreasing lung injury induced by silica.[617]

[616] Zhai R, et al., "Serum levels of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) and their soluble receptors in coal workers' pneumoconiosis," *Respiratory Med.* 2002; 96:829-834.

[617] Gao H-S, et al., "Cross-talk of the related bioactivity mediators in serum after injection of soluble TNF-α receptor on silicosis model of rats," *Toxicol. Ind. Health* 2011; 27(&):607-616.

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6. Infliximab

724. "Infliximab is a purified, recombinant DNA-derived chimeric, human-mouse IgG monoclonal antibody that neutralises the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α, inhibiting thus the effective binding of TNF-α with its receptors."[618]

725. "On August 24, 1998, Remicade® (infliximab), the first tumor necrosis factor-α (TNF) inhibitor, received its initial marketing approval from the US Food and Drug Administration for the treatment of Crohn's disease. Subsequently, Remicade was approved in another five adult and two pediatric indications both in the USA and across the globe. In the 20 years since this first approval, Remicade has made several important contributions to the advancement of science and medicine: 1) clinical trials with Remicade established the proof of concept that targeted therapy can be effective in immune-mediated inflammatory diseases; 2) as the first monoclonal antibody approved for use in a chronic condition, Remicade helped in identifying methods of administering large, foreign proteins repeatedly while limiting the body's immune response to them; 3) the need to establish Remicade's safety profile required developing new methods and setting new standards for postmarketing safety studies, specifically in the real-world setting, in terms of approach, size, and duration of follow-up; 4) the study of Remicade has improved our understanding of TNF's role in the immune system, as well as our understanding of the pathophysiology of a range of diseases characterized by chronic inflammation; and 5) Remicade and other TNF inhibitors have transformed treatment practices in these chronic inflammatory diseases: remission has become a realistic goal of therapy and long-term disability resulting from structural damage can be prevented."[619]

726. In 2014, Brazilian researchers published results of a study in which they instilled silica particles intranasally in rats and then treated the rats therapeutically with Xpro 1595, a dominant-negative inhibitor of soluble Tnf and infliximab. Increased levels of cytokines (MIP-1α, MIP-2, KC, MCP-1, IL-1β, TGF-β) and NF-kB activation were detected in lungs of the silica-

[618] Karampitsakos T, et al., "Infliximab-induced interstitial lung disease," *BMJ Case Rep.* 2021; 14:e245726.

[619] Melsheimer R, et al., "Remicade® (infliximab): 20 years of contributions to science and medicine," *Biologics: Target and Therapy* 2019; 13:139-178.

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challenged mice. Therapeutic administration of XPro 1595 and infliximab significantly inhibited the decreased lung function and hyperreactivity as well as fibrosis, including augmentation in collagen deposition and granuloma formation in silica-stimulated mice. Cytokine generation and NF-kB activation were also sensitive to treatment with XPro 1595 and infliximab. The investigators concluded that their findings showed that treatment with XPro 1595 and infliximab effectively inhibited critical features of silicosis, including alteration of lung function and fibrogenic response.[620]

727. In 2016, Turkish researchers published a study investigating the preventive effect of Infliximab on bleomycin (BLC)-induced lung fibrosis in rats. BLC installation worsened antioxidant status (such as SOD, CAT, GPx, GSH, MPO) and serum TNF-α, TGF-β, IL-6, periostin, YKL-40, and lipid peroxidation, and collagen deposition. Infliximab pretreatment improved antioxidant status as well as BLC-induced lung pathological changes, and decreased the TNF-α, TGF-β, IL-6, periostin, YKL-40, lipid peroxidation and collagen deposition. Histological, immunohistochemical, and other evidence supported the ability of Infliximab to prevent BLC-induced lung fibrosis. The researchers concluded that Infliximab pretreatment can attenuate BLC-induced pulmonary fibrosis.[621]

728. In 2018, Chinese researchers published a study of the influence of Infliximab in rats with silicosis. Forty-eight Wistar rats were randomly divided into 3 groups of 16 rats each. In the study group silicosis was induced by intratracheal instillation of 50 mg silica on day 1, and Infliximab was subcutaneously administered at a dose of 15 mg/kg of body weight from day 2 to day 6. In the vehicle group silica was administered as in the study group but without Infliximab, and in the sham group 1 ml of saline was instilled intratracheally. Eight rats in each group were euthanized on day 7 and on day 14, respectively. Infliximab treatment significantly improved silica-induced lung pathological changes (inflammatory cells, collagen deposition) and decreased the TNF-α inhibited NF-κB signaling (I-κB, NF-κB p65) as well as oxidant status (iNOS). The investigators concluded that Infliximab may improve silica-induced pulmonary inflammation by decreasing the TNF-α, inhibiting NF-κB signaling (I-κB, NF-κB p65) as well as oxidant status (iNOS), and that

[620] Ciambarella B, et al., "Dominant-Negative Inhibitor Of Soluble Tnf Xpro 1595 Suppresses Experimental Silicosis in Mice," *Am. J. Respir. Crit. Care Med.* 2014; 189:A1973.

[621] Altintas N, et al., "Protective Effect of Infliximab, a Tumor Necrosis Factor-Alfa Inhibitor, on Bleomycin-Induced Lung Fibrosis in Rats," *Inflammation* 2016; 39(1):65-78.

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Infliximab therefore has potential role in the treatment of silica-induced lung damage.[622]

729. In 2019, Dutch researchers reported the case of a patient diagnosed with silicosis who underwent an open lung biopsy, and was diagnosed with sarcoidosis with silica particles detected in granulomas. After 7 months of treatment with Infliximab, the patient's pulmonary function test improved and pulmonary consolidations on HRCT as well as the inflammatory activity measured by 18F-fluorodeoxyglucose by positron emission tomography/computed tomography (18 F-FDG PET/CT) decreased. Forced Vital Capacity (FVC) rose from 1.97 L to 2.35 L (44 and 53% of predicted, respectively) and the diffusing capacity of the lung for carbon monoxide (DLCO) rose from 5.46 mmol/(min*kPa) (54% of predicted) to 6.26 mmol/(min*kPa) (62% of predicted). The researchers concluded that Infliximab was effective in treating this silico-sarcoidosis patient.[623]

730. In 2023, a review of pulmonary fibrosis in sarcoidosis noted that "Infliximab has been studied extensively and found to be superior to other TNF-inhibitors in a systematic review."[624]

731. Although Infliximab has beneficial effects on silicosis, a few cases of Infliximab-associated pulmonary fibrosis have been reported.[625] While some patients may develop pulmonary fibrosis as a consequence of Infliximab treatment, data from a national database of 4,452 pulmonary fibrosis cases from treatment with the top 10 pulmonary fibrosis drugs showed that Infliximab was associated with the development of pulmonary fibrosis in just 107 patients (2.4% of patients) – the lowest percentage of pulmonary fibrosis cases resulting from the top 10 pulmonary fibrosis drugs.[626]

732. Australian researchers began a clinical trial in countertop fabricators with silicosis.[627]

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[622] Zhang H, et al., "Subcutaneous Administration of Infliximab-Attenuated Silica-Induced Lung Fibrosis," *Int. J. Occup. Med. Environ. Health* 2018; 31(4):503–515

[623] Beijer E, et al., "Sarcoidosis in a patient clinically diagnosed with silicosis; is silica associated sarcoidosis a new phenotype?" *Respir. Med. Case Rep.* 2019; 28:100906.

[624] Gupta R, et al., "An expert overview of pulmonary fibrosis in sarcoidosis," *Expert. Rev. Respir. Med.* 2023; 17(2):119-130, citing Adler BL, et al., "Anti-tumor necrosis factor agents in sarcoidosis: a systematic review of efficacy and safety," *Semin. Arthritis Rheum.* 2019; 48(6):1093-1104.

[625] Makkawy EA, et al., "Infliximab-Induced Interstitial Pneumonitis: A Case Report," *Cureus* 2023; 15(6): e40812; Karampitsakos T, et al., "Infliximab-induced interstitial lung disease," *BMJ Case Rep.* 2021; 14: 3245726.

[626] Butranova OI, et al., "Drug-Induced Pulmonary Fibrosis: National Database Analysis," *Biomedicines* 2024; 12:2650.

[627] Alfred Health, "New hope for silicosis sufferers," August 8, 2025.

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F. Inflammasone Activation Blockers

733. "NLRP3 inflammasome is the best characterized inflammasome at present, named after the NLRP3 protein in the complex which belongs to the NLR family . . . ."[628] "NLRP3 is a 115 kDa cytosolic protein expressed in monocytes, neutrophils, dendritic cells, lymphocytes, osteoblasts, and epithelial cells."[629] "It contains three domains which are: a leucine-rich repeat (LRR) at the C-terminal, a central nucleotide-binding and oligomerization domain NACHT which possesses ATPase activity, and a pyrin domain (PYD) at the N-terminal which recruits ASC."[630]

734. "NLRP3 acts as a general sensor of cellular stress, and several factors have been recognized as activators of NLRP3 inflammasome."[631] "Silica-induced activation of inflammasome is a fundamental pathway leading to lung injury."[632] "Crystalline silica may be also engulfed by airway epithelial cells leading to activation of NLRP3 inflammasome with a subsequent release of IL-1β."[633] "These findings suggest that the mechanism of NLRP3 activation is not restricted only

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[628] Zahid Y, et al., "Pharmacological Inhibitors of the NLRP3 Inflammasome," *Front. Immunol.* 2019; 10:2538, citing Inoue M, et al., "The role of interferon-β in the treatment of multiple sclerosis and experimental autoimmune encephalomyeloitis – in the perspective of inflammasomes," *Immunology* 2013; 139:11-18.

[629] Zahid Y, et al., "Pharmacological Inhibitors of the NLRP3 Inflammasome," *Front. Immunol.* 2019; 10:2538, citing Zhong Y, et al., "Functions of NOD-like receptors in human diseases," *Front. Immunol.* 2013; 4:333.

[630] Zahid Y, et al., "Pharmacological Inhibitors of the NLRP3 Inflammasome," *Front. Immunol.* 2019; 10:2538, citing Halle A, et al., "The NALP3 inflammasome is involved in the innate immune response to amyloid-β," *Nat. Ummunol.* 2008; 9:857-865.

[631] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Tschopp J, et al., "NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production?" *Nat. Rev. Immunol.* 2010; 10:210-215.

[632] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Harijith A, et al., "Reactive oxygen species at the crossroads of inflammasome and inflammation," *Front. Physiol.* 2014; 5:352; Sayan M, et al., "The NLRP3 inflammasome in pathologenic particle and fibre-associated lung inflammation and diseases," *Part. Fibre Toxicol.* 2016; 13:51; Janssen YM, et al., "Expression of antioxidant enzymes in rat lungs after inhalation of asbestos or silica," *J. Biol. Chem.* 1992; 267:10625-10630; Hoffman HM, et al., "Inflammasome and IL-1beta-mediated disorders," *Curr. Allergy Asthma Rep.* 2010; 10:229-235; Tschopp J, et al., "NLRP3 inflammasome activation: The convergence of multiple signalling pathways on ROS production?" *Nat. Rev. Immunol.* 2010; 10:210-215.

[633] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Øvrevik J, et al., "Mechanisms of silica-induced IL-8 release from A549 cells: Initial kinase-activation does not require EGFR activation or particle uptake," *Toxicology* 2006; 227:105-116; Peeters PM, et al., "Silica induces NLRP3 inflammasome activation in human lung epithelial cells," *Part. Fibre Toxicol.* 2013; 10:3.

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to classical phagocytes."[634]

735. "[I]nflammasome activity may be suppressed by . . . inhibitors acting at various levels."[635] "[I]nflammasome activation may be prevented by suppression of the factors leading to its activation, i.e., blocking NF-κB expression, mitochondrial stress, lysosomal damage, extracellular ATP, K+ efflux, etc. Oxidized ATP as an antagonist of ATP declined inflammasome activation, caspase-1-mediated cleavage of IL-1β, and K^+ efflux in hyperoxia-exposed alveolar macrophages."[636]

736. "Suppression of activation of NLRP3 inflammasome with a subsequent reduction in IL-1 responses was observed after inhibition of phagocytosis, phagosomal acidification or cathepsin B activity,[637] or via inhibition of K^+ efflux by high extracellular K^+ concentration."[638] "[T]here is a variety of small-molecule agents acting as indirect or direct inhibitors of inflammasome activation, inhibitors of constituents of NLRP3 inflammasome, direct inhibitors of NLRP3 protein, or caspase-1 inhibitors."[639] Many NLRP3 inflammasome inhibitors have remarkable therapeutic potential."[640]

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[634] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162.

[635] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Zahid Y, et al., "Pharmacological Inhibitors of the NLRP3 Inflammasome," *Front. Immunol.* 2019; 10:2538.

[636] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Kolliputi N, et al., "The inflammasome mediates hyperoxia-induced alveolar cell permeability," *J. Immunol.* 2010; 184:5819-5826.

[637] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Hornung V, et al., "Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization," *Nat. Immunol.* 2008; 9:847-856; Sandberg WJ, et al., "Comparison of non-crystalline silica nanoparticles in IL-1β release from macrophages," *Part. Fibre Toxicol.* 2012; 9:32.

[638] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Pétrilli V, et al., "Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration," *Cell Death Differ.* 2007; 14:1583-1589; Martinon F, et al., "The inflammasomes: Guardians of the body," *Annu. Rev. Immunol.* 2009; 27:229-265.

[639] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Zahid Y, et al., "Pharmacological Inhibitors of the NLRP3 Inflammasome," *Front. Immunol.* 2019; 10:2538; Sandberg WJ, et al., "Comparison of non-crystalline silica nanoparticles in IL-1β release from macrophages," *Part. Fibre Toxicol.* 2012; 9:32; Saleh M, et al., "Enhanced bacterial clearance and sepsis resistance in caspase-12-deficient mice," *Nature* 2006; 440:1064-1068; Caseley EA, et al., "Immunome project consortium for autoinflammatory disorders (ImmunAID), McDermott JF. Inflammasome inhibition under physiological and pharmacological conditions," *Genes Immun.* 2020; 21:211-223.

[640] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162.

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G. Autophagy-Lysosomal System Treatments

737. "Autophagy is a normal physiological process in the body involved in cellular homeostasis and survival mechanisms in normal respiring cells. Autophagy is a fundamental intracellular process responsible for the lysosomal degradation of microorganisms (viruses, bacteria, fungi and protists/protozoa), damaged organelles and damaged proteins that cannot be degraded by the proteasome."[641] "An immediate, strong, and highly regulated inflammatory defense mechanism is needed for the timely elimination of pathogens and noxious particles from the lung. In addition the successful maintenance of homeostasis within the respiratory system depends on proper crosstalk between the innate and adaptive immune systems. Autophagy plays an essential role in the inflammatory response of the lung to infection and stress. At baseline, autophagy in AMs [alveolar macrophages] is critical for inhibiting spontaneous pulmonary inflammation."[642]

738. "Autophagy plays an important role in the pathogenesis of pulmonary fibrosis. Whether the autophagic flux is blocked or not is directly related to the development direction of pulmonary fibrosis."[643] "Autophagy is known to be associated with some pulmonary conditions and serves a vital role in lung infections, acute lung lesions, interstitial lung fibrosis, chronic obstructive pulmonary disease, and an array of other pertinent disorders."[644]

739. Autophagy is an important therapeutic target for fibrotic pulmonary diseases.[645] Macrophage autophagy also plays an important role in the progression of silicosis.[646]

740. "Silica dust particles have been observed in AM autophagolysosome of silicosis

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[641] Racanelli AC, et al., "Autophagy and inflammation in chronic respiratory disease," *Autophagy* 2018; 14(2):221-232.

[642] Racanelli AC, et al., "Autophagy and inflammation in chronic respiratory disease," *Autophagy* 2018; 14(2):221-232, citing Kanayama M, et al., "The lung is protected from spontaneous inflammation by autophagy in myeloid cells," *J. Immunol. 2015;* 194(11);5465-5471.

[643] Lv X, et al., "Autophagy and Pulmonary Fibrosis," *Adv. Exp. Med. Biol.* 2020; 1207:569-579.

[644] Wang H, et al., "Autophagy in Disease Onset and Progression," *Aging Disease* 2024; 15(4):1646-1671.

[645] Zhao H, et al., "Autophagy, an important therapeutic target for pulmonary fibrosis diseases," *Clinica Chimica Acta* 2020; 502:139-147.

[646] Tan S, et al., "Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453.

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patients. Moreover, abnormal autophagy activity has been observed in the lung tissues of the silicosis rat model."[647] "These findings suggest that AM autophagy is associated with silicosis."[648] "Another study has shown that with the development of human silicosis, AM lysosomes gradually decrease, whereas AM autophagosomes increase; furthermore, the expression of BCL2-Associated X (Bax) and cleaved caspase3 increase, whereas the expression of BCL2 decreases."[649] "Therefore, the blockade of autophagic degradation may aggravate AM apoptosis in human silicosis."[650]

741. "Crystalline silica-induced destruction of lysosomes impairs autophagic substrate degradation in alveolar macrophages. As accumulation of autophagosomes causes damage to macrophages, restoring the function of the autophagy-lysosomal system and enhancing the autophagic flux could alleviate silica-induced persistent inflammation and fibrosis."[651]

742. "Various inhibitors of lysosomal processing, which, e.g., increase lysosomal pH (lysosomotropic weak base ammonium chloride), inhibit cathepsin D (pepstatin A) or acidic sphingomyelinase (despiramine), or blunt the surface-active sites of silica crystals (aluminium lactate), may reduce activation of caspase and cell apoptosis."[652]

743. "[A]utophagy is an intracellular process regulating the cycle of synthesis and

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[647] Tan S, et al., "Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453, citing Wang M, et al., "The Study of Autophagy in Avleolar Macrophages of Patients with Coal Workers' Pneumoconiosis," *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2014; 33:41-44; Chen S, et al., "Autophagy in Lung Tissue of Rats Exposed to Silica Dust," *Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi* 2013; 31:607-610.

[648] Tan S, et al., "Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453.

[649] Tan S, et al., "Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453, citing Chen S, et al., "Lipopolysaccharides May Aggravate Apoptosis Through Accumulation of Autophagosomes in Alveolar Macrophages of Human Silicosis," *Autophagy* 2015; 11:2356-2357.

[650] Tan S, et al., "Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453.

[651] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing He X, et al., "Trehalose alleviates crystalline silica-induced pulmonary fibrosis via activation fo the TFEB-mediated autophay-lysosomal system in alveolar macrophages," *Cells* 2020; 9:122.

[652] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Thibodeau MS, et al., "Silica-induced apoptosis in mouse alveolar macrophages is initiated by lysosomal enzyme activity," *Toxicol. Sci.* 2004, 80:34–48.

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degradation of cellular components. Engulfment of silica results in a lysosomal rupture, which may cause an accumulation of autophagosomes in the alveolar macrophages. The abundant accumulation of autophagosomes may lead to apoptosis in alveolar macrophages. Thus, autophagy may alleviate silica-induced pulmonary fibrosis by decreasing apoptosis of macrophages . . . ."[653]

744. "Several possibilities of how to influence the autophagy activity have been recently reviewed."[654] "[T]he autophagy activity in fibroblasts may be increased by upregulated expression of miR325, and alveolar macrophage-specific autophagy is stimulated by dioscin."[655] "Enhancement of autophagy by rapamycin and cAMP protected epithelial cells from apoptosis and attenuated silica-induced pulmonary fibrosis in mice."[656] "Autophagy in macrophages can be also promoted by dioscin, a component of traditional Chinese medicine, which stimulates the process of autophagic degradation, further protecting alveolar macrophages from mitochondria-dependent apoptosis."[657] "Accelerated activity of autophagy and decreased apoptosis of alveolar macrophages were also observed for another natural extract, a component of Atractylodes rhizome atractylenolide III."[658]

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[653] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Tan S, et al., "Trehalose alleviates apoptosis by protecting the autophagy-lysosomal system in alveolar macrophages during human silicosis," *Life Sci.* 2020; 257:118043; Tan S, et al.,"Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453.

[654] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Tan S, et al.,"Macrophage Autophagy and Silicosis: Current Perspective and Latest Insights," *Int. J. Mol. Sci.* 2021; 22:453; Zhao H, et al., "Autophagy, an important therapeutic target for pulmonary fibrosis diseases," *Clin. Chim. Acta* 2020; 502:139-147.

[655] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Xu T, et al., "MiR-326 inhibits inflammation and promotes autophagy in silica-induced pulmonary fibrosis through targeting TNFSF14 and PTBP1," *Chem. Res. Toxicol.* 2019; 32:2192-2203; Piguet PF, et al., "Effective treatment of the pulmonary fibrosis elicited in mice by bleomycin or silica with anti-CD-11 antibodies," *Am. Rev. Respir. Dis.* 1993; 147:435-441.

[656] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Zhao X, et al., "Autophagic flux blockage in alveolar epithelial cells is essential in silica nanoparticle-induced pulmonary fibrosis," *Cell Death Dis.* 2019; 10:127.

[657] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Piguet PF, et al., "Effective treatment of the pulmonary fibrosis elicited in mice by bleomycin or silica with anti-CD-11 antibodies," *Am. Rev. Respir. Dis.* 1993; 147:435-441.

[658] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Chen S, et al., "Atractylenolide III alleviates the apoptosis through inhibition of autophagy by the mTOR-dependent pathway in alveolar macrophages of human silicosis," *Mol. Cell. Biochem.* 2021; 476:809-818.

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745. "Another substance influencing autophagy is trehalose, a non-reducing disaccharide, which acts as a regulator of transcription factor EB (TFEB), a master gene for lysosomal biogenesis driving expression of autophagy and lysosomal genes."[659] "In silica-exposed mice, silica increased TFEB nuclear localization and expression in macrophages, while TFEB overexpression or treatment with trehalose acting as a TFEB activator alleviated lysosomal dysfunction, enhanced autophagic flux, and reduced apoptosis, inflammatory cytokine levels, and fibrosis."[660] "Similarly, in alveolar macrophages collected from workers professionally exposed to silica, the addition of trehalose restored autophagylysosomal function, accelerated the process of autophagic degradation, and decreased levels of cleaved caspase-3."[661]

746. "Autophagy may also be influenced by administration of mesenchymal cells [which] can affect autophagy in the immune cells involved in injury-induced inflammation, reducing their survival, proliferation, and function and favoring the resolution of inflammation."[662] "Bone-marrow-derived MSCs decreased expressions of autophagy-associated proteins, microtubule-associated protein light chain 3 (LC-3) and autophagy-related gene Beclin-1 in alveolar macrophages and attenuated immune and autophagic activity, which may inhibit the progress of silicosis caused by damage of alveolar macrophages and promote a fibrotic lung recovery in a rat model of silicosis."[663]

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[659] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Settembre C, et al., "TFEB links autophagy to lysosomal biogenesis," *Science* 2011; 332:1429-1433.

[660] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing He X, et al., "Trehalose alleviates crystalline silica-induced pulmonary fibrosis via activation fo the TFEB-mediated autophay-lysosomal system in alveolar macrophages," *Cells* 2020; 9:122.

[661] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Tan S, et al., "Trehalose alleviates apoptosis by protecting the autophay-lysosomal system in alveolar macrophages during human silicosis," *Life Sci.* 2020; 257:118043.

[662] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Ceccariglia S, et al., "Autophagy: A potential key contributor to the therapeutic action of mesenchymal stem cells," *Autophage* 2020; 16:28-37.

[663] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Zhu HX, et al., "Effects of bone marrow-derived mesenchymal stem cells on the autophagic activity of alveolar macrophages in a rat model of silicosis," *Exp. Ther. Med.* 2016; 11:2577-2582.

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H. Antioxidant Treatments

747. "Several NADPH oxidases associated with phagocytosis of silica have a common P22PHOX subunit. Blocking it may impair NLRP3 activation and thereby may be used as a therapeutic target."[664] "Another promising target may be NAD-dependent deacetylase sirtuin (SIRT)-1, which stimulates the expression of antioxidants through the FoxO pathway and suppresses NF-κB signaling and NLRP3 activity. . . . [H]igh concentrations of ROS [reactive oxygen species] can inhibit the activity of the SIRT-1 enzyme, e.g., by evoking oxidative modifications on its cysteine residues, which enhances NF-κB signaling and inflammatory responses."[665]

748. "N-acetylcysteine (NAC) is a tripeptide precursor of glutathione and has postulated antioxidant properties as a scavenger of ROS and inhibitor of cyclo-oxygenase-2 and membrane lipid peroxidation."[666] "NAC possesses antioxidant, cytoprotective, anti-inflammatory, antimicrobial, and mucolytic properties, making it a promising therapeutic agent for a wide range of diseases in both humans and domesticated animals. Oxidative stress and inflammation play a major role in the onset and progression of all these diseases. NAC's primary role is to replenish glutathione (GSH) stores, the master antioxidant in all tissues; however, it can also reduce levels of pro-inflammatory tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β), inhibit the formation of microbial biofilms and destroy biofilms, and break down disulfide bonds between mucin molecules."[667]

749. "Due to the known effects of oxidative damage in the development of silicosis, administration of antioxidant agents is a potential strategy for the . . . treatment of silicosis."[668]

750. "In a rat model of silica-induced lung injury treatment with N-acetylcysteine (NAC)

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[664] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Dostert C, et al., "Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica," *Science* 2008; 320:674-677.

[665] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Salminen A, et al., "Crosstalk between oxidative stress and SIRT1: Impact on the aging process," *Int. J. Mol. Sci.* 2013; 14:3834-3859.

[666] Barnes H, et al., "Toward targeted treatments for silicosis," *Curr. Opin. Pulm. Med.* 2024; 30:185-194.

[667] Tieu S, et al.,, "N-Acetylcysteine and Its Immunomodulatory Properties in Humans and Domesticated Animals," *Antioxidants* 2023; 12:1867.

[668] Miao R-M, et al., "Effect of oxidative stress on development of silicosis," *World J. Respirology* 2012; 2(1):1-5.

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reduced the fibrotic score, decreased hydroxyproline and malondialdehyde (MDA) concentrations in the lung, and prevented silica-induced increases in TNFα, IL-8 and high-sensitivity C-reactive protein in BALF and serum, as well as reducing the mitochondrial apoptosis pathway."[669]

751. "[I]n silica-damaged mice, NAC ameliorated silica-induced pulmonary inflammation, lung injury , as demonstrated by down-regulation of oxidising enzyemes and lower levels of MDA, enhanced antioxidant activity, increased expression of E-cadherin, and decreased expressions of vimentin and cytochrome C."[670]

752. "In . . . clinical studies carried out on patients with silicosis, NAC was combined with a calcium channel blocker tetrandrine, which can also alleviate pulmonary fibrosis and inflammation by reducing the level of type I and III collagen mRNA and collagen deposition in the lung. This treatment combination improved the pulmonary function and exercise tolerance of patients and inhibited levels of IL-6, TNFα, TGFβ1, and matrix metalloproteinase (MMP)-7."[671]

753. In a study published in 2024 by Chinese investigators, 94 patients with Chronic Obstructive Pulmonary Disease (COPD) with pulmonary interstitial fibrosis (PIF) were equally randomized into study and control groups. The study group was given N-actylcysteine in addition to conventional treatment while the control group was given only conventional treatment. The study group showed significantly higher efficacy, FEV1, FVC, FEV1/FVC compared to the control group, as well as significantly higher partial pressure of oxygen, blood oxygen saturation, superoxide dismutase, and glutathione levels after treatment compared to controls. Further, platelet-derived growth factor, transforming growth factor, vascular cell adhesion molecule, tumor necrosis factor,

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[669] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Zhang H, et al., "High dose N-acetylcysteine decreases silica-induced lung fibrosis in the rat," *J. Int. Med. Res.* 2013; 41:1179-1186; Zhang L, et al., "N-acetylcysteine alleviated silica-induced lung fibrosis in rats by down-regulation of ROS and mitochondrial apoptosis signaling," *Toxicol. Mech. Methods* 2014; 24:212-219.

[670] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Huang H, et al., "N-acetylcysteine therapeutically protects against pulmonary fibrosis in a mouse model of silicosis," *Biosci. Rep.* 2019; 39:BSR20190681.

[671] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162, citing Sun J, et al., "Clinical efficacy of actylcysteine combined with tetrandrine tablets in the treatment of silicosis and the effect on serum IL-6 and TNF-alpha," *Exp. Ther. Med.* 2019; 18:3383-3388; Zhang J, et al., "Effects of tetrandrine combined with actylcysteine on exercise tolerance, pulmonary function and serum TNF-β1 and MMP-7 in silicosis patients," *Exp. Ther. Med.* 2020; 19:2195-2201.

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interleukin-6, and vascular endothelial growth factor levels after treatment were significantly lower in the study group than in the control group. The investigators concluded that N-actylcysteine, as an adjuvant therapy for COPD-IF is highly effective, improves lung function and oxidative stress, reduces airway inflammation, and attenuates the degree of hypoxia and pulmonary fibrosis with no serious adverse effects.[672]

754. In 2024, Australian researchers published a randomized, double-blinded placebo-controlled study in which they sought to determine the effect of high dose N-acetylcysteine on lung function and quality of life of patients with bronchiectasis. Participants were randomized to receive 2,400 mg N-acetylcysteine or placebo for 6 weeks. Sputum neutrophil elastase (a surrogate marker for exacerbations), sputum MUC5B, IL-8, lung function, quality of life and adverse effects were measured. Clinical and sputum measurements were assessed at week 3 and week 6. The study was terminated due to the Covid pandemic, but 17 patients completed all aspects of the study. At 6 weeks, sputum neutrophil elastase fell by 47% in the NAC group relative to placebo, and MUC5B increased by 48% with NAC compared with placebo. Lung function FVC improved significantly with NAC compared with placebo at 6 weeks. Quality of life measures within the respiratory and social functioning domains also demonstrated clinically meaningful improvements, with social functioning reaching statistical significance. Adverse effects were similar in both groups. The investigators concluded that high dose NAC exhibits anti-inflammatory benefits and improvements in aspects of quality of life and lung function measures, and was well tolerated and safe, without significant adverse effects.[673]

755. In addition to N-acetylcysteine, corticosteroids, dexamethasone and flunisolide are considered to have therapeutic potential for silicosis due to their antioxidant properties.[674]

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[672] Yang J, et al., "Effect of N-acetylcysteine in treatment of COPD with pulmonary interstitial fibrosis, inflammatory factors and VEGF levels," *Tropical J. Pharmaceutical Res.* 2024; 23(9):1549-1555.

[673] Jayaram L, et al., "Evaluation of high dose N-Acetylcysteine on airway inflammation and quality of life outcomes in adults with bronchiectasis: A randomised placebo-controlled pilot study," *Pulm. Pharmacol. Ther.* 2024; 84:102283.

[674] Adamcakova J, et al., "New Insights into Pathomechanisms and Treatment Possibilities for Lung Silicosis," *Int. J. Mol. Sci.* 2021; 22:4162,

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I. Oxygen Therapy

756. "Supplemental oxygen therapy is commonly prescribed in clinical practice for patients with fibrosing interstitial lung disease (ILD) to reduce breathlessness and increase physical capacity."[675] "Oxygen therapy is critical in comprehensively managing these challenging respiratory disorders. The rationale behind employing oxygen therapy in ILDs extends beyond addressing hypoxemia; it encompasses mitigating symptoms, enhancing the quality of life, and potentially influencing disease progression."[676] "Supplemental oxygen can provide relief by reducing the work of breathing and improving exercise tolerance, allowing patients to engage in daily activities more comfortably."[677] Numerous retrospective studies have depicted the value of supplemental oxygen in idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases."[678]

757. In 2013, Japanese researchers published the results of a double-blind, placebo-controlled, randomized crossover trial of ambulatory oxygen versus ambulatory air. Patients with IPF who had a partial pressure of arterial oxygen (PaO2) between 60 mm Hg and 80 mm Hg at rest, and desaturation of 88% or less in a room-air 6-min walk test were eligible. Patients underwent a standardized 6-min walk test and a 6-min free walk test under each ambulatory gas. Oxygen and air were provided at 4 L/min intranasally. Dyspnea was evaluated immediately, 1, and 2 min after the tests. Twenty patients with a mean age of 73.5 (SD 4.1) years, % predicted FVC of 71.0 (13.3) %, % predicted diffusion capacity for carbon monoxide (Dlco) of 57.0 (13.3) %, and PaO2 of 72.5 (5.4) mm Hg were recruited. No significant differences in dyspnea were observed between ambulatory oxygen and air at each time point. The researchers recommended that long-term effect on daily

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[675] Yang J, et al., "Supplemental oxygen therapy use among patients with fibrosing interstitial lung disease in the United States," *Respir. Res.* 2025; 26:80.

[676] Ramadan A, et al., "Revitalizing respiration: A comprehensive review of oxygen therapy in interstitial lung diseases," *Health Sciences Rev.* 2025; 13:100202, citing Yossif SF, et al., "Role of long-term oxygen therapy in interstitial lung diseases," *Egypt. J. Bronchol.* 2023; 17:56.

[677] Ramadan A, et al., "Revitalizing respiration: A comprehensive review of oxygen therapy in interstitial lung diseases," *Health Sciences Rev.* 2025; 13:100202, citing Clark KP, et al., "Supplemental oxygen therapy in interstitial lung disease: a narrative review," *Ann. ATS* 2023; 20:1541-1549 and Faverio P., et al., "Management of chronic respiratory failure in interstitial lung disease: overview and clinical insights," *Int. J. Med. Sci.* 2019; 16:967-980.

[678] Kataoka K, et al., "Cohort study to evaluate prognostic factors in diopathic pulmonary fibrosis patients introduced to oxygen therapy," *Sci. Rep.* 2023; 13:13664.

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dyspnea should be investigated in studies using stationary and ambulatory oxygen.[679]

758. In 2021, Italian researchers published results of AmbOx, a multi-center, randomized, open label, mixed-method, cross-over controlled clinical trial evaluating whether ambulatory oxygen for a two-week period improved HRQoL, compared to no treatment. Patients with fibrotic ILD were recruited from 3 UK centers if their resting SpO2 was ≥94%, but dropped to ≤88% on a 6-minute-walk-test (6MWT). On a second 6MWT, oxygen flow was titrated to maintain SpO2>90% for > ½ of 6MWT duration and/or maximum flow of 6 liters/minute, to determine the appropriate oxygen flow for each patient. Patients were randomly assigned to the order of treatment. The primary outcome, assessed on intention to treat, was the score-change on the King's Brief ILD questionnaire (K-BILD) after two weeks on oxygen compared to two weeks off oxygen. A total of 84 patients were randomized to the trial. Of these, 41 were randomized to ambulatory oxygen first, and 43 to no oxygen, crossing to the alternative arm after two weeks. 76 (90.5%) completed the trial. Ambulatory oxygen, compared to no oxygen, was associated with improvements in total K-BILD score [mean (SD) on oxygen: 55.5 (13.8) versus 51.8 (13.6) on no oxygen, difference adjusted for order of treatment: 3.7-95% CI 1.8 to 5.6; p<0.0001)], breathlessness and activity domain [44.4 (22.6) on oxygen vs 35.8 (20.4) on no oxygen; difference: 8.6; 95% CI:4.7 to 12.5; p<0.0001], and chest symptoms domain [65.5 (25.2) on oxygen vs 57.9 (29.2) on no oxygen; difference: 7.6; 95% CI:1.9 to 13.2; p=0.009)]. The most common adverse events were upper respiratory tract infections. Five serious adverse events, including two deaths occurred, but were considered not related to oxygen usage. Patients considered oxygen largely beneficial, with challenges including visibility, work-related issues and perceived prognostic significance. The researchers concluded that ambulatory oxygen appears to be associated with improved HRQoL in ILD patients with isolated exertional hypoxia, suggesting it can be an effective intervention in patients with limited therapeutic options.[680]

759. In 2023, Japanese researchers published a multi-center prospective cohort study of

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[679] Nishiyama O, et al., "Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia," *Respir. Med.* 2013; 107:1241-1246.

[680] Visca D, et al., "Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): A prospective, open-label, mixed-method, crossover randomised controlled trial," *Lancet Respir. Med.* 2018; 6(10):759-770.

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IPF patients who started oxygen therapy at 19 hospitals with expertise in interstitial lung disease. Baseline clinical data at start of oxygen therapy and 3-year follow-up data including death and cause of death were assessed. Of 147 eligible patients, 86 (59%) were prescribed ambulatory oxygen therapy; 61 (41%) were prescribed long-term oxygen therapy. Of them, 111 died (76%) during a median follow-up of 479 days. Median survival from the start of oxygen therapy was 537 ± 74 days. In the univariable analysis, low body mass index, low forced vital capacity, low diffusion capacity, resting hypoxemia, short 6 min-walk distance, and high COPD assessment test score were significantly associated with poor prognosis. Multivariable analysis revealed low BMI, low FVC, low DLCO, low minimum SpO2 on 6MWT, and high CAT score were independent factors for poor prognosis. The overall survival of IPF patients after starting oxygen therapy was about 1.5 years.[681]

760. In 2025, Italian researchers published results of a randomized double-blind placebo-controlled crossover trial with 32 patients with fibrotic interstitial lung diseases desaturating to ≤88% during a baseline 6-minute walk test (6MWT) on ambient air. Patients completed two double-blind 6MWTs with either oxygen or placebo (compressed medical air) at the same personalised flow. Ambulatory oxygen, compared to placebo, prevented desaturation, reduced tachycardia, increased walking distance by 37 m (95% CI: 10–74, $p = 0.008$), and lessened dyspnoea and fatigue. The mean preference score for oxygen over placebo was 2.6 (95% CI 1.9–3.2, $p<0.0005$), significantly greater than equivalence. The preference score for placebo over ambient air was −1.5 (−2.4 to 0.64, $p = 0.005$), significantly lower than equivalence, while the score for oxygen over ambient air was 0.4 (−0.7 to 1.5), not significantly different from equivalence. The researchers concluded that their data confirm that ambulatory oxygen provides significant benefits beyond a placebo effect, although in some patients it is associated with a negative perception that may hinder treatment acceptance, and their study strengthens the evidence supporting current oxygen therapy recommendations.[682]

761. In 2024, Taiwanese researchers conducted a systematic review and meta-analysis of

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[681] Kataoka K, et al., "Cohort study to evaluate prognostic factors in diopathic pulmonary fibrosis patients introduced to oxygen therapy," *Sci. Rep.* 2023; 13:13664.

[682] Ciarleglio G, et al., "Objective Effects and Patient Preferences for Ambulatory Oxygen in Fibrotic Interstitial Lung Disease With Isolated Exertional Hypoxaemia: A Placebo-Controlled 6–Minute Walk Test Study," *Respirology* 2025; 30:644-651.

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randomized controlled trials (RCTs) to evaluate the effectiveness of oxygen therapy in improving the exertional capacity of patients with fibrotic interstitial lung disease. The primary outcome was peripheral oxygen saturation (SpO_2) during exercise. Fourteen RCTs involving 370 patients were included. Oxygen therapy improved SpO_2 during exercise (mean difference, MD = 6.26 %), exercise duration (MD = 122.15 s), fatigue (standard mean difference, SMD = -0.30), and dyspnea (MD = -0.75 Borg score units). High-flow oxygen systems tended to be more effective than low-flow systems in improving exercising SpO_2, duration, fatigue, dyspnea, and heart rate. High-flow nasal cannulas yielded better outcomes regarding SpO_2 and fatigue than did high-flow Venturi masks (MD = 1.60 % and MD = -1.19 Borg score units, respectively). No major adverse events were reported. The researchers concluded the evidence from RCTs supports the short-term use of oxygen supplementation to improve SpO_2, exercise capacity, fatigue, and dyspnea among patients with fibrotic interstitial lung disease. While high-flow nasal cannulas yield more favorable outcomes, the long-term effects of oxygen therapy on quality of life and mortality remained unclear.[683]

762. In 2024, American researchers performed a systematic review and meta-analysis of randomized clinical trials to evaluate the efficacy of supplementary oxygen for exertion-induced desaturation in pulmonary disorders. RCTs that met predefined inclusion criteria were included. Fifteen studies were included in the analysis. Oxygen supplementation to treat adult exertion-induced desaturation had only been investigated for chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). Oxygen supplementation was superior to placebo for its immediate effect on exercise capacity for COPD (SMD 0.42, 95% CI 0.15–0.69, I2=3%) and IPF (SMD 0.41, 95% CI 0.08–0.75, I2=57%) and exercise dyspnea for COPD (SMD −0.40, 95% CI −0.76–−0.04, I2=31%). The investigators concluded that their stud revealed the efficacy of supplemental oxygen for exertion-induced desaturation and only a positive immediate effect on exercise capacity and dyspnea, but no improvement in other short-term or long-term measures.[684]

[683] Lin L-Y, et al., "Oxygen therapy for exercise capacity in fibrotic interstitial lung disease: A systematic review and meta-analysis of randomised controlled trials," *Respir. Med.* 2024; 227:107657.

[684] Archontakis B, et al., "Supplementary oxygen efficacy for chronic pulmonary disorders and exertion desaturation," *Eur. Respir. J. Open Res.* 2024; 10:00411-2024.

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J. Pulmonary Rehabilitation

763. Pulmonary rehabilitation is "a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health enhancing behaviors."[685]

764. A study of 31 patients with pulmonary fibrosis undergoing a 6-week pulmonary rehabilitation program showed reductions in dyspnea, increased quality of life, and increased performance on the 6-minute walk test. However, only one of the subjects had silicosis, so it is unclear whether the results observed in this study are generalizable to other workers with silicosis.[686]

765. In a study of 263 individuals with occupational respiratory disease, 42 with silicosis showed immediate improvements in the 6 minute walk test and anxiety measures following a 4-week inpatient pulmonary rehabilitation program. However, no acute or long-term improvements in lung function measures or respiratory muscle function were found in those with silicosis. Respiratory infections and health care utilization decreased significantly as a result of the pulmonary rehabilitation program, but there were no improvements in quality of life, anxiety and depression.[687]

766. A study by a researcher from India assessed the effect of pulmonary rehabilitation in agate grinders, an occupation associated with a high prevalence of silicosis. Of 60 patients, 48 subjects were selected based on inclusion and exclusion criteria and divided equally into two groups. Forced vital capacity (FVC) and FEV1/FVC ratio were measured to evaluate lung function and MRC Scale was used to measure dyspnea. Significant improvements were observed following pulmonary rehabilitation. The author of the study concluded it showed that a pulmonary rehabilitation program

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[685] Spruit MA, et al., "ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation," *Am. J. Respir. Crit. Care Med.* 2013; 188(8):e13-64.

[686] Jastrzebski D, et al., "Dyspnea and quality of life in patients with pulmonary fibrosis after six weeks of respiratory rehabilitation," *J. Physiol. Pharmacol.* 2006; 57 Suppl 4:139-148.

[687] Ochmann U, et al., "Long-Term Efficacy of Pulmonary Rehabilitation in Patients with Occupational Respiratory Diseases," *Respiration* 2012; 84:396-405.

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of 4 weeks' duration improves pulmonary function and reduces dyspnea in patients with silicosis.[688]

767. Turkish investigators reported improvement in the 6 minute walk test and hand grip force and strength for two silicosis patients from an 8-week pulmonary rehabilitation program.[689]

768. In 2020, Chinese researchers published a systematic review and meta-analysis of randomized controlled trials of pulmonary rehabilitation for pneumoconiosis. Sixteen randomized controlled trials with 1307 subjects were included for analysis. Compared with routine treatment, pulmonary rehabilitation was able to improve the 6-minute walking distance (mean difference (MD) 69.10, 95% confidence interval (CI) 61.95 - 76.25); the 36-Item Short Form Health Survey total score (MD 17.60, 95% CI 13.59 - 21.61); physical function score (MD 15.45, 95% CI 3.20 - 27.69); role physical score (MD 17.87, 95% CI 12.06 – 23.69); body pain score (MD 14.34, 95% CI 10.33 – 18.36); general health score (MD 20.86, 95% CI 16.87 – 24.84); vitality score (MD 11.66, 95% CI 0.18 - 23.13); social function score (MD 9.67, 95% CI 1.27 - 18.08); mental health score (MD 20.60, 95% CI 13.61-27.59); forced vital capacity (FVC) (MD 0.20, 95% CI 0.12 - 0.29); forced expiratory volume in 1 second (FEV1) (MD 0.23, 95% CI 0.09 - 0.38); FEV1% (MD 5.19, 95% CI 1.48 - 8.90); maximal voluntary ventilation (MD 4.47, 95% CI 1.14 - 7.81); reduction in the St. George's Respiratory Questionnaire score (MD -9.60, 95% CI -16.40 to -2.80); and the modified Medical Research Council Scale score. Pulmonary rehabilitation did not increase the FEV1/FVC (MD 3.61, 95% CI -3.43 to 10.65), nor the emotional score (MD 6.18, 95% CI -23.01 to 35.38) compared with the control. No reports of adverse events associated with pulmonary rehabilitation were found. Based on their results, the investigators concluded that pulmonary rehabilitation can improve functional capacity and quality of life to some extent in patients with pneumoconiosis.[690]

769. In 2023, researchers from Chengdu China reviewed published studies to assess the effective-ness of pulmonary rehabilitation strategies for the treatment of pneumoconiosis. They

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[688] Trivedi SJ, "Effect of Pulmonary Rehabilitation on Functional Capacity of Lungs and Dyspnea in Patient with Silicosis in Anand District of Gujarat," *Indian J. Physiother. Occup. Ther.* 2017; 11(3):207-209.

[689] Aydin R, et al., "Pulmonary Rehabilitation for Silicosis Patients," *Turkish Thoracic J.* 2019; 20:380 [Abstract of presentation at the 22nd Annual Congress of the European Respiratory Society]

[690] Zhao H, et al., "Pulmonary Rehabilitation Can improve the Functional Capacity and Quality of Life for Pneumoconiosis Patients: A Systematic Review and Meta-Analysis," *BioMed Res. Int.* 2020; 6174936.

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found that pneumoconiosis patients are increasingly being treated with a multimodal pulmonary rehabilitation program and that pulmonary rehabilitation interventions are effective in improving respiratory function and quality of life in patients with pneumoconiosis. They concluded that pulmonary rehabilitation interventions could save healthcare costs, reduce dyspnea, improve exercise performance, and enhance overall health-related quality of life in patients with pneumoconiosis.[691]

770. In 2023, Chinese researchers explored the potential intervention effect of physical exercise on silicotic mice. They randomly divided 40 SPF C57BL/6 male mice into four groups, 10 in each group, including a control group, a physical exercise group, a silicosis model group, and a silicosis model + physical exercise intervention group. A silicotic mouse model was established by using 50 μL SiO_2 suspension (200 $mg \cdot L^{-1}$). A treadmill was used to prepare mice receiving physical exercise at 0° inclination, 12.3 $m \cdot min^{-1}$, 60 $min \cdot d^{-1}$, 5 $d \cdot week^{-1}$ for 4 weeks. Pathological morphology of lung tissues was evaluated after hematoxylin-eosin (HE) staining; deposition of collagen in lung tissues was evaluated after Van Gieson (VG) staining; expression of p-protein kinase R-like endoplasmic reticulum kinase (PERK) was detected by immunofluorescence staining; expressions of cyclin dependent kinase inhibitors (p21) and p-p38 mitogen activated protein kinase (p38) were detected by immunohistochemistry. The protein expressions of endoplasmic reticulum stress signal factors [p-inositol-requiring enzyme-1α(p-IRE-1α, p-PERK, and p-eukaryotic initiation factor-2α(p-eIF-2α], senescence signal factors (p-p53, p21, and p16), mitogen-activated protein kinase (MAPK) signal factors [p-p38, p-extracellular regulated protein kinases (p-ERK), and p-stress-activated protein kinase (p-JNK)] were detected by Western blotting. Following SiO2 exposure, the images of micro computed tomography (CT) showed high density shadows in lung tissues of the silicotic mice and less shadows in lung tissues of the physical exercise intervention mice. After HE staining, the proportions of silicotic nodule area in lung tissues was (18.67±.89)% in the silicosis model group, and significantly decreased to (8.78±.05)% in the silicosis model + physical exercise intervention group ($P < 0.05$). After VG staining, the proportion of collagen fiber area of lung tissues was (10.37± .18)% in the silicosis model group, and significantly decreased to

[691] Zhou D, et al., "Pulmonary Rehabilitation Strategies for the Treatment of Pneumoconiosis: A Narrative Review," *Iran J. Public Health* 2023; 52(11):2234-2247.

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(4.35±.89)% in the silicosis model + physical exercise intervention group (P<0.05). The results of immunofluorescence staining showed that in the silicosis model group, expression of p-PERK increased at the location of silicotic nodules, while in the silicotic model + physical exercise intervention group, expression of p-PERK decreased. The immunohistochemical staining results showed that the expression of p21 and p-p38 increased in lung tissues of the silicosis model group; the expression of p21 and p-p38 decreased in lung tissues of the silicosis model + physical exercise intervention group. Results of Western blotting showed that compared with the control group, the expression levels of p-IRE-1α(0.11±.03), p-PERK (0.95±.40), peIF-2α(3.53±.91), p-p53 (1.78±.07), p21 (1.98±.10), p16 (1.26±.17), p-p38 (0.41±.09), p-ERK (0.42±.05), and p-JNK (3.20±.23) of the silicosis model group were all upregulated (P < 0.05). Compared with the silicosis model group, the expression levels of p-IRE-1α(0.03±.01), p-PERK (0.31±.12), p-eIF-2α(0.30±.06), p-p53 (0.76±.08), p21 (0.18±.11), p16 (0.70±.24), p-p38 (0.03±.00), p-ERK (0.19±.03), and p-JNK (0.46±.21) of the silicosis model+physical exercise intervention group were downregulated (P<0.05). The researchers concluded that physical exercise may alleviate pulmonary fibrosis in silicotic mice, and inhibit abnormal expressions of endoplasmic reticulum stress signal, MAPK signal, and senescent signal.[692]

771. In 2023, the same research group evaluated the effects of exercise training and pharmacologic interventions on silicosis pathways in silicotic mice. Exercise training mitigated silicosis progression in mice by suppressing scavenger receptor B (SRB)/NOD-like receptor thermal protein domain associated protein 3 (NLRP3) and Toll-like receptor 4 (TLR4) pathways. Macrophage-derived IL-17A emerged as primary source and trigger for silica-induced pulmonary inflammation and fibrosis. Exercise training effectively inhibited IL-17A-CXC motif chemokine ligand 5 (CXCL5)-Chemokine (C-X-C motif) Receptor 2 (CXCR2) axis in silicotic mice. The investigators concluded that their study evidenced exercise training's potential to reduce collagen deposition, preserve elastic fibers, slow pulmonary fibrosis advancement, and enhance pulmonary function post-silica exposure by impeding the macrophage-derived IL-17A-CXCL5-CXCR2 axis.[693]

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[692] Jin F, et al., "Intervention effect of physical exercise on silicotic mice," *J. Environ. Occup. Med.* 2023; 40(9):997-1004.

[693] Jin F, et al., "Exercise training inhibits macrophage-derived IL-17A-CXCL5-CSCR2 inflammatory axis to attenuate pulmonary fibrosis in mice exposed to silica," *Sci. Total Environ.* 2023; 902:166443.

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772. In 2024, researchers from India published a study of 160 workers exposed to silica working in cement factories. They divided the workers into experimental and control groups, each of 80 workers. Pulmonary parameters, baseline clinical variables, spirometry to check pulmonary function, 6-MWT stress tolerance test, Hemoglobin (HB), Erythrocyte Sedimentation Rate (ESR), Random Blood Sugar (RBS) blood investigations, pranayama (yoga), and nutritional education were done for the experimental group. Supervised pulmonary rehabilitation was carried out, with post-test evaluations after 12, 18, and 24 weeks. The investigators found that pulmonary rehabilitation (pranayama and nutritional education) showed significant improvements in lung capacity and pulmonary functions, with highly significant improvements in improved quality of life ($P < 0.001$).[694]

773. In 2025, Egyptian researchers conducted a randomized controlled trial to evaluate the effect of aerobic exercises compared to respiratory muscle training on lung function in quarry workers exposed to crystalline silica. Patients were randomly allocated to two groups. Group A was given aerobic exercises by engaging in a 30 minute session of walking on a treadmill for eight weeks, three times a week [control group]. Group B was given a respiratory muscle training program using an incentive spirometer, diaphragmatic breathing exercises, lateral costal breathing exercises, and pursed lip breathing exercises in addition to aerobic exercise for eight weeks [study group]. A spirometer was used for a pulmonary function test, which evaluated lung function by measuring Forced Vital Capacity [FVC], Forced Expiratory Volume in one second [FEV1], and the ratio of FEV1 to FVC. Substantial improvements of FVC, FEV1 and FEV1/FVC were found after treatment in both groups values [$P < 0.00001$]. There were significant differences between both groups after treatment regarding FVC, FEV1, and FEV1/FVC, with favored results in Group B. The investigators concluded that their study showed that respiratory muscle training is an essential supplement to aerobic exercise for pulmonary rehabilitation to improve pulmonary function in quarry workers.[695]

774. In a study commissioned by WorkCover Queensland to understand the current state

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[694] Tasrufoon K, et al., "Pulmonary Rehabilitation Effect on Physiological and Biochemical Parameters Occupationally Exposed to Silica Workers: A Quasi-Experimental Study," *Int. J. Nutr. Pharmacol. Neurol. Dis.* 2024; 14:468-471.

[695] Mahmoud TH, et al., "Effect of Respiratory Muscle Training on Lung Function on Quarry Workers in Minia Governorate Egypt," *Egyptian J. Physical Therapy* 2025; 21(1):32-40.

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of knowledge regarding vocational rehabilitation for workers diagnosed with silicosis, researchers from University of Illinois and the Monash University Centre for Occupational and Environmental Health issued a report "recommending that workers with clinical, radiographic, or pathologic findings consistent with silicosis be removed from further exposure to silica dust" and "supported further trials of anti-fibrotic medication, pulmonary rehabilitation and ongoing research."[696]

775. Recently, researchers from India published a study in which they evaluated the effect of pulmonary rehabilitation on physiological and biochemical parameters in workers exposed to silica in cement factories. A total of 160 cement factory workers exposed to silica were divided into experimental and control groups, each of 80 workers. Quality of life (QoL) was assessed using the World Health Organization Quality of Life in Brief (WHO-QoL-BREF) questionnaire along with demographic variables (pre-test). The experimental group underwent spirometry, breathing exercises, and walking exercises 4 days a week for 12 weeks. The QoL was reassessed for the experimental group at 12, 18, and 24 weeks (post-tests 1, 2, and 3). For the control group, reassessment was conducted at 24 weeks (post-test 3). Comparison between the control and experimental groups, pre-test, and post-tests revealed overall significance in WHO-QoLBREF scores across physical, psychological, social, environmental, and total score domains ($P < 0.001$ for all). The comparison of pre-test scores between the control and experimental groups did not reveal significance ($P > 0.05$ for all). Post-test 3 showed significance (P=0.037, <0.001, 0.030, <0.001, and <0.001, respectively). The investigators concluded that their study demonstrated that pulmonary rehabilitation significantly improves the quality of life of occupationally exposed silica workers.[697]

776. In summary, studies of workers exposed to silica and workers diagnosed with silicosis who undergo pulmonary rehabilitation show improvements in the 6-minute walk test and quality of life. Pulmonary rehabilitation therefore appears to be a viable therapy to improve exercise ability and slow progression of disease in silicosis patients, without adverse events or effects being reported.

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[696] Almberg KS, et al., *Silicosis Return to Work review: Return to Work and Vocational Rehabilitation Support for Workers Suffering from Silicosis* (WorkCover Queensland, January 2020).

[697] Tasrufoon K, et al., "Effectiveness of pulmonary rehabilitation using spirometry, and breathing and walking exercises on qualify of life among occupationally exposed silica workers," *Int. J. Nutr. Pharmacol. Neurol. Dis.* 2025; 0:0.

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K. Whole Lung Lavage

777. Large volume whole-lung lavage is often used in early silicosis to improve chest tightness, chest pain, shortness of breath, and other related symptoms.

778. Whole lung lavage (WLL) is the gold standard treatment for pulmonary alveolar proteinosis (PAP), effectively removing the accumulated surfactant material from the alveoli and improving oxygenation.[698] The procedure involves the infusion of large volumes of warmed saline into one lung while ventilating the contralateral lung to facilitate removal of the proteinaceous material.[699] During lavage, cycles of normal saline infusion and degassing were performed until the effluent fluid became clear, indicating adequate removal of pathological material.[700] In cases of acute silicoproteinosis, staged whole lung lavage with veno-venous extracorporeal membrane oxygenation (VV-ECMO) support can be necessary due to periprocedural hypoxemia.[701]

779. The first article regarding whole lung lavage as a treatment for silicosis was published by American researchers in 1982. They described a patient with silicosis and progressive dyspnea on exertion in whom open lung biopsy revealed active chronic inflammation with many macrophages filling alveolar spaces. Because of the extensive involvement by the disease of small air spaces, bilateral whole lung lavage was performed. Particles in the tissue and lavage were analyzed using scanning electron microscopy and energy dispersive X-ray analysis. The dry weight of the material removed was approximately 25 g, of which an estimated 135 mg was silica. The procedure resulted in immediate symptomatic improvement, although pulmonary function in the patient did not change significantly.[702]

780. Whole lung lavage has been reported to slow the decline in lung function and improve

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[698] Sandeep G, et al,. "Fast-Track Extubation in a Patient Undergoing Whole Lung Lavage: A Case Report," *Ann. Card. Anaesth*. 2025; 28:80-83.

[699] Naamany E, et al,. "A novel, rapid, and effective technique for whole lung lavage in patients with pulmonary alveolar proteinosis and silicosis: retrospective study," *BMC Pulmonary Med.* 2025; 25:87.

[700] Naamany, et al., *supra.*

[701] Mittal A, et al., "Treatment of Acute Silicoproteinosis With Whole Lung Lavage: A Case Report," *Respir Med Case Rep.* 2023; 38:101582.

[702] Mason GR, et al., "Treatment of mixed-dust pneumoconiosis with whole lung lavage," *Am. Rev. Respir. Dis.* 1982; 126(6):1102-1107.

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radiological findings in pneumoconiosis patients, indicating a modification in disease progression.[703] WLL treatment in pneumoconiosis has shown to relieve symptoms such as cough and dyspnea, although effects on quality of life remain variable.[704] Fast-track extubation post-WLL requires meticulous ventilatory management, serial blood gas analysis, and point-of-care ultrasound examination to facilitate early removal of mechanical ventilation.[705]

781. A recent study reported significant radiological improvement in patients with artificial stone-associated silicosis that may have better long-term outcomes in terms of symptomatology, functional capacity, lung function, and mortality.[706] "Whole lung lavage (WLL) has been demonstrated to control the symptoms of silicosis and improve the quality of life, particularly in the early stages of the ailment."[707]

782. In 2021, Australian researchers reported their experience of Whole Lung Lavage in 6 workers with artificial stone-associated silicosis. All 6 patients were male with a median age of 37 (25–56) years. All had worked in the artificial stone countertop fabrication industry without adequate dust suppression or personal protective equipment. The median forced expiratory volume in 1 s (FEV1) was 3.88 L (3.18–4.57, 90.5% (75–107)), forced vital capacity (FVC) 4.80 L (3.9–6.46, 95.5% (73–102)), FEV1/FVC 0.82 (0.65–0.90) and diffusing capacity for carbon monoxide (DLCO) 26.0 mL/min/mm Hg (18.0–31.1, 84% (54–99)). All patients underwent bilateral lavage (total of 12 lavages) with a median lavage volume of 26.8 L (15–30.8) per lung. The only complications were radiological pulmonary oedema in the lavaged lung (n=4), vocal cord irritation (n=1) and chest wall soreness (n=3). Whole Lung Lavage led to almost complete resolution of the semi-solid centrilobular nodules which characterize early artificial stone-associated silicosis. There

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[703] Zeng Y, et al,. "The Effectiveness of Whole Lung Lavage in Pneumoconiosis: A Systematic Review and Meta-Analysis," *Occup Environ Med.* 2022; 79(7):500-508.

[704] Sandeep, et al., *supra.*

[705] Sandeep, et al., *supra.*

[706] Li T, et al., "Early Identification, Accurate Diagnosis, and Treatment of Silicosis," *Canadian Respir. J.* 2022: 3769134, citing, Chambers DC, et al., "Radiological outcomes of whole lung lavage for artificial stone-associated silicosis," *Respirology* 2021; 26(5):501–503.

[707] Li R, et al., "From Basic Research to Clinical Practice: Considerations for Treatment Drugs for Silicosis," *Int. J. Molecular Sci.* 2023; 24:8333.

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was no change in areas of reticulation. The investigators concluded that their case series confirmed the feasibility and safety of conducting Whole Lung Lavage in patients with artificial stone-associated silicosis and that their findings suggested significant radiological improvement in workers presenting with early disease characterized by diffuse semi-solid centrilobular ground-glass attenuation nodules.[708]

783. In a prospective observational study of artificial stone silicosis in Australia, eight patients underwent WLL between June 2021 and November 2022. Five participants had an improvement in the International Classification of High Resolution Computed Tomography for Occupational and Environmental Respiratory Diseases (ICOERD) CT scores and reduction in XV regional ventilation distribution pre- and six months post-WLL but no difference in lung function. The investigators concluded that WLL for artificial stone silicosis is safe in an expert center that has experience in performing WLL in this population, and that there may be limited benefit in selected patients.[709]

784. A recent retrospective study evaluated the efficacy of a Whole Lung Lavage (WLL) technique using a cardiopulmonary bypass system for infusing lavage fluid in 52 patients, of whom complete data was available for 33 procedures. Of these, 91% were due to pulmonary alveolar proteinosis and 9% were due to silicosis. Almost half of the patients did not require additional WLL, while 43% needed sequential contralateral WLL. Median operative and mechanical ventilation times were 65 and 118 minutes, respectively. The median length of hospital stay was two days. Although not statistically significant, O2 saturation and a 6-minute walk distance increase were observed after the WLL. The investigators concluded that their WLL technique reduced procedure time while maintaining safety and efficacy for treating pulmonary alveolar proteinosis and silicosis.[710]

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[708] Chambers DC, et al., "Radiologoical outcomes of whole lung lavage for artificial stone-associated silicosis," *Respirology* 2021; 26:501-503.

[709] Barnes H, et al., "Efficacy and safety of a whole lung lavage program for artificial stone silicosis," *J. Thorac. Dis.* 2024; 16(11):7630-7639.

[710] Naamany E., et al., "A novel, rapid, and effective technique for whole lung lavage in patients with pulmonary alveolar proteinosis and silicosis: retrospective study," *BMC Pulm. Med.* 2025; 25:87.

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L. Lung Transplantation

785. Lung transplantation is the only therapeutic treatment for advanced stage silicosis. Since artificial stone silicosis is a rapidly progressive and incurable lung disease that afflicts young men (some of whom who are diagnosed with complicated silicosis with progressive massive fibrosis or acute silicosis with pulmonary alveolar proteinosis as young as their twenties), lung transplantation is the only available treatment for these patients who would otherwise die so young.

786. In 2012, Israeli researchers published a retrospective cohort study in which they systematically assessed an outbreak of silicosis among artificial stone workers referred to their center for lung transplantation. The study included all patients with a diagnosis of silicosis who were referred for evaluation to the National Lung Transplantation Program in Israel from January 1997 through December 2010. The researchers also compared the incidence of lung transplantation due to silicosis in Israel with that of the International Society for Heart and Lung Transplantation registry. During the 14-year study period, 25 patients with silicosis were referred for evaluation, including 10 patients who went on to undergo lung transplantation. All patients were exposed by dry cutting a relatively new, artificial, decorative stone product with high crystalline silica content used primarily for kitchen and bathroom countertops. The patients had moderate-to-severe restrictive lung disease. Two patients developed progressive massive fibrosis; none manifested acute silicosis (silicoproteinosis). Three patients died during follow-up, without lung transplantation. Based on the ISHLT registry incidence, 0.68 silicosis cases would have been expected instead of the 10 observed (incidence ratio 14.6, 95% CI 7.02 - 26.8). The researchers noted that their study revealed an unusually high incidence of advanced, life-threatening silicosis linked to a specific, relatively new, engineered product with a high silica content. They concluded that a cause-and-effect relationship was supported by the extraordinary case incidence observed over a short period linked to a single exposure scenario – a nearly 15-fold increase in the expected transplant rate for this condition.[711]

787. In 2017, Israeli researchers published a study in which they analyzed the survival

[711] Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-242. The article was originally titled "Caesarstone Silicosis," but the journal editors changed the titled to "Artificial Stone Silicosis," after Caesarstone's lawyers threatened to sue the American College of Chest Physicians, the publisher of the journal, for trademark infringement].

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experience of artificial stone silicosis patients following lung transplantation. They reviewed data for all patients who underwent lung transplantation for silicosis and a matched group undergoing lung transplantation for idiopathic pulmonary fibrosis at a the Israeli lung transplant center between March 2006 and the end of December 2013. Survival was followed through 2015. A total of 17 lung transplants were performed for silicosis among 342 lung transplants (4.9%) during the study period. They observed a non-statistically significant survival advantage (hazard ratio 0.6; 95%CI 0.24–1.55) for those undergoing lung transplantation for silicosis relative to idiopathic pulmonary fibrosis patients undergoing lung transplantation during the same period.[712]

788. In 2024, Taiwanese researchers published a case report of a 43-yr-old man who developed severe silicosis due to his work cutting and polishing artificial stone materials. A retrospective analysis of the patient's medical records and occupational history was conducted. The diagnosis of severe silicosis, moderate restrictive lung disease, and bilateral pneumothorax was based on clinical manifestations, pulmonary function test, radiological findings, and histological reports. The patient underwent lung transplantation; his pulmonary function improved post-surgery.[713]

789. In 2024, Israeli researchers published a study in which they assessed survival outcomes in artificial stone silicosis patients undergoing lung transplantation in which they compared outcomes for single and double lung transplantation. They identified all patients who underwent lung transplantation for silicosis at the Israeli lung transplant center between March 2006 and June 2023. Thirty-nine lung transplantations were performed for silicosis during the study period. They observed no significant difference in survival for those who underwent double lung transplantation compared to single lung transplantation. Additionally, the two groups had no significant disparities in pulmonary function test results at one- and three years post-transplant. However, double lung transplant recipients experienced a more challenging surgical course due to adhesions and difficulty

[712] Rosengarten D, et al., "Survival Following Lung Transplantation for Artificial Stone Silicosis Relative to Idiopathic Pulmonary Fibrosis," *Am. J. Ind. Med.* 2017; 60:248-254.

[713] Hsu S-C, et al., "Successful lung transplantation for artificial stone-associated accelerated silicosis: a case report," *Ind. Health* 2024; 62:209-214.

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in explanation, resulting in a significantly higher volume of blood products and longer ischemic times. The investigators concluded that given the intricate surgical procedure required for transplanting lungs in cases of silicosis, longer ischemic times, increased need for blood products, and the absence of definitive evidence supporting double lung transplantation in this population, it might be prudent to contemplate prioritizing single lung transplantation for these patients.[714]

790. In 2025, American researchers published a study comparing outcomes for silicosis and non-silicosis interstitial lung disease patients who received lung transplants at UC San Diego. They identified 7 patients with silicosis and 69 with non-silicosis interstitial lung disease who underwent double lung transplantation at UC San Diego from 2019-2023. They compared pretransplant, perioperative, and 1-year post- transplant outcomes between groups. Recipients with silicosis were younger than those with non-silicosis ILD (43.1 ± 9.9 vs 59.3 ± 7.1 years; $p < 0.001$). All 7 patients with silicosis were male, and 6 reported Hispanic/Latino ethnicity. All silicosis patients reported employment in the countertop industry using engineered stone products. Before transplant, patients with silicosis had significantly lower mean percent predicted (PP) forced expiratory volume in 1 second (24.3 PP vs 46.6 PP; $p < 0.001$) and forced vital capacity (28.7 PP vs 43.3 PP; $p < 0.01$) than patients with non-silicosis interstitial lung diseases. Though ischemic times were greater for silicosis recipients, perioperative complication rates were similar. At 1-year post-transplant, there were no differences in survival, allograft rejection rates, or pulmonary function tests. The investigators concluded that lung transplantation should be considered as a therapeutic option for patients with end-stage silicosis from exposure to engineered stone.[715]

791. As of December 19, the California Department of Public Health has reported that 47 engineered stone workers in California underwent lung transplantation, another 38 have been referred for lung transplant evaluation, and 16 have been found ineligible for lung transplantation.[716]

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[714] Dotan M, et al., "Survival Analysis and Surgical Considerations in Lung Transplantation for Silicosis: Single vs. Double Lung Transplants," *J. Heart Lung Transplant.* 2024; 43:S654 [Abstract No. 1425].

[715] Robinson R, et al., "One-year lung transplantation outcomes for engineered stone countertop workers with silicosis at a single center in Southern California, 2019 to 2023," *J. Heart Lung Transpl. Open* 2025; 9:100280.

[716] California Department of Public Health, "Engineered Stone (ES) Silicosis Surveillance Dashboard," December 19, 2025, at https://www.cdph.ca.gov/Programs/CCDPHP/DEODC/OHB/Pages/essdashboard.aspx.

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VIII. CLASS ALLEGATIONS

792. This action is brought by Plaintiffs, Ismael Pedro Calderon Rodriguez, Eleodoro Calixto Rodriguez, Otoniel Ramirez Escobar, Mario Sanchez Cano, and Rogeiro Torres, on their own behalf and on behalf of all other persons similarly situated, pursuant to Rule 23 of the Federal Rules of Civil Procedure for medical monitoring and other relief.

793. The Class represented by Plaintiffs, Ismael Pedro Calderon Rodriguez, Eleodoro Calixto Rodriguez, Otoniel Ramirez Escobar, Mario Sanchez Cano, and Rogeiro Torres, consists of all persons (1) who have not been diagnosed with any disease attributed to respiratory exposure to crystalline silica, (2) who worked in the State of California for at least 30 days from January 1, 2000 to December 31, 2025, (3) during which time period they cut, fabricated, polished, and/or installed artificial stone products (4) that were manufactured, imported, distributed, or sold by Defendants.

794. In 2023 the Occupational Health Branch of the California Department of Public Health, Occupational Safety and Health Administration (Cal-OSHA), identified 841 stone countertop fabrication shops which employ 4,955 shop-floor workers, not including managers and clerical staff. Assuming a prevalence rate for silicosis among these workers of just 12% to 21%, Cal-OSHA estimated that about 600 to 1000 cases of silicosis will likely occur among these 4,955 workers and about 100 to 200 of these workers will likely die of silicosis. Of these 4,955 workers thus far about 150 have been diagnosed with silicosis, such that the class consists of approximately 4,800 workers.

795. Common questions of law and fact predominate in this action that relate to and affect the rights of each member of the Class and the relief sought, for example, that Plaintiffs were exposed to respirable crystalline silica from cutting, fabricating, and/or polishing the artificial stone slabs that were manufactured, imported, distributed and/or sold in California, such that Plaintiffs require medical monitoring to detect the development of silicosis and other silica-related diseases, including, but not limited to, lung cancer, chronic kidney disease, and autoimmune diseases including, but not limited to, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus, connective tissue disease, psoriatic arthritis, ankylosing spondylitis, dermatomyositis, polymyositis, and antineutrophil cytoplasmic antibody-positive vasculitis.

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796. Having fabricated artificial stone slab products and or having installed finished countertops fabricated from artificial stone products for more than 30 days, the representative plaintiffs and all of the class members are at a significantly increased risk of developing silica-related diseases, including, but not limited to, silicosis, lung cancer, chronic kidney disease, and autoimmune diseases including, but not limited to, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, systemic lupus erythematosus, connective tissue disease, psoriatic arthritis, ankylosing spondylitis, dermatomyositis, polymyositis, and antineutrophil cytoplasmic antibody-positive vasculitis.

797. As a result of their occupational exposure to respirable crystalline silica and their significantly increased risk of silicosis, lung cancer, chronic kidney disease and autoimmune diseases, all members of the class require medical monitoring to detect the development of silicosis and such other silica-related diseases so that they may obtain prompt medical treatment for such diseases before they become irreversible, incurable, or untreatable, thereby resulting in death.

798. A fund to provide regular periodic medical monitoring for Plaintiffs to detect the onset of silica-related diseases in this population of workers who have extremely high risks of developing silica-related diseases and lack access to medical diagnostic procedures and medical care is essential for the health and well-being of Plaintiffs whose health has been severely jeopardized by Defendants' lethal artificial stone products.

799. The claims of the representative plaintiffs are typical of the claims of the class in that the claims of all members of the class, including the named plaintiffs, depend on a showing of the acts and omissions of defendants upon which liability is based.

800. The representative plaintiffs can and will fairly and adequately protect the interests of the class.

801. The questions of law and fact common to the members of the class predominate over questions affecting individual class members. A class action is superior to other available methods for the fair and efficient adjudication of this controversy. Moreover, in order for plaintiffs to proceed against defendants in an economical manner, and to prevent the massive duplication of

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discovery and other similar proceedings which would occur if there were a multiplicity of actions, plaintiffs seek the benefits of Rule 23 of the Federal Rules of Civil Procedure.

IX. ARTIFICIAL STONE DEFENDANTS

802. The following companies that are Defendants in this case all manufactured, imported, distributed, supplied and/or sold artificial stone products containing approximately 95% crystalline silica to which Plaintiffs were exposed in the State of California as hereinabove alleged.

A. Architectural Surfaces Group, LLC

803. ARCHITECTURAL SURFACES GROUP, LLC, is a Delaware limited liability company, which, at all material times hereto, has had its principal place of business at19012 State Highway 71 West, Spicewood, Texas 78669 and has the following alternate entities: PENTAL GRANITE AND MARBLE, LCC; PENTAL SURFACES, ARCHITECTURAL GRANITE AND MARBLE, LCC, CERAMIC MATRIX, AND MODUL MARBLE.

804. On November 10, 2015, Architectural Granite & Marble, LLC, a Delaware limited liability company, filed an Application to Register a Foreign Limited Liability Company to conduct business in the State of California with the California Secretary of State.

805. On July 12, 2017, an article published in *Stone Update* titled "Architectural Surfaces Group New Parent Company of Three Brands" announced: "The consolidated company comprised of Architectural Granite & Marble (AG&M), Pental Surfaces and Modul Marble now have a new joint parent name: Architectural Surfaces Group (ASG). . . . Each business will continue to operate under its respective brands that are recognized as marketplace leaders."

806. On February 16, 2018, a press release appeared in Business Wire, announcing the acquisition by Architectural Surfaces Group's Select Interior Concepts of Bedrock International, a natural stone distributor in the Midwest. [https://www.businesswire.com/news/home/20180215005728/en/Architectural-Surfaces-Group-Announces-Acquisition-of-Bedrock-International]

807. On October 21, 2021, Sun Capital Partners, Inc., a private equity fund, issued a press release announcing the acquisition by an affiliate of the company (presumably Architectural Surfaces) of Select Interior Concepts, a premier distributor of interior building products. [https://arcsurfaces.com/select-interior-concepts-acquired-by-affiliate-of-sun-capital-partners/]

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808. On November 5, 2021, Architectural Surfaces issued a press release on PR Newswire, announcing the acquisition of Ceramic Matrix, a Florida-based distributor of stone slabs. The press release stated: "The partnership will allow Ceramic Matrix to offer customers the same great products and service along with additional resources including access to more natural stone, and an established quartz product line with the ability to expand across existing facilities."

809. On March 10, 2022, Architectural Surfaces issued a press release on EIN Presswire, announcing acquisition of two companies in the Dallas, Texas market: Stone Boutique and Allure. [https://www.einpresswire.com/article/565202793/architectural-surfaces-acquires-stone-boutique-and-allure]

810. On April 1, 2022, the company issued a press release on EIN Presswire, announcing the acquisition of ARC Natural Surfaces in Virginia Beach and Ashland, Virginia. [https://arcsurfaces.com/architectural-surfaces-acquires-arc-natural-surfaces/]

811. On May 17, 2022, the company filed an amendment with the California Secretary of State whereby it changed its name from Architectural Granite & Marble, LLC to Architectural Surfaces Group, LLC.

812. On May 3, 2022, Architectural Surfaces announced the acquisition of Pacifica Wholesale Tile and Stone in Anaheim, California. The announcement stated: "Pacifica is a premier source for distinctive stone slab and tile products for the Southern California market. From their expansive showroom and warehouse located in central Anaheim, they focus on exceptional customer service and superior product quality. Ranging from masterfully crafted porcelain to stunning natural stone quarried from around the world, Pacifica offers an extensive selection to fit all unique specifications." The announcement quoted Architectural Surfaces' CEO Patrick Dussinger as saying: "We're excited to combine our buying power, product offering, and operational synergies with Pacifica's deep local industry expertise."

813. On January 17, 2023, a Certificate of Merger was filed with the California Secretary of State, whereby Da Vinci Marble, LLC a California limited liability company, merged into Architectural Surfaces Group, LLC.

814. The Architectural Surfaces website states: "Quartz countertops are a great choice for

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any application in the home due to their low-maintenance, long-lasting appeal and many design possibilities. Both PentalQuartz® and MetroQuartz® are leading quartz brands, providing quality choice and variety to customers nationwide." The website has a map of the United States, showing that it offers PentalQuartz for sale in the western states, Alaska, and the Northeastern states, west and northeast, and offers MetroQuartz for sale in the rest of the country.

1. Knowledge of the Silicosis Hazard

815. Jesse Bogan is currently the Chief Operating Officer of Architectural Surfaces Group, LLC. He began working for the company in Texas in May of 2006, at which time the company was called Architectural Granite and Marble. At a deposition that Mr. Bogan gave on May 2, 2024 in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs,* Los Angeles Superior Court Case No. 22STCV31907, he testified that Architectural Surfaces Group, LLC is a distributor of natural and artificial stone slabs that are primarily used in kitchens and bathrooms, and that the company also distributes tile.

816. Mr. Bogan also testified that the company was the exclusive distributor of Vicostone artificial stone slabs in California from 2012 to 2022. He further testified that Architectural Surfaces Group, LLC has also distributed artificial stone manufactured by various companies under the MetroQuartz brand -- Polarstone, Herostone, Technistone, Quantra, Mahi, Prism Johnson, Camrrola, Global Surfaces, pacific Quartz, Tab India, Arider, Santa Margherita, Top Quartz, Compaq, LE Surfaces, Guidoni, Vickers, Belanco, Kwontae, and Costla.

817. At his deposition of May 2, 2024, given in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs,* Los Angeles Superior Court Case No. 22STCV31907, Mr. Bogan testified since 2006, when he began working in the stone slab distribution business, he has known that stone products distributed by the company contain levels of crystalline silica and that exposure to crystalline silica can cause silicosis and pulmonary fibrosis, but this was not disclosed in Safety Data Sheets. He also testified that the first time that labels about silicosis were put on the slabs was in 2018, at which time they were put on the back of the slabs.

818. Although Architectural Surfaces Group and the companies it acquired have long

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known of the hazard to workers who fabricate stone countertops, it was not until 2023 that a warning of the hazard of silicosis to fabricators was posted on Architectural Surfaces' website. [https://arcsurfaces.com/wp-content/uploads/Arc-Silica-Warning-English-Spanish-PDF.pdf]

819. Although Architectural Surfaces Group has long known of the hazard to workers who fabricate stone countertops from slabs of artificial stone, as of the Fall of 2023, only one Material Safety Data Sheet for an artificial stone product was provided on the company's website – an outdated Material Safety Data Sheet (MSDS) for Metro Quartz™ that provided false and misleading information. The Hazards Identification section of this MSDS dated December 10, 2013 states regarding the "Potential Health Effects" of Metro Quartz™: "Quartz surface products are not hazardous as shipped." This language is misleading because it intentionally and wrongfully suggests that (1) the health hazards associated with crystalline silica are merely "potential" rather than well known and actual, and (2) the product presents health hazards, which is false. The falsity of this information is compounded by the information in this section of the MSDS regarding the hazards of "Acute Inhalation," which states: "Dusts from product may cause irritation to respiratory tract, nose, throat and lungs." This language is misleading, because it trivializes the hazard of acute inhalation by indicating that the only hazard of acute inhalation is "irritation to the respiratory tract" - a transitory effect that is common to most inhaled substances (e.g., the respiratory irritation that one experiences when cutting an onion) – even though acute inhalation of dust of the product causes an acute lung disease called "acute silicosis" that is characterized by pulmonary alveolar proteinosis and a lung disease called "accelerated silicosis" that is characterized by progressive massive fibrosis. This MSDS also fails to provide information that is necessary to protect workers from developing silicosis from fabricating the product. Thus, MSDS states that one should "avoid breathing dust," but states that "in case of insufficient ventilation, wear appropriate respiratory equipment," an instruction that is harmful, because regardless of the sufficiency of ventilation, to prevent silicosis respiratory protection is always necessary and the only type of respiratory protection that can prevent silicosis from exposure to the product is an air-supplied respirator, which is not disclosed on the MSDS. Additionally, the MSDS states that "[g]eneral room ventilation is satisfactory under anticipated use conditions," which is a false statement and a prescription for causing disease and

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death, because general room ventilation is never adequate to protect against crystalline silica dust. Information in the Toxicological Information section of the MSDS is also false and misleading, because it states that "[p]rolonged and/or massive inhalation of crystalline silica can cause pulmonary fibrosis and pneumoconiosis and silicosis," although "prolonged" and "massive" inhalation of crystalline silica are not necessary to cause these effects, which can and do occur from exposure to extremely small amounts of crystalline silica particles that so tiny they are invisible to the human eye and the effects can occur after brief periods of exposure of a few years or less, rather than decades. The information in this outdated MSDS of a product that is not even sold in the western states and is the only MSDS available on the Architectural Surfaces website is not merely inadequate; the information in this document is a prescription for causing silicosis.

820. Plaintiff is informed and believes and thereon alleges that the false and misleading statements on the Architectural Surfaces website were approved and ratified by officers, directors and managing agents of Architectural Surfaces Group and the companies that it acquired over the years, including, but not limited to the following officers of the company: Dave Bushland, Chief Executive Officer; Scott Jarvis, Chief Administrative Officer; Lance D. Brown, Chief Financial Officer; Everett Plante, Chief Information and Digital Officer; Cindi Grace, Vice President of Sales Operations; Jesse Bogan, Regional Vice President, Western Region; Gary Arney, Regional Vice President, Central Region; and Joyce Beshada, Regional Vice President, Eastern Region.

821. PENTAL GRANITE AND MARBLE, LCC and PENTAL SURFACES, products consist of tile and slabs made of natural stone, ceramic, glass, metal, porcelain, terrazzo, and quartz. (Affidavit of Parminder Singh Pental dated March 13, 2012, Docket No. 8 in *Cambria Company, LLC v. Pental Granite & Marble, Inc.* et al., United States District Court, D. Minn., Civil No. 12-228, March 27, 2013, 2013 WL1249216).

822. Some of the products sold by Pental were manufactured by Vicostone, a Vietnamese corporation. (Second Declaration of Parminder Singh Pental dated May 8, 2012, Docket No. 29 in *Cambria Company, LLC v. Pental Granite & Marble, Inc.* et al., United States District Court, D. Minn., Civil No. 12-228, March 27, 2013, 2013 WL1249216).

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2. Pental Quartz's 2015 Safety Data Sheet

823. At some point in time, Architectural Surfaces Group posted a Safety Data Sheet for Vicostone Quartz Surfaces (also known as PentalQuartz in North America) that was dated May 5, 2015. Section 3 of the Safety Data Sheet (Composition/information on ingredients) identifies three ingredients in the product: Crystalline Silica (quartz) (~90%), Polymeric resin (7-12%), and Pigment and Trace Minerals (~2%).

824. Section 2 of the Safety Data Sheet (Hazard(s) identification) states: "VICOSTONE® Quartz Surfaces are safe for delivery, storage and use as certified by GREENGUARD for indoor air quality, children and schools and by NSF for food safety (ANSI 051). However, operations such as sawing, drilling, grinding, sanding and routing can generate silica dust. The fine dust of quartz (silicon dioxide) containing crystalline silica can cause potential health effects." These statements are misleading, because the product supplied is not a finished product that is sold to schools or consumers. Rather, the product is a slab of artificial stone, an industrial product that is sold to countertop fabrication companies that fabricate the slab into a countertop that is sold to consumers. It is the finished countertops that are safe for children and for schools - not the industrial product. The statement that "operations such as sawing, drilling, grinding, sanding and routing can generate silica dust" is also misleading, because the statement suggests that these operations do not necessarily generated silica dust, although they invariably generate high concentrations of respirable crystalline silica dust. Further, the fine crystalline silica dust generated by fabrication processes is not such as merely "can cause potential health effects;" those operations ***do*** cause ***real*** health effects, including silicosis, chronic obstructive pulmonary disease, lung cancer, chronic kidney disease, and several autoimmune diseases. Thus, the statement in the Safety Data Sheet minimizes these hazards.

825. Section 2 of the Safety Data Sheet provides the following statements regarding Chronic Exposure: "Prolonged exposure to respirable crystalline silica can cause silicosis and has been linked to other diseases, such as lung cancer, tuberculosis, fibrosis of the lungs, chronic obstructive pulmonary disease and kidney disease." The statement that "prolonged exposure to respirable crystalline silica can cause silicosis" is misleading, because it does not state how many days, weeks, months, years, or decades of exposure to crystalline constitutes the "prolonged

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exposure" that can cause silicosis. The statement is also misleading, because exposure to artificial stone dust typically causes accelerated silicosis within 5-10 years of exposure or acute silicosis within 1-5 years of exposure, which are relatively short durations of occupational exposure.

826. Section 8 of the Safety Data Sheet, titled "Exposure controls/personal protection," provides the following information regarding Respiratory Protection: "Respirators may protect workers from inhaling crystalline silica dust when carefully and properly selected, worn and used. Use only respiratory protection authorized in the U.S. Federal OSHA Standard (29 CFR 1910.134), applicable U.S. State regulations, or the Canadian CSA Standard Z94.4-93 and applicable standards of Canadian Provinces." This statement is inadequate, because it does not inform workers that the only type of respirator that will protect them from inhaling crystalline dust when fabricating artificial stone products is a NIOSH-approved air supply respirator. By failing to provide this critical safety information, the Safety Data Sheet misleads workers to believe that a NIOSH-approved air purifying respirator will adequately protect them. However, studies have shown that air-purifying respirators are inadequate to prevent silicosis from the fabrication of artificial stone because of its extremely high crystalline silica content. The statement is therefore inadequate, misleading and thus harmful.

827. Section 11 of the Safety Data Sheet, regarding Toxicological information, provides three statements regarding chronic effects of exposure: The first statement is: "Prolonged and/or massive inhalation of crystalline silica can cause pulmonary fibrosis and pneumoconiosis and silicosis, as well as a worsening of other pulmonary diseases (bronchitis, emphysema, etc)." This statement is misleading, because it is not only "prolonged" or "massive" inhalation of crystalline silica that causes silicosis and other lung diseases. Studies have shown that exposure to artificial stone dust either causes accelerated silicosis within 5-10 years of exposure or acute silicosis within just 1-5 years of exposure. Studies have also shown that tiny amounts of crystalline silica where exposures are below the permissible exposure limit also cause silicosis. Thus, the statement that "prolonged and/or massive inhalation of crystalline silica can cause pulmonary fibrosis and pneumoconiosis and silicosis" is misleading because workers can also get silicosis from relatively short and low-level exposure to crystalline silica from fabricating artificial stone.

828. The second statement regarding chronic effects of exposure is: "The main symptom

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of silicosis is the loss of pulmonary capacity." The second statement is also misleading and incorrect, because loss of pulmonary capacity is not a symptom of silicosis, but is rather an adverse effect of the disease. The main symptoms of silicosis are shortness of breath after exercise, chest pain, a harsh dry cough and fatigue - not loss of pulmonary capacity. Indeed, it is not until workers have lost about half of their lung function that they begin to have symptoms, at which point the worker has advanced disease that is irreversible and progresses even after silica exposure ceases.

The third statement regarding chronic effects of exposure is: "People with silicosis have a greater risk of getting lung cancer." Although true, this statement is misleading, because it suggests that silicosis causes cancer. However, silicosis does not cause cancer; it is exposure to respirable crystalline silica that causes cancer. Persons who have been diagnosed with silicosis typically have had a greater cumulative exposure to crystalline silica than do persons who have not been diagnosed with silicosis, so persons who have silicosis have an increased risk of developing lung cancer because of their greater exposure to crystalline silica.

829. Thus, all three statements regarding the effects of chronic exposure to the product are incorrect and misleading, and are therefore potentially harmful to workers exposed to the product.

3. Knowledge of the Silicosis Hazard by Pental's Managers and Members

830. Throughout the time that Pental Granite & Marble LLC sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, Pental's managers were aware that the company's artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that Pental provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by Pental's defective artificial stone products. Among Pental's managers and members who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers is Parminder "Peter" Pental, the Founder and Chief Executive Officer of Pental Granite & Marble, LLC.

831. Throughout the time that Architectural Granite & Marble LLC sold its artificial stone

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products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, its managers and members were aware that its artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that it provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by its defective artificial stone products. Among Architectural Granite & Marble LLC's managers and members who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers were:

Dave Bushland, Chief Executive Officer;

Scott Jarvis, Chief Administrative Officer;

Lance D. Brown, Chief Financial Officer;

Everett Plante, Chief Information and Digital Officer;

Cindi Grace, Vice President of Sales Operations;

Jesse Bogan, Regional Vice President, Western Region;

Gary Arney, Regional Vice President, Central Region; and

Joyce Beshada, Regional Vice President, Eastern Region.

832. More recently, the Architectural Surfaces LLC managers and members who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers were:

Jesse Bogan

Bill Varner

Nadeem Moiz

Shawn K. Baldwin.

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B. Arizona Tile, L.L.C.

833. According to its website, Defendant, "Arizona Tile has become one of the leading tile and slab distributors in the U.S.," with its products being "distributed to residential and commercial customers throughout the Western United States." According to the company's website, "John Huarte, CEO and Owner of Arizona Tile, founded the company in 1977. Beginning with a small store in San Diego, California, the company has since grown to have locations in 10 western states." Arizona Tile sells natural stone and artificial stone at its facilities in the following California cities: Anaheim, Livermore, Miramar, Murrieta, Ontario, Palm Desert, Roseville, and Sun Valley.

834. On its Linked-In webpage, Arizona Tile states: "Since we have been in the stone and tile business for over 45 years, our relationships with quarries and factories allow us to be at the forefront of new product developments. This has led to our importing of more than 300 varieties of granite, marble, quartzite, limestone and travertine slabs and stone tile. In addition, we stock over 60 series of porcelain, ceramic and glass tile and over 65 colors of Della Terra® Quartz, making us one of the largest independently-owned importers of stone, quartz and tile in the United States."

835. On June 19, 2006, Arizona Tile opened a new location in Roseville, California. This facility comprises more than 60,000 square feet and included a stone slab warehouse, a tile warehouse, and a showroom. Among the company's products on display at the showroom were granite, travertine, slate, marble, porcelain and ceramic. Additionally, more than 130 varieties of granite, marble, limestone, travertine and onyx were to be found in the slab warehouse. See, "Arizona Tile Opens New facility in California," *Stone World* (October 12, 2006).

836. On October 4, 2011, a news report from La Mirada, California, titled "Arizona Tile Adds Radianz™," appeared in Stone Update, the 24/7 Hard-Surface News Portal. This report announced: "Arizona Tile is the newest authorized distributor for Samsung's Radianz™ quartz surfaces. Arizona Tile's distribution channel includes Arizona, California, Nevada and Texas. The agreement comes a month after Samsung's decorative surfacing products division announced its partnership with Triton Stone Group to cover the Southeast region. 'Partnering with Arizona Tile demonstrates our commitment to bring Radianz Quartz products to market through first-quality distributors,' said Dale Mandell, Samsung's surfacing division's North American sales director."

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837. On January 29, 2018, an article was published in *Stone World* titled "Arizona Tile Introduces Della Terra Quartz." This article stated: "Made from one of the hardest minerals on earth, quartz is one of the most durable countertop surfaces. Because it's comprised of a mixture of quartz and resin, Della Terra Quartz boasts the ease of maintenance of a man-made product, while still having the natural look and edging options of natural stone slabs." Thus, in 2018 Arizona Tile expanded its business to sell slabs of this artificial stone product, as well as Radianz Quartz and other artificial stone products that Arizona was importing.

1. Arizona Tile's 2018 Safety Data Sheet

838. In March 2018, Arizona Tile issued a Safety Data Sheet for its "Engineered Stone - Quartz" product whose "Common Name" Arizona Tile stated was "Quartz" and that the "for purposes of this SDS, the term "Quartz" encompasses all types of engineered quartz stone products sourced/ imported by Arizona Tile, LLC."

839. In the "Hazards Identification" section of its March 2018 Safety Data Sheet, Arizona Tile stated that its products "are mixtures of ... naturally occurring minerals" that "pose no immediate hazard to health," and that its "quartz products are not hazardous as shipped and used by the end user." This statement was false and misleading, because all the artificial stone products that Arizona Tile imported contained extremely high concentrations of crystalline silica, and the slabs of artificial stone products that Arizona Tile sold were not finished products ready for use by consumers, but were instead unfinished industrial products typically sold to industrial companies, i.e., artificial stone slabs that required substantial processing to become finished countertops and, when used as intended and expected, presented extreme health hazards to the workers who performed such work on behalf of the industrial companies to whom they were sold.

840. In the Hazards Identification section of its March 2018 Safety Data Sheet, Arizona Tile stated: "Fabrication and processing of engineered stone (i.e. cutting, saying, grinding, breaking, crushing, drilling, sanding or scultping) will generate dust that can expose you to crystalline silica (quartz)" and that "[u]nprotected and uncontrolled exposure to such dust is dangerous to health and

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can cause severe illness such a [sic] silicosis, lung cancer, fibrosis of the lungs, tuberculosis, kidney disease, abrasions of the cornea and irritation of the skin and eyes. Quartz products are not hazardous as shipped and used by the end user." This statement was false, misleading and confusing for several reasons: First, workers who fabricate artificial stone ***are*** always exposed to crystalline silica dust, so it is misleading to merely state that dust "can expose" them to crystalline silica. More importantly, the statement is false because even "protected and controlled exposure to such dust" causes silicosis in artificial stone fabricators, because multiple published and peer-reviewed studies have shown that even artificial stone fabricators who use wet processing methods and wear air purifying respirators are nevertheless exposed to dangerous levels of respirable crystalline silica and develop and die from silicosis. Lastly, the concluding statement that "quartz products are not hazardous as shipped and used by the end user," is misleading and confusing, because these slabs of stone are not finished products and are "used" by fabrication companies and fabricators and installers to produce finished countertops, so the workers are the end users of the product, rather than consumers in whose homes finished countertops are installed.

841. In the Hazards Identification section of its March 2018 Safety Data Sheet, Arizona Tile provided five "Precautionary Statements" - none of which were to wear any respirators: (1) "Do not handle until all safety precautions have been read and understood," (as though Plaintiff, who neither speaks nor reads English could possibly read and understand the "safety precautions"), (2) "Do not breathe dust/spray" (as though Plaintiff should hold his breath throughout the work day), (3) "Wash skin thoroughly after handling" (although the products do not present appreciable health hazards by skin absorption) (4) "Do not eat, drink or smoke when using this product" (although the products do not present any significant health hazards by ingestion); and (5) "Wear protective gloves, protective clothing, eye protection, face protection," (rather than the critical information that it is essential to wear an air supplied respirator when fabricating and/or installing Defendant's products).

842. In Section 7 of its March 2018 Safety Data Sheet, regarding Handling and Storage, Arizona Tile directed workers to "use respiratory protection in the absence of effective engineering controls," without specifying the type of respiratory protection necessary to prevent silicosis and without specifying what engineering controls are effective. This was a dangerous instruction that

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would cause silicosis, because workers could not know whether engineering controls were effective and they would assume that wearing an air-purifying respirator would protect them from silicosis. By merely prescribing workers to "use respiratory protection," Arizona Tile concealed from workers the particular type of respiratory protection (an air supplied respirator) necessary to prevent silicosis.

843. In Section 8.2 of its March 2018 Safety Data Sheet, regarding Exposure Controls/ Personal Protection, Arizona Tile provided the following ventilation instruction: "Use adequate ventilation to keep dust below recommended exposure levels." This is an inadequate use instruction, because Arizona Tile did not specify what ventilation devices and systems were needed to do this, without specifying the exposure levels that cause silicosis, and without specifying how dust could be kept below such unspecified exposure levels, especially when installing countertops in the kitchens and bathrooms of customers where no special ventilation systems could be installed.

844. In Section 8.2 of its March 2018 Safety Data Sheet, regarding Exposure Controls/ Personal Protection, Arizona Tile provided the following ventilation instruction: "Avoid inhalation of dust." However, Arizona Tile did not explain how fabricators and installers could avoid inhaling dust from the artificial stone products that it sold, i.e., whether workers should try to hold their breath to avoid inhaling dust, which workers could not do and it would dangerous for them to attempt to do for a work shift. Most critically, Arizona Tile did not inform workers that the only way that they could avoid inhaling dust of the product was to wear independent air supply respirators, which Arizona Tile did not advise was necessary to protect workers from harm.

845. In Section 8.2 of its March 2018 Safety Data Sheet, regarding Exposure Controls/ Personal Protection, Arizona Tile provided the following information regarding Respiratory Protection: "Use of a properly fitted NIOSH/MSHA approved particulate respirator is recommended when cutting engineered stone products for installation." This was an inadequate and dangerous instruction that was inadequate to prevent silicosis, because there are innumerable NIOSH/MSHA approved particulate respirators, i.e., air-purifying respirators, but wearing an air-purifying respirator is inadequate to prevent silicosis from artificial stone products, the only type of NIOSH-approved respirator that is adequate to prevent silicosis from artificial stone products being a NIOSH-approved air-supplied respirator. By recommending the use of a NIOSH-approved respirator without

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specifying that the respirator had to be a NIOSH-approved air-supplied respirator, Arizona Tile endangered workers who wore NIOSH-approved air-purifying particulate respirators, believing that such respirators would protect them from silicosis and other harms caused by crystalline silica. In Section 11 of its March 2018 Safety Data Sheet, regarding Toxicological Information, Arizona Tile provided the following statement regarding Chronic Effects of exposure: "No chronic effects are known for exposure to intact engineered stone products" (emphasis in original) even though the major health effects of exposure to Defendants' products are chronic health effects such as silicosis and lung cancer. This statement was therefore misleading and confusing. The next sentence in the Safety Data Sheet said: "Long-term, continual exposure to respirable crystalline silica at or above established permissible occupational exposure limits may lead to the development of silicosis, a nodular pulmonary fibrosis (NPF)." This statement was also false and misleading for a number of reasons. First, workers could not know whether in doing their work they were being exposed to crystalline silica at or above established permissible occupational exposure limits. Second, the statement that only "long-term, continual exposure to respirable crystalline silica" is vague and confusing, because "long-term exposure" and "continual exposure" are not quantified, so workers could believe that they could not get silicosis unless they were exposed to dust from the product for decades or their use of the product was continuous and uninterrupted throughout their careers. Third, the statement implied that workers could only get silicosis if they had "long-term, continual exposure to respirable crystalline silica," although exposure to respirable crystalline silica among artificial stone fabricators has been associated with the development of acute silicosis and has been most strongly associated with the development of accelerated silicosis, which diseases manifest within as little as 1 to just over 5 years of exposure. Lastly, the statement falsely indicates that silicosis only occurs when workers are exposed to respirable crystalline silica above permissible occupational exposure limits, although the disease also occurs from exposures below such levels.

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2. Knowledge of the Silicosis Hazard By Arizona Tile Officers and Directors

846. At his deposition of May 10, 2024, given in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs,* Los Angeles Superior Court Case No. 22STCV31907, Rick Collins, Arizona Tile's Vice-President of Operations, testified that crystalline silica has always been a known hazard to the company, that it was known to the company when he first began working at Arizona Tile in 1986. However, he testified that Arizona Tile only provides Safety Data Sheets for its stone slab products to its customers upon request.

847. At his deposition of May 1, 2024, given in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs,* Los Angeles Superior Court Case No. 22STCV31907, Roy Kunihiro, Arizona Tile's Vice-President of Quartz and Stone, testified that the company had artificial stone slabs that it purchased from foreign vendors tested by a laboratory to determine the percentage of quartz content, because the higher the quartz content of the slab, the better the product from a marketing point. He also testified that Cristobalite was a highly processed quartz material that had a translucent appearance that made artificial stone slabs look like marble.

848. At his deposition of May 1, 2024, given in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs,* Los Angeles Superior Court Case No. 22STCV31907, Mr. Kunihiro testified that when the company received artificial stone slabs from the manufacturers, the manufacturers never provided any warnings with the slabs. He also testified that Arizona Tile did not provide Safety Data Sheets for the slabs that it distributed to its customers, but that it made them available through the company's website.

849. Throughout the time that Arizona Tile sold artificial stone products, the following officers of the company were aware of the defective nature of those products, that the instructions it provided were inadequate to prevent silicosis, and consciously disregarded the health and safety of exposed workers:

John Huarte, Chief Executive Officer;

Joe Kennedy, President;

Mark Huarte, Vice-President of Operations; and later Rick Collins.

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C. Caesarstone USA, Inc.

850. Defendant, Caesarstone USA, Inc., is the American subsidiary of the Israeli company Caesarstone, Ltd., known as "Caesarstone." The name of the company derives from its location near the ancient town Caesarea on Israel's Mediterranean coast. Caesarstone, Ltd. is a publicly traded company that produces artificial stone slabs used to make kitchen and bathroom countertops.

851. Caesarstone Ltd. was founded in 1987 and is traded on the NASDAQ in New York (CSTE). Its headquarters are located in Kibbutz Sdot Yam in Israel; its production facilities are in Israel and the US. Caesarstone products are sold in approximately 50 countries around the world through a network of 6 subsidiaries, including Caesarstone U.S.A., Inc., and numerous distributors.

852. Today Caesarstone Ltd. manufactures Caesarstone in three different factories, two in Israel – Kibbutz Sdot Yam and the Bar Lev Industrial Zone near Karmiel, and, since May 27, 2015, at its plant in Richmond Hill, Georgia, in the United States. Caesarstone also has established warehouses and refinery plants in Shanghai, Beijing, Shenzhen, and Hong Kong.

853. The initial Caesarstone factory commenced its operations in 1987, at Kibbutz Sdot Yam, in Israel, replacing its terrazzo tile factory. After changing the focus from sale of floor tiles to quartz surfaces and establishing itself in the domestic market, the company started to export its products to different countries around the world.

854. At the time that Caesarstone first began producing and exporting its artificial stone product in 1987, the officers, directors, and managing agents of the company knew that Caesarstone was an extremely toxic and dangerous product because it contained extremely high concentrations of crystalline silica and the product had to be fabricated and installed by workmen, which involved cutting, grinding, drilling, edging, and polishing the product with electric-powered saws and tools that generates huge amounts of respirable crystalline silica dust.

855. In 2023, Caesarstone submitted a formal "Opening Statement" to Australian regulators in response to questions that they posed to Caesarstone in determining whether importation of Caesarstone and other artificial stone products into Australia should be banned due to the dangers of the products. One of the questions that the Australian regulators asked Caesarstone

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was: "What level of silica was in the engineered stone in 1987? 95 per cent?" In its "Opening Statement," Caesarstone answered the question as follows: "At that time, the silica content was in the vicinity of 90%." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. The next question that the Australian regulators posed to Caesarstone was: "When Caesarstone started selling artificial stone slabs in 1987 did it know that it contained high levels of silica, a level that is vastly higher than natural stone such as granite and marble and considered carcinogenic to humans if the crystalline silica dust is inhaled?" In its "Opening Statement," Caesarstone responded to this question as follows: "Engineered stone has traditionally contained 60-97% silica." Available at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5.

856. At the time Caesarstone first began producing its artificial stone product in 1987, the company's officers and directors were aware that the product presented extraordinary risks of silicosis because, unlike marble (which contained about 5% crystalline silica) and granite (which contained about 35% crystalline silica), Caesarstone contained as much as 95% crystalline silica.

Caesarstone essentially made one product - an artificial stone product that it claimed was comprised of approximately 93% crystalline silica, 7% polymeric resin and lesser amounts of pigments and additives. At all times the product was known simply as "Caesarstone" and was marketed as "Caesarstone®", a registered tradename. While the slabs were sold in different sizes and colors, for all practical intents and purposes they were a single product, all called "Caesarstone."

857. Caesarstone marketed its Caesarstone® product in a few collections, with such names as "Classico," "Concetto," "Motivo," "Supernatural," and more recently "Metropolitan." Although marketed in these "collections," all Caesarstone was essentially the same artificial stone product made of the same essential ingredients (crystalline silica, polymeric resin, pigments and additives), and all of these "collections" had the same essential toxic properties and hazards.

858. Caesarstone was the first company in the world to export to the United States artificial stone slabs that were designed and intended to be fabricated and thereupon installed as kitchen and bathroom countertops in American homes and businesses. Prior to 2010 the only artificial stone product that was generally available in the United States for such use was Caesarstone®.

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859. Caesarstone® is not and never has been a consumer product. Indeed, an article published in *Business of Home* on January 28, 2020, in response to a series of reports by National Public Radio regarding the artificial stone silicosis epidemic in the United States, explained that consumers - even designers - can't go to a stone supplier or a Caesarstone showroom and order the company's product. In that article, Elizabeth Margles, Caesarstone's vice president of marketing was quoted, admitting "We sell to the fabricator." Thus, at all times the product Caesarstone® was never a finished end-use product offered for sale to consumers, but was instead an industrial product that Caesarstone intended and expected would have to be fabricated by being cut, ground, and polished before the material could be installed as finished countertops in consumers' kitchens and bathrooms.

860. In 2005, an additional production facility was opened at the Bar-Lev Industrial Park.

861. In 2006, TENE Investment Fund invested 25 million dollars in exchange for 21.7% control in the company, which led to the adding of another production line at the Bar-Lev facility.

862. Caesarstone began establishing subsidiaries in Australia (in 2008), Canada (in 2010), USA and Singapore (in 2011) and the UK (in 2017), and had distributors in about 50 countries.

1. 1998 Material Safety Data Sheet

863. On June 20, 1998, Caesarstone prepared its First Material Safety Data Sheet.

864. In Section 1 (Identification) of this Material Safety Data Sheet, Caesarstone identified its product as "Composite - Stone Slabs, and Fabricated Items and identifying the manufacturer as CaesarStone Sdot-Yam LTD, located at Kibbutz Sdot-Yam M.P. Menashe 38805 Israel.

865. Section 2 (Hazardous Ingredients) contained a table with four columns: Hazardous Ingredients, % by Weight, % by Volume, U.N. #, and Other Limits. The table contained three rows for data, but only the first row contained information identifying Unsaturated polyester as a hazardous ingredient at 9% < % by weight, 12% < % by volume, with U.N. # 1866. The other two rows were empty. Critically, this Material Safety Data Sheet did not identify as a hazardous ingredient in the product either crystalline silica or any of the metals in the product.

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866. Section 7 (Toxicological Properties) contained the following table:

Entry through skin contact?	No
Entry through eye contact?	No
Entry through skin absorption?	No
Entry through inhalation?	See sections 7&8
Entry acute exposure effects?	No
Product acute exposure effects?	See sections 7&8
Exposure Limit	See sections 7&8
Product irritancy	See sections 7&8
Product sensitization	No
Product carcinogenicity	No
Product teratogenicity	No
Product mutagenicity	No
Product reproductive toxicity	No
Synergistic by-products	None

867. Thus, Section 7 (Toxicological Properties) of Material Safety Data Sheet disclosed no toxicological properties of the product but merely referred readers to subsequent sections of the Material Safety Data Sheet.

868. Critically Section 7 of the Material Safety Data Sheet falsely stated that the product was not carcinogenic even though it contained more than 90% crystalline silica, which the International Agency for Research on Cancer had concluded the year before that "there is *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources." International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 68: Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils," (IARC 1997).

869. Section 7 (Preventative Measures) of the Material Safety Data Sheet provided the following information regarding Personal Protective Equipment:

Gloves	Observed local safe handling procedures
Respirator	Use respirator or particular mask when cutting or abrading material
Eye Protection	Use eye protection with side shields when cutting or abrading material
Footwear	Use steel toed footwear when handling slabs or tiles.
Clothing	Observe local safe handling procedures.
Other	Additional information is available in ASTM E-1132-86.

870. The instruction to "Observe local safe handling producers" for gloves and clothing was totally inadequate to apprise fabricators of the type of gloves and clothing they needed to wear to handle the product safely. The instruction to "Use respirator or particular mask when cutting or

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abrading material" was totally inadequate because it failed to specify that fabricators needed to wear air-supplied respirators or at least powered air purifying respirators to protect themselves from getting silicosis, and there is no such thing as a "particular mask." The statement that "Additional information is available in ASTM E-1132-86" was grossly inadequate and concealed critical health information, because none of the important information in this standard published by the American Society of Testing Materials titled "Standard Practice for Health Requirements Relating to Occupational Exposure to Quartz Dust" was disclosed and the ASTM Standards are proprietary, were not easily accessed, and could not be downloaded from the Internet without payment of money.

871. The second part of Section 7 of the Material Safety Data Sheet was titled "Procedures and Controls." The only instructions provided regarding "Handling Equipment & Procedures" were to "Observe local safe handling procedures" and "Handle with care," both of which are meaningless and provide no information whatsoever how to handle the product safely. Critically, no information was provided that wet processing methods should be used to reduce airborne crystalline silica levels.

872. Section 8 (First Aid Procedures) of the Material Safety Data Sheet provided the following information regarding inhalation: "The prolonged inhalation of airborne silica can cause the respiratory disease silicosis, a progressive, incapacitating and sometimes fatal disease of the lungs. The risk of lung disease increases if smoking is combined with silica inhalation. Always use a respirator or particular mask when cutting or abrading this material. If symptoms develop, seek medical assistance immediately."

873. This information was grossly inadequate for several reasons. First, this is the first and only place in the MSDS that silicosis -- the major health hazard of the product - was mentioned. Pursuant to the Hazard Communication Standard, the silicosis hazard had to be mentioned in Section 3 of the Material Safety Data Sheet under a heading titled "Health Hazards." Caesarstone did not disclose the silicosis hazard in Section 3 of the Material Safety Data Sheet which it instead titled "Hazardous Ingredients" and did not identify crystalline silica as an ingredient of the product (even though it comprised more than 90% of the product) and did not mention silicosis as a health hazard. Caesarstone intentionally put this critical health hazard information in the penultimate section of the Material Safety Data Sheet where it would unlikely be seen or read. Worse yet, Caesarstone put this

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information in a section of the MSDS titled "First Aid Procedures" which are inapplicable to silicosis, which is a chronic disease for which there are no first aid procedures. Lastly, the instruction concluded by stating "If symptoms develop, seek medical assistance immediately," without identifying those symptoms (coughing, shortness of breath on exertion, fatigue, weight loss, etc.) that would alert a worker that he may have silicosis and needs to see a pulmonologist.

2. U.S. Quartz Products, Inc.

874. On June 22, 1999, Articles of Incorporation of Caesar Stone U.S.A., Inc. were filed with the California Secretary of State. The Articles of Incorporation were dated June 14, 1999 and signed by Steven D. Kramar as Incorporator.

875. According to a Certificate of Status of Domestic Corporation issued by Debra Bowen, Secretary of State of the State of California, U.S. Quartz Products, Inc. became incorporated under the law of the State of California by filing its Articles of Incorporation with the Secretary of State on June 22, 1999 – the same date that Articles of Incorporation were filed for Caesar Stone U.S.A., Inc. Oddly, no company by the name of U.S. Quartz Products, Inc. is listed on the website of the California Secretary of State. However, on June 20, 2011 a Certificate of Amendment of Amended and Restated Articles of Incorporation of U.S. Quartz Products, Inc. was filed with the California Secretary of State. The Certificate of Amendment was signed by Arik Tendler, President and Chief Executive Officer and Alex Vorissis, Secretary of the corporation. Pursuant to this Certificate of Amendment, the name of the corporation was changed to Caesarstone USA, Inc.

3. Caesarstone USA Launches Website

876. In 2000 Caesarstone launched a website whose url was www.caesarstoneus.com. Each page of this website bore a heading that said "Welcome to the World of Caesar Stone US."

877. The website contained a webpage titled "About CaesarStone" which said:

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CaesarStone is the world's leading manufacturer of engineered quartz slabs.

Founded in Founded in Israel in 1987, CaesarStone has offices and licensed product specialists around the world. The US distributorship, which currently serves California, is one of the largest and fastest growing licensed distributors of CaesarStone products in the world.

The main plant employs over 100 workers and operates three shifts a day to meet both the high demand for our products – producing over 2.7 million square feet of product each year – and the high quality standards we set for them.

CaesarStone uses the Bretonstone technology to manufacture quartz slabs that are more colorful than granite, with greater durability and many more uses. This product has gained worldwide recognition as the leading residential and commercial quartz product.

We've recently added a new computer-controlled production line that turns out slabs large enough to make kitchen and vanity countertops without excess cutting and seams, and yet it is thinner and lighter than other stone products.

And the innovation hasn't stopped there – CaesarStone's advanced research and development labs work constantly on quality improvement and product development.

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4. Caesarstone Admits That At Least As Early As 2010 It Knew That People Working With Its Product Were Getting Sick As A Result

878. Among the questions that Australian regulators posed to Caesarstone in 2023 was the following question: "When did Caesarstone first learn that people working with the product were getting sick as a result?" In its "Opening Statement," Caesarstone answered the question: "2010." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5

879. The Australian regulators also asked Caesarstone the following question: "In response to a series of questions from Safework NSW as to the alleged first findings of silicosis among artificial stone workers following tests of patients, Caesarstone said it became aware in 2010 as part of the first lawsuit filed against it. How does this correspond with your 2021 annual report which says the first court case was filed in Israel in 2008?" In its "Opening Statement," Caesarstone responded to this question as follows: "A single action filed in 2008 does not give rise to a more serious issue in the industry. Caesarstone was not aware of a number of cases of silicosis until 2010." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5 While Caesarstone discounted the significance of the 2008 silicosis lawsuit that it acknowledges was filed against the company in 2008, that lawsuit nevertheless put Caesarstone on notice of the harmful nature of its product.

880. The next question that the Australian regulators posed to Caesarstone was the following: "Is Caesarstone suggesting that it never heard about an outbreak of workers being diagnosed with silicosis before the 2008 legal action in Israel?" Caesarstone responded to this question as follows: "A single action filed in 2008 does not give rise to a more serious issue in the industry. Caesarstone was not aware of a number of cases of silicosis until 2010." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Notably, in responding to this question posed by the Australian regulators, Caesarstone did not deny that before 2008 it had heard about the outbreak of silicosis in workers who used Caesarstone's product in Israel. Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5.

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5. Caesarstone Failed to Put Hazard Warnings On Its Product Prior To 2010

881. Among the questions that the Australian regulators posed to Caesarstone in 2023 was the following question: "In 2010 Caesarstone started putting so-called warning stickers on the slabs it was selling. Why did it wait until 2010?" In its "Opening Statement" Caesarstone responded to this question as follows: "Caesarstone placed warning labels on slabs of stone when it became aware that workers were contracting silicosis in 2010." Caesarstone's "Opening Statement," available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Caesarstone's response did not answer the question why it waited until 2010 to start putting "warning stickers" on the slabs it was selling. Nevertheless, Caesarstone's response constitutes an admission that from 1987 when Caesarstone began making the product to 2010 (a period of 23 years), Caesarstone did not put any warnings on slabs of its product, so that workers handling them could see the warnings.

882. The next series of questions that the Australian regulators posed to Caesarstone was: "How big was the warning sticker in Feb 2010 on the slab? - can you provide the measurement? How big is the slab? What part of the slab was the sticker put - on top, the bottom or was there no specific place?" In its "Opening Statement" Caesarstone responded to these questions as follows: "The warning label is affixed to the back of each slab .... The labels started in 2010 at approximately 14cm x 14cm." Although Caesarstone did not answer the question how big the slab was, in response to the regulators' first question, which asked Caesarstone about the size of each slab, Caesarstone responded: "The 'standard' current size is 3050mm v 1440mm . . . . There are other sizes available, such as 3340 mm x 1640 mm ...." Caesarstone's "Opening Statement," available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Converting the odd metric system measurements provided by Caesarstone in its response to American measurements, the 14 cm x 14 cm sticker measured about 5½ square inches, and the 3050 mm x 1440 mm slab measured about 10 feet by $4^{3}/_{4}$ feet. The sticker in 2010 contained warnings in English, Italian, French, Spanish and Arabic – all in a 5½ inch square. Thus, the sticker that Caesarstone first began affixing to the slabs of its product in 2010 was tiny, the printing on the sticker was necessarily in a very small font, and the entire "warning" sticker covered less than ½ of one percent of the surface area of the slab!

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6. Why Caesarstone First Began Putting Stickers On Slabs In 2010

883. Another question that the Australian regulators posed to Caesarstone in 2023 was the following question: "In early 2010 a documentary in Israel aired which exposed workers dying of silicosis due to engineered stone. The documentary had ben in the works months before it aired. Is that what triggered the decision by Caesarstone to start attempting to put warning labels on the products?" Caesarstone answered this question: "Yes." Thus, Caesarstone admitted that it only began putting warning labels on its product *after* deaths of Israeli workers from silicosis were aired on Israeli television. Caesarstone's "Opening Statement" to the Australian regulators, available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5.

884. When Caesarstone began putting so-called "warning" stickers on the slabs of its product in 2010, it did not include any hazard warning symbols, i.e., pictograms. Indeed, it appears that Caesarstone did not include pictograms on its labels until 2020. In 2023 the Australian regulators therefore posed the following question to Caesarstone about the absence of pictograms: "When did Caesarstone start putting hazard warning symbols on the labels to Australia? Why did it take so long? Why didn't it do it from 2010?" In its "Opening Statement," Caesarstone responded to this question as follows: "While the first labels did not include the warning symbols, they clearly included the word: WARNING." However, Caesarstone did not explain why it did not put hazard warning *symbols*, i.e., pictograms, on the labels in 2010, or why it took the company another 10 years to do this. See, Caesarstone's "Opening Statement" to the Australian regulators, available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5.

7. Caesar Stone Sdot-Yam Ltd. Purchases All The Shares Of U.S. Quartz

885. On May 18, 2011, Caesar Stone Sdot-Yam Ltd., an Israeli company, entered into a Share Purchase Agreement with U.S. Quartz Products, Inc. and its shareholders whereby Caesar Stone Sdot-Yam Ltd. purchased all of the shares of stock of U.S. Quartz Products. This transaction resulted in Caesarstone Sdot-Yam Ltd. (currently known as Caesarstone Ltd.) obtaining total control

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over U.S. Quartz Products, Inc. (currently known as Caesarstone U.S.A., Inc.). A copy of the Share Purchase Agreement was filed as Exhibit 2.1 of Caesarstone's Form F-1 Registration Statement that it filed with the U.S. Securities and Exchange Commission on February 16, 2012. See https://www.sec.gov/Archives/edgar/data/1504379/000119312512065539/d258108dex21.htm.

886. According to an Application by a Foreign Profit Corporation to File Amendment to Application for Authorization to Transact Business in Florida filed with the Florida Secretary of State in February 2012, U.S. Quartz Products, Inc. changed its name to Caesarstone USA, Inc.

8. Caesarstone Registers with the U.S. Securities and Exchange Commission

887. On February 16, 2012, Caesarstone Sdot-Yam Ltd., an Israeli company, filed its Form F-1 Registration Statement under the Securities and Exchange Commission, identifying Caesarstone USA, Inc., 6840 Hayvenhurst Ave. Suite 100, Van Nuys, California 91406; (818) 779-0999 its as its agent for service.

888. In this document Caesarstone acknowledged that "Silicosis and related claims could have a material adverse effect on our business, operating results and financial condition." In its Form F-1 Registration Statement, Caesarstone described the hazards of its product and the risks of silicosis from exposure to its product as follows:

> Silicosis and related claims could have a material adverse effect on our business, operating results and financial condition. Since 2008, fourteen lawsuits have been filed against us or named us as third party defendants in Israel and we have received a number of additional letters threatening lawsuits on behalf of certain fabricators of our products in Israel or their employees in Israel alleging that they contracted illnesses, including silicosis, through exposure to fine silica particles when cutting, polishing, sawing, grinding, breaking, crushing, drilling, sanding or sculpting our products. Each of the lawsuits which has been filed names defendants in addition to us, including, in certain cases, fabricators that employed the plaintiff, the Israeli Ministry of Industry, Trade and Employment, distributors of our products and insurance companies. Silicosis is an occupational lung disease that is progressive and sometimes fatal, and is characterized by scarring of the lungs and damage to the breathing function. Inhalation of dust containing fine silica particles as a result of not well protected and not well controlled, or unprotected and uncontrolled, exposure while processing quartz, granite, marble and other materials can cause silicosis. Various types of claims are raised in these lawsuits and in the letters submitted to us, including product liability claims such as claims related to failure to provide warnings regarding the risks associated with silica dust. We believe that we have valid defenses to the lawsuits pending against us and to potential claims and intend

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to contest them vigorously. Damages totaling $6.1 million are specified in the lawsuits currently filed; however, the amount of general damages, which includes items such as pain and suffering and loss of future earnings, has not yet been specified in most of the lawsuits. As a result, there is uncertainty regarding the total amount of damages that may ultimately be sought. At present, we do not believe that it is reasonably possible that the lawsuits filed against us to date will have a material adverse effect on our financial position, results of operations, or cash flows, in part due to the current availability of insurance coverage. Nevertheless, all but one of the lawsuits are at a preliminary stage and no material determinations, including those relating to attribution of fault or amount of damages, have been made. There can also be no assurance that our insurance coverage will be adequate or that we will prevail in these cases. We are party to a settlement agreement that is pending court approval with respect to one of the lawsuits filed. In that instance, the total settlement is for NIS 275,000 ($71,970) of which we have agreed to pay NIS 10,000 ($2,617) without admitting liability. Substantially all of the balance is payable by the fabricator that employed the individual in question and insurance companies. We can provide no assurance that other lawsuits will be settled in this manner or at all.

Our current liability insurance provider renewed our product liability insurance policy in October 2011 through November 2012. However, there is no assurance that we will be able to obtain product liability insurance in the future on the same terms, including with the premium under our current policy, or at all. If our current insurance provider does not renew our product liability insurance policy in the future, it is uncertain at this time whether we will be able to obtain insurance coverage from other insurance providers in the future. We are not currently subject to any claims from our employees related to silicosis; however, we may be subject to such claims in the future. Our employer liability insurance policy excludes silicosis claims by our employees and, to the extent we become subject to any such claims, we may be liable for claims in excess of the portion covered by the National Insurance Institute of Israel. If our insurance providers refuse to renew our insurance, we are unable to obtain coverage from other providers, our policy is terminated early or we become subject to silicosis claims excluded by our employer liability insurance policy, we may incur significant legal expenses and become liable for damages, in each case, that are not covered by insurance, and our management could expend significant time addressing such claims. These events could have a material adverse effect on our business and results of operations.

Consistent with the experience of other companies involved in silica-related litigation, there may be an increase in the number of asserted claims against us. Such claims could be asserted by claimants in jurisdictions other than Israel, including the United States where we recently acquired our former U.S. third-party distributor, Canada where we recently established a joint venture for the distribution of products there and Australia and could result in significant legal expenses and damages. Existing or future claimants against us, in Israel or elsewhere, may seek to have their claims certified as class actions on behalf of a defined group. We believe that claimants in future silica-related claims involving us, if any, should be limited to persons involved in the fabrication of our products, including, but not limited to, cutting, polishing, sawing, grinding, breaking, crushing, drilling, sanding or sculpting, and those in the immediate vicinity of fabrication activities, but may potentially include our employees. Any pending or future litigation, including any future litigation in the United States, where in May 2011 we acquired our former third-party distributor, Caesarstone USA, formerly known as U.S. Quartz Products, Inc., is subject to significant uncertainty. We cannot determine the amount of potential damages, if any, in the event of an adverse development in a pending or future case, in part because the defendants in these types of lawsuits are often

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numerous, the claims generally do not specify the amount of damages sought, our product's involvement may be speculative, and the degree to which our product may have caused the alleged illness may be unclear. In addition, punitive damages may be awarded in certain jurisdictions.

Furthermore, we may face future engineering and compliance costs to enhance our compliance with existing standards relating to silica, or to meet new standards if such standards are heightened. Such costs may adversely impact our profitability.

889. Caesarstone's Form F-1 filed with the Securities and Exchange Commission on February 16, 2016, identified the following executive officers, directors and director nominees, all of whom were aware of the filing of the Form F-1 Registration Statement with the Securities and Exchange Commission, and the toxic hazards of Caesarstone artificial stone products and the risks of silicosis to fabricators and installers of Caesarstone's products, as set forth therein:

Executive Officers

Yosef Shiran	Chief Executive Officer
Yair Averbuch	Chief Financial Officer
David Cullen	Chief Executive Officer Caesarstone Australia
Sagi Cohen	Chief Executive Officer Caesarstone USA
Giora Wegman	Deputy Chief Executive Officer
Michal Baumwald Oron	General Counsel
Eli Feiglin	Vice President Marketing
Erez Schweppe	Vice President Sales
Harel Boker	Vice President of Operations
Tzvika Rimon	Israel Country Manager
Dr. Ramon Albalak	Vice President Research and Development
Lilach Gilboa	Vice President Human Resources

Directors and Director Nominees

Maxim Ohana	Chairman
Dori Brown	Director
Yonathan Melamed	Director
Moshe Ronen	Director
Oded Goldstein	Director
Ariel Halperin	Director
Eitan Shachar	Director
Boaz Shani	Director
Shachar Degani	Director
Gal Cohen	Director
Irit Ben-Dov	Director Nominee
Ofer Borovsky	Director Nominee

890. Caesarstone's Form F-1 Registration Statement that was filed with the Securities and Exchange Commission on February 16, 2012 is available on the SEC website at: https://www.sec.gov/Archives/edgar/data/1504379/000119312512065539/d258108df1.htm.

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9. As of 2012 Caesarstone Was Well Aware that Workers Were Getting Silicosis and Needed Lung Transplants

891. Due to the extremely high crystalline silica content of Caesarstone, it was not surprising that workers (i.e., fabricators and installers) exposed to Caesarstone in Israel soon began developing silicosis and needing lung transplants.

892. As previously mentioned, the first case of artificial stone-induced silicosis was seen in 1997 by researchers at the National Lung Transplantation Center in Israel. This worker was occupationally exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Plaintiff is informed and believes and thereon alleges, that the researchers at the National Lung Transplant Center in Israel shared their conclusion that the cause of the silicosis in the worker whom they diagnosed with silicosis in 1997 who thereafter underwent lung transplantation, was his occupational exposure to Caesarstone's artificial stone product.

893. In 2005, an additional production facility was opened at the Bar-Lev Industrial Park.

894. In 2006, TENE Investment Fund invested 25 million dollars in exchange for 21.7% control in the company, which led to the adding of another production line at the Bar-Lev facility.

895. In 2008, Caesarstone began establishing subsidiaries in its main markets: Australia (2008), Canada (2010), USA and Singapore (2011) and UK (2017), along with activity conducted through distributors in approximately 50 countries.

896. During the 14 years following the first case of Caesarstone®-induced silicosis diagnosed at the National Lung Transplant Center in Israel in 1997, Israeli physicians diagnosed silicosis in 25 patients occupationally exposed to Caesarstone®. All of these cases were diagnosed based on detailed occupational history, with histologic confirmation of silicosis in all but two of the cases. Of these 15 (60%) were determined to be lung transplant candidates. According to the authors of this study, all of these patients worked with the same commercial brand of synthetic stone material, i.e. Caesarstone, which the investigators analyzed and determined that it contained at least 85% crystalline silica. All 25 patients reported that more than 90% of their typical work duties

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involved handling Caesarstone®. Less than 10% included exposure to other potential sources of silica, primarily natural granite. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. The data and the results of this study were published in the journal *Chest*, which is one of the most widely read medical journals in the world, with an impact factor of 11.393 (an impact factor of 3 is considered good and an impact factor of 10 or higher is considered remarkable).

897. The results of the study by the Israeli researchers that were published in the journal *Chest* concerning 25 workers with silicosis who were occupationally exposed to Caesarstone®, 60% of whom needed lung transplants, were known to the officers, directors and managing agents of Caesarstone at the time. Originally, the article used the term "Caesarstone silicosis" in its title, in reference to the company's major position in the Israeli market for engineered stone. But soon after the study appeared, Caesarstone threatened to bring a lawsuit against the American College of Chest Physicians, the organization that publishes the journal, unless the term was removed. "Utilization of Caesarstone's trademark and trade name as a name of a disease causes the company significant damage and irreparably harms its good will," the company wrote in a 2012 letter to the American College of Chest Physicians. Dr. Richard S. Irwin, the publication's editor in chief, said he decided to remove the term "Caesarstone silicosis" from the published article because the types of silicosis described in it were not unique to Caesarstone but applied to engineered stone products in general. "Chest did not make the change because of threatened legal action," Dr. Irwin said in the statement. Dr. Irwin added that the report's authors agreed with his decision. Dr. Kramer, the Israeli physician who led the study, estimated that Caesarstone accounted for 99 percent of the market there, adding that the company had faced dozens of lawsuits from injured workers." Barry Meier, "Popular Quartz Countertops Pose a Risk to Workers," *New York Times* (April 1, 2016).

898. In 2023, Australian regulators posed the following questions to Caesarstone about its threat of litigation against the journal in which the 2012 study first appeared under the title "Caesarstone® Silicosis": "In 2012 a study was released with the title Caesarstone and silicosis. Why did Caesarstone send legal letters to the publisher threatening legal action if it wasn't changed? At the time more than 90 per cent of the products sold in Israel were Caesarstone. It is claimed by

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one of the authors it was an attempt to cover up the role of Caesarstone products in the surge in silicosis cases in Israel?" In its "Opening Statement" Caesarstone responded to this question by the Australian regulators as follows: "The objection to the article was on the basis that it targeted Caesarstone. The article was entitled "Caesarstone® Silicosis: Disease Resurgence among Artificial Stone". The invented name "Caesarstone® Silicosis" did not (and still does not) exist in the World Health Organization's international Classification of Diseases (ICD)." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Thus, Caesarstone did not deny that it sent "legal letters" to the publisher of the medical journal threatening to sue the publisher if the title of the article, "Caesarstone® Silicosis" were not changed to its liking.

899. The next question that the Australian regulators posed to Caesarstone was: "Did Caesarstone ever offer one of the authors of the report a donation to the lab?" In its "Opening Statement" to the Australian regulators Caesarstone responded to this question as follows: "In the short time provided to respond, we have been unable to find any evidence of this." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Notably, in its response to the implicit accusation of one of the authors that Caesarstone attempted to bribe them to change the name of the study, Caesarstone did not deny that it offered one of the authors of the report a donation to the laboratory.

900. In 2023, the Australian regulators also posed the following question to Caesarstone: "When the Israeli study in Israel was finally published in 2012 it was based on a study of workers from 1997 to 2010 who had been diagnosed with silicosis and they all used the Caesarstone product. What did caesarstone do in Australia to warn customers about the study?" In its "Opening Statement" Caesarstone responding to this question as follows: "Caesarstone first became aware of this issue in 2010. In terms of customer warnings, see responses to Q5, Q6, Q8, and Q10." Available online at https://prod.static9.net.au/fs/d4f39ceb-c239-489c-ba03-6b1edc830af5. Thus, Caesarstone did not answer the question as to what it did in Australia to warn customers about the study. Indeed, Caesarstone's responses to the referenced questions and the referenced "customer warnings" did not mention the 2012 Israeli study at all.

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10. Caesarstone's March 26, 2012 Safety Data Sheet

901. On March 26, 2012, Caesarstone issued a Safety Data Sheet for its product identified as "Caesarstone® / Concetto®." This document listed four constituents of the product: (1) "Crystalline Silica and other natural stone" at a concentration of >85%, (2) Cristobalite at a concentration of <50%, (3) "Polymeric resin" at a concentration of 7-15%, and (4) "Additives" at a concentration of 0-8%. Since Cristobalite is a form of crystalline silica, according to this document, the crystalline silica concentration of the product was extremely high and at least in excess of 90% of the product, presenting an extreme hazard to the health of workers throughout the world whose job was to fabricate countertops for installation in kitchens and bathrooms.

902. Notwithstanding the extreme respiratory hazard of its product, on the first page of Safety Data Sheet issued March 26, 2012, Caesarstone concealed the true nature and severity of the hazards of its Caesarstone® product by stating that "this preparation is not classified as hazardous according to the latest adaption of European Union Directives 67/548/EEC and 1995/45/EC." This was a false statement, because EU Directive 67/548/EEC classifies as "dangerous" "substances and preparations" those that are "very toxic," "which if they are inhaled . . . may involve extremely serious . . . chronic health risks and even death."

903. Caesarstone also concealed the true nature and severity of the hazards of its Caesarstone® product by stating in its March 26, 2012 Safety Data Sheet that "Quartz surfaces products are not hazardous as shipped," although Caesarstone® is not a finished consumer product, but is rather than industrial product that must be sawed, ground, routed, drilled, sanded, and polished in fabricating and installing the product, thereby generating respirable crystalline silica dust that causes silicosis.

904. In its March 26, 2012 Safety Data Sheet, Caesarstone also concealed the true nature and severity of the health hazards of Caesarstone® by making misleading statements about the product, e.g., that "[i]nhalation of . . . dusts, smoke and vapors may cause upper respiratory tract irritation," where the primary respiratory hazard of the product is not upper respiratory tract irritation (as one experiences when cutting an onion), but is rather chronic and progressive severe lung disease,

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i.e., silicosis and resultant death.

905. In its March 26, 2012 Safety Data Sheet, Caesarstone also concealed the true nature and severity of the health hazards of Caesarstone® by making other misleading statements such as "Overexposure to airborne crystalline silica can cause silicosis, a chronic and progressively debilitating disease, characterized by the formation of silica-containing scar tissue in the lungs." This statement falsely suggested to Caesarstone's customers and to their workers who fabricated Caesarstone® that workers would have to be "overexposed" to airborne crystalline silica to develop silicosis, whereas the truth, which was known to Caesarstone at the time, was that silicosis is caused by inhalation of extremely small amounts of respirable crystalline silica, i.e., 0.05 milligrams of respirable crystalline silica per cubic meter of air, which is 0.00000175 of an ounce of respirable crystalline silica equally dispersed in one cubic meter of air, which is slightly larger than 1 cubic yard (27 cubic feet). That tiny amount of respirable crystalline silica would appear as a speck of white dust on of the eye of President Lincoln on a penny, but when dispersed in air is so small that it is invisible to the human eye and cannot be discerned by smell, taste or any other human sense. Indeed, in 1996 – the year before the first Israeli worker was diagnosed with silicosis caused by exposure to Caesarstone® - researchers from the University of Michigan and the University of Cincinnati published a study regarding silicosis among foundry workers in which they observed that "[a]t the NIOSH recommended exposure limit of 0.05 mg/m^3, there was a 0.3-0.8 percent prevalence of radiographs consistent with silicosis" and concluded that "our data show that the current OSHA standard is not sufficiently low to protect workers against the development of radiologic evidence of silicosis." Rosenman KD, et al., "Silicosis among foundry Workers: Implication for the Need to Revise the OSHA Standard," *Am. J. Epidemiol.* 1996; 144:890-900. At the time that Caesarstone issued its March 26, 2012 Safety Data Sheet for Caesarstone®, indicating that workers would have to be "overexposed" to respirable crystalline silica to develop silicosis, Caesarstone's officers, directors and managing agents were aware that 25 Israeli workers who reported that more than 90% of their typical work duties involved handling Caesarstone® had been diagnosed with silicosis at the National Lung Transplant Center in Israel and that 15 of them needed lung transplants at the time. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone

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Workers," *Chest* 2012; 142(2):419-424. Although Caesarstone's statement in its March 26, 2012 Safety Data Sheet for Caesarstone® indicated that only "overexposure to airborne crystalline silica" causes silicosis, nowhere in this document did Caesarstone specify the amount of airborne crystalline silica to which one must be exposed to get silicosis so as to enable Caesarstone's customers to determine whether their workers were being dangerously "overexposed" to respirable crystalline silica from Caesarstone®.

906. In its March 26, 2012 Safety Data Sheet, Caesarstone also falsely stated that "epidemiology studies show limited evidence of an excess of lung cancer in occupations involving exposures to crystalline silica, such as stone cutters and granite industry workers," which statement is contrary to the determination and classification of the International Agency for Research on Cancer (IARC) in its monograph on silica published 15 years earlier, which had concluded: "there is *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources." International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 68: Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils," (IARC 1997).

907. In its March 26, 2012 Safety Data Sheet, Caesarstone also provided misleading information regarding the engineering controls necessary to prevent countertop fabricators and installers from getting silicosis, by stating: "General room ventilation is satisfactory under anticipated use conditions." This statement is not merely false; it is extremely and inexcusably harmful, because general room ventilation is never adequate to control occupational exposure to respirable crystalline silica and published studies regarding crystalline silica exposure of artificial stone fabricators all show that general room ventilation is inadequate to prevent harmful respirable crystalline silica exposure in countertop fabricators. See, NIOSH, *Evaluation of Crystalline Silica Exposure during Fabrication of Natural and Engineered Stone Countertops.* (HHE Report No. 2014-0215-3250).

908. In its March 26, 2012 Safety Data Sheet, Caesarstone also provided misleading information regarding the respiratory protection necessary to prevent silicosis, by stating: "Respiratory equipment approved by NIOSH/MSHA for protection against organic vapors and dusts

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is necessary to avoid inhalation of excessive air contaminants. The appropriate respirator selection depends on the type and magnitude of exposure (refer to 29 CFR 1910.134 for appropriate NIOSH approved respirators and to the NIOSH Pocket Guide to Chemical Hazards, DHHS (NIOSH) Publication NO. 2001-145 for equipment selection)." This information was misleading, because NIOSH-approved air-purifying respirators that provide protection against organic vapors and some dusts are inadequate to prevent silicosis among fabricators and installers who are exposed to respirable crystalline silica dust, especially from artificial stone products, due to their extremely high crystalline silica content. Indeed, studies have shown that the use of air-purifying respirators is inadequate to prevent silicosis among fabricators and installers, and that only NIOSH-approved *air-supplied* respirators (respirators attached to a tank of fresh air which workers wear in a backpack) are adequate to prevent silicosis and death to artificial stone countertop fabricators and installers.

909. In its Safety Data Sheet, Caesarstone also provided the following use instruction: "Do not breathe dust generated in the cutting, grinding and polishing processes." This instruction was inadequate and harmful, because dust is *always* generated when artificial stone is fabricated and workers must breathe to work and to live. The instruction did not inform workers how they could do their work and "not breathe dust generated in the cutting, grinding and polishing processes."

11. Caesarstone's 2015 Annual Report Filed with the SEC

910. In 2015, Caesarstone Sdot-Yam Ltd. filed its Annual report for the fiscal year ended December 31, 2014 with the Securities and Exchange Commission. In this report Caesarstone wrote:

> ***Silicosis and related claims might have a material adverse effect on our business, operating results and financial condition.***
>
> We are party to 60 pending bodily injury lawsuits that have been filed against us directly since 2008 in Israel or that have named us as third-party defendants by fabricators or their employees in Israel, by the injured successors, by the State of Israel or by others. Such lawsuits include, among others, one lawsuit filed by three fabricators, one lawsuit filed by the National Insurance Institute ("NII"), an appeal which was filed in connection with a judgment granted in one of the lawsuits and a lawsuit filed against us where the claimants applied for its certification by the court as a class action. As of today, we have also received ten letters threatening to file claims against us on behalf

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of certain fabricators and their employees in Israel. The plaintiffs claim that they contracted illnesses, including silicosis, through exposure to silica particles during cutting, polishing, sawing, grinding, breaking, crushing, drilling, sanding or sculpting our products. Silicosis is an occupational lung disease that is progressive and sometimes fatal, and is characterized by scarring of the lungs and damage to the breathing function. Inhalation of dust containing fine silica particles as a result of poorly protected and controlled, or unprotected and uncontrolled, exposure, while working in different occupations, including among other things, processing quartz, granite, marble and other materials and working with quartz, can cause silicosis and other diseases. Silica comprises approximately 90% of engineered stones such as our products, and smaller concentrations of silica are present in natural stones. Therefore, fabrication of engineered stones may create higher exposure to silica dust and, accordingly, may cause a higher risk of silicosis. Recently the Occupational Safety and Health Administration "OSHA" and the National Institute for Occupational Safety and Health "NIOSH" have published a hazard alert, according to which they identified exposure to silica as a health hazard to workers involved in manufacturing, finishing and installing natural and manufactured (engineered) stone countertop products, both in fabrication shops and during in-home finishing/installation.

Most of the claims do not specify a total amount of damages sought and the plaintiffs' future damages, if any, will be determined at trial. Although we intend to vigorously contest the claims, we cannot provide any assurance that we will be successful. We currently estimate that our total potential exposure with respect to the 47 pending lawsuits is approximately $12.1 million, although the actual result of such lawsuits may vary significantly from such estimate. We cannot make an estimate with respect to the other pending lawsuits. As of today, only one claim was resolved in court proceedings with an Israeli district court, finding that the self-employed plaintiff was 40% at fault and dividing the remaining 60% of liability between the State of Israel and us, with 55% imposed on us and 45% imposed on the State of Israel. This judgment is currently on appeal in Israel to the Supreme Court.

In April 2014, a lawsuit by a single plaintiff and a motion for the recognition of this lawsuit as a class action were filed against us in the Central District Court in Israel. The plaintiff alleges that, if the lawsuit is recognized as a class action, the claim against us is estimated to be for NIS 216 million (approximately $56 million). In addition, the claim includes an unstated sum in compensation for special and general damages. We intend to vigorously contest recognition of the lawsuit as a class action and to defend the lawsuit on its merits, although, considering the preliminary stage of this lawsuit, there can be no assurance as to the probability of success or the range of potential exposure, if any. We may be subject to putative class action lawsuits in the future in Israel and abroad and we cannot be certain whether such claims will succeed in being certified.

We are exposed in Israel to potential future subrogation claims by the NII, providing for reimbursement of its payments related to damages

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paid or that will be paid to plaintiffs, if we are found liable for the plaintiffs' damages. As of today, one of the 60 pending claims against us was brought by the NII, for payments the NII had made or will make in the future with respect to three fabricators who allegedly contracted silicosis. The amount of damages to which we may be liable to the NII in such a subrogation claim may not exceed the actual amount of an injured person's damages for which we are liable after deducting any compensation which we would pay to such injured pursuant to his/her direct or indirect claim against us.

Any pending or future litigation is subject to significant uncertainty. We cannot determine the amount of potential damages, if any, in the event of an adverse development in a pending or future case, in part because the defendants in these types of claims are often numerous, the contraction of the alleged illness or its degree of severity is unclear, the claims generally do not specify the amount of damages sought, our product's involvement may be speculative and the degree to which our product may have caused the alleged illness may be unclear. In addition, punitive damages may be awarded in certain jurisdictions, even though they are rare in Israel. Furthermore, we may face future engineering and compliance costs to enhance our compliance with existing standards relating to silica or to meet new standards if such standards are heightened. Our fabricator customers may also face engineering and compliance costs related to the fabrication of our products and similar products, which could cause them to resort to fabricating alternative products that do not carry the same risks associated with silica dust generated from the fabrication of our products. OSHA is currently considering lowering the permissible exposure limit to silica dust. Any damages to which we are subject in litigation, the cost of defending any claims, compliance costs, and the loss of business from fabricators who no longer find it practical to fabricate our products may have a materially adverse impact on our profitability. Moreover, because Israeli law and the laws of several other jurisdictions recognize joint and several liability among co-defendants in civil suits, even if we are found only partially liable to a plaintiff's damages, the plaintiff may seek to collect all his damages from us, requiring us to collect separately from our co-defendants their allocated portion of the damages and there can be no assurance that we will succeed in such collection.

We currently have product liability insurance in Israel, which applies to claims that may be submitted against us worldwide during the insurance policy term and our Australian and U.S. subsidiaries have product liability insurance in Australia and the United States, respectively, that covers silicosis. We believe that our current insurance in Israel covers the pending individual product liability claims; however with respect to the claim brought in April 2014 where the plaintiff applied for class certification, our insurer has notified us that our product liability insurance covers such claim only partially. While we believe such class action is fully covered by our product liability insurance policy, there is no certainty that our insurance would also cover the class action. In addition, as discussed in "ITEM 8.A: Financial Information—Legal Proceedings," the amount claimed in the currently pending class action exceeds our insurance coverage by a material amount.

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> In the scenario that we are unable to renew our insurance at all or in part, from our current insurers or from others, we are unable to obtain coverage from other insurance providers, we cannot obtain insurance on as favorable terms as previously, our insurance is terminated early, our insurance coverage is decreased, our insurance coverage inadequately covers damages for which we are found liable, or we become subject to silicosis claims excluded by our employer liability insurance policy, we may incur significant legal expenses and become liable for damages, in each case, that are not covered by insurance, and our management could expend significant time addressing such claims. Such events might have a material adverse effect on our business and results of operations.
>
> Consistent with the experience of other companies involved in silica-related litigation, there may be an increase in the number of asserted claims against us. Such claims could be asserted by claimants in different jurisdictions, including Israel, the United States, Canada, Australia and other markets where our products are distributed and sold and could result in significant legal expenses and damages. Although we believe that claimants in any future silica-related claims involving us should be limited to persons involved in the fabrication of our products and those in the immediate vicinity of fabrication activities, claimants may potentially include our employees or end consumers, seeking compensation for bodily or emotional/non-physical damages. Four employees currently employed in our plants have been diagnosed with suspected cases of silicosis. For more information, see "ITEM 8.A: Financial Information— Legal Proceedings—Claims related to alleged silicosis injuries."

911. The 2015 annual report contains a section "ITEM 8.A." regarding legal proceedings concerning "Claims related to alleged silicosis injuries" that provides the following information:

> ***Overview***
>
> We are subject to a number of claims in Israel by fabricators or their employees alleging that they contracted illnesses, including silicosis, through exposure to silica particles during cutting, polishing, sawing, grinding, breaking, crushing, drilling, sanding or sculpting our products. Silicosis is an occupational lung disease that is progressive and sometimes fatal, and is characterized by scarring of the lungs and damage to the breathing function. Inhalation of dust containing fine silica particles as a result of poorly protected and controlled, or unprotected and uncontrolled, exposure while working in different occupations, including among other things, processing quartz, granite, marble and other materials and working with quartz can cause silicosis. Silica comprises approximately 90% of engineered stones, including our products, and smaller concentrations of silica are present in natural stones and, therefore, fabrication of engineered stones may create higher exposure to silica dust and, accordingly, may cause a higher risk of silicosis.

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Individual Claims

As of today, we are party to 60 pending claims of bodily injury that have been filed against us directly since 2008 in Israel or that have named us as third-party defendants by fabricators or their employees in Israel, by the injured successors, by the State of Israel, or by others. Such lawsuits include one lawsuit filed by the Israeli NII which was filed with respect to three individuals who filed personal claims against us and one lawsuit where the claimants applied for its class certification. Of 63 claims that had been filed against us, including the 60 pending claims, 62 were filed in Israel and one in the United States, two claims were settled and one claim which was filed in the United States was dismissed, as further detailed below. Out of the 63 claims mentioned above, one claim was filed in 2008, two in 2009, four in 2010, seven in 2011, eight in 2012, eight in 2013, 28 in 2014 and five in 2015 through the filing of this annual report. As of today, we have also received ten letters threatening to file claims against us on behalf of certain fabricators in Israel or their employees in Israel alleging that they contracted illnesses as a result of fabricating our products. Each of the claims named other defendants, such as fabricators that employed the plaintiffs, the Israeli Ministry of Industry, Trade and Employment, distributors of our products and insurance companies. The pending claims include one lawsuit filed with a petition to be certified as class action, one lawsuit filed by three stone fabricators together and one appeal which was filed in connection with a judgment granted in one of the lawsuits (as further detailed below). In addition, one claim was filed by the NII for subrogation of compensation paid by the NII to certain fabricators who allegedly contracted silicosis. Various arguments are raised in the claims, including, among others, product liability arguments and failure to provide warnings regarding the risks associated with silica dust generated by the fabrication of our products.

Most of the claims do not specify a total amount of damages sought, as the plaintiff's future damages will be determined at trial; however, damages totaling approximately $22.3 million are specified in 55 of the claims currently pending against us in Israel (excluding the claim that is seeking class action recognition). A claim filed with the magistrates court in Israel is limited to a maximum of NIS 2.5 million (approximately $642 thousands) plus any fees, and among the 60 pending claims filed against us in Israel, 35 claims were filed in the magistrates court. A claim filed in the district court is not subject to such limitation. As a result, there is uncertainty regarding the total amount of damages that may ultimately be claimed.

We intend to vigorously contest pending claims against us, although there can be no assurance that we will succeed in these claims and there is a reasonable possibility that we will be liable for damages in such lawsuits. We currently estimate our total reasonably possible exposure with respect to 47 pending lawsuits (other than the lawsuits filed with a motion to be recognized as a class action) to be approximately $12.1 million, although the actual result of such lawsuits may significantly vary from such estimate. As of today, only one claim was resolved by an Israeli District court, imposing liability of 40% on the self-employed plaintiff and dividing the remaining

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60% liability between the State of Israel and us, with 55% imposed on us and 45% on the State of Israel. That judgment was appealed to the Supreme Court by the plaintiff, the State of Israel and us.

Israeli law, as well as the law of other jurisdictions, recognizes joint and several liability among co-defendants in civil suits. In cases where co-defendants are found liable, the plaintiff is entitled to collect all damages from only one of the liable defendants. Thus, even if we are found only partially liable to a plaintiff's damages, the plaintiff may seek to collect all his damages from us, requiring us to collect separately from our co-defendants their allocated portion of the damages. If defendants are insolvent or we are unsuccessful in collecting their portion of the damages for any other reason, we may incur damages beyond the damages we are liable for.

We currently estimate that contingent losses related to the pending claims mentioned above are no more than reasonably possible. In addition, we believe that an adverse outcome to the claims filed against us to date (other than the class action) would not have a material adverse effect on our financial position, results of operations, or cash flows, in part, due to the current availability of insurance coverage; however, there can be no assurance that our insurance coverage will be adequate or that we will prevail in these cases.

Class Action Claim

A lawsuit by a single plaintiff and a motion for its class certification were filed against us in April 2014 in the Central District Court in Israel. The plaintiff claims to be the owner of a fabrication plant and to have contracted silicosis as a result of fabricating our products. In connection therewith, the plaintiff claims that we did not provide adequate warnings with respect to the risks and protection measures required with respect to fabrication of our products, and that we intentionally hid and did not warn about the high risk and irreversible damages that may occur to the persons processing our products and misled the fabricators in Israel by comparing the hazards related to the fabrication of our products to those associated with the fabrication of natural stones. In acting so, the plaintiff claims that we did not act as a reasonable manufacturer; we violated the law and Israeli standards, committed an assault, acted negligently and are liable under the Israeli Law for Liability for Defective Products, 1980. The plaintiff also claims that our products are a "dangerous item" under the Israeli Tort Ordinance, 5728-1968 and, therefore, the plaintiff claims that the burden of proof falls on us to prove that there was no carelessness for which we are liable in connection with our products. The plaintiff claims that by our wrongful conduct we violated the plaintiff's freedom to choose whether to be exposed to the risks associated with the fabrication of our products.

The plaintiff alleges that, if the lawsuit is recognized as a class action, the claim against us is estimated to be NIS 216 million (approximately $56 million), calculated by claiming damages of NIS 18,000 ($4,628) for each individual who worked in fabrication workshops in Israel in fabrication or administrative roles and who have been exposed to dust generated by the fabrication of our

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products. The plaintiff claims that there are 12,000 such individuals who worked at 400 fabrication workshops in Israel, each of which employed 10 fabricators and five administrative persons, with one rotation during the relevant period. In addition, such claim includes an unstated sum in compensation for special and general damages, such as medical disability, functional disability, pain and suffering, medical expenses, medical and nursing assistance, which will require proof and quantification for each injured person in the purported class action. The plaintiff seeks, among other things, to compel us to notify the alleged group (and potential members of the group) and each individual about the risks, recommending that they undertake a medical examination and assert their rights.

We intend to vigorously contest recognition of the lawsuit as a class action and to defend the lawsuit on its merits, although, considering the preliminary stage of this lawsuit, there can be no assurance as to the probability of success or the range of potential exposure, if any.

December 2013 Judgment

The plaintiff alleges that, if the lawsuit is recognized as a class action, the claim against us is estimated to be NIS 216 million (approximately $56 million), calculated by claiming damages of NIS 18,000 ($4,628) for each individual who worked in fabrication workshops in Israel in fabrication or administrative roles and who have been exposed to dust generated by the fabrication of our products. The plaintiff claims that there are 12,000 such individuals who worked at 400 fabrication workshops in Israel, each of which employed 10 fabricators and five administrative persons, with one rotation during the relevant period. In addition, such claim includes an unstated sum in compensation for special and general damages, such as medical disability, functional disability, pain and suffering, medical expenses, medical and nursing assistance, which will require proof and quantification for each injured person in the purported class action. The plaintiff seeks, among other things, to compel us to notify the alleged group (and potential members of the group) and each individual about the risks, recommending that they undertake a medical examination and assert their rights.

We intend to vigorously contest recognition of the lawsuit as a class action and to defend the lawsuit on its merits, although, considering the preliminary stage of this lawsuit, there can be no assurance as to the probability of success or the range of potential exposure, if any.

December 2013 Judgment

In December 2013, a judgment was entered by the Central District Court of Israel in one of the lawsuits, according to which we were found to be comparatively liable for 33% of the plaintiff's total damages. The remaining liability was imposed on the plaintiff at 40%, as contributory negligence, and on the Israeli Ministry of Industry at 27%. The total damages of the plaintiff were found by the court to be NIS 5.3 million ($1.4 million). Since the plaintiff received payments from the NII, such payments were subtracted from the total damages after reduction of the damages contributed to the plaintiff's

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contributory negligence. However, under Israeli law, under certain condition a plaintiff may be awarded as compensation from third party injurers, other than his employer, at least 25% of the damages claimed even if the payments that the plaintiff received from the NII equal or exceed the actual damages of the plaintiff after deducting his contributory liability. Accordingly, in the above claim, the court awarded the plaintiff additional compensation of approximately NIS 800,000 ($0.2 million) plus legal fees and expenses, which reflected 25% of the plaintiff actual damages, after deducting the plaintiff's contributory negligence and the amount of NIS 3.3 million ($0.8 million) to which the claimant is entitled from the NII. After giving effect to the Israeli Ministry of Industry's comparative responsibility, the total liability imposed on us in this case was NIS 436,669 ($0.1 million) plus the claimant's legal expenses. Such amount was fully paid by our insurer in January 2014 (apart from our deductible). We, as well as the Israeli Ministry of Industry and the plaintiff, appealed on the judgment to the Israeli Supreme Court. There is no assurance whether we or any of the other appellant shall succeed in the appeals.

Claim by Former Employee

One of the fabricators who filed a claim against us was employed by us in the past and claimed that his illness was, in part, the result of his employment with us. Although there can be no assurance that we will succeed in such claim, we believe that his illness is not related to his employment by us. We are not currently subject to any other claim from our employees related to silicosis; however we may be subject to such claims in the future. Our employers' liability insurance policy excludes silicosis claims by our employees, and to the extent we become subject to any such claims, we may face claims in excess of the portion covered by the NII.

Settled Claims

We were also a party to two settlement agreements that had been approved by a court with respect to two of the claims filed. In one case, the total settlement was for NIS 275,000 (approximately $71,000) of which we had agreed to pay NIS 10,000 (approximately $3,000) without admitting liability. Substantially all of the balance was payable by the fabricator that employed the individual in question and insurance companies. In the other case, the total settlement was for NIS 130,000 (approximately $33,000) of which we agreed to pay NIS 80,000 (approximately $21,000). The balance was payable by the fabricator that employed the deceased plaintiff.

We can provide no assurance that other lawsuits will be settled in this manner or at all.

Dismissed U.S. Claim

In 2012, Caesarstone USA was added as a 26th defendant approximately one year after commencement of a lawsuit bodily injury claim in the United States by a fabricator in the United States. The other 25 defendants were manufacturers of equipment utilized in

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stone fabricating or finishing operations or manufacturers and marketers of stone and engineered stone products. Total damages of approximately $56 million, including approximately $20 million of punitive damages, were sought in the U.S. claim. The case was ultimately dismissed and we were removed as a defendant.

Insurance

We currently have product liability insurance in Israel, which applies to claims that may be submitted against us worldwide during the insurance policy term and our Australian, and U.S. subsidiaries have product liability insurance in Australia, and the United States, respectively, covering their activities. Our product liability insurance, currently covers claims that are submitted worldwide during the insurance policy term up to an amount of $20 million per claim and per insurance policy term, plus legal fees and litigation costs in three layers. Commencing in 2008, we had five consecutive insurance policies in Israel, effective for periods of 12 to 18 months.

We believe that our current insurance covers the pending individual product liability claims; however, with respect to the claim which was required to be recognized as a class action, our insurer has notified us that our product liability insurance covers such claim only partially. Although, it is our position that such class action is fully covered by our product liability insurance, but subject to the coverage amount limit and to the insurer position, there is no certainty whether our insurance would also cover the class action. In addition, the amount claimed in the currently pending class action exceeds our insurance coverage by a material amount.

Our product liability insurance includes coverage of up to $20 million, plus legal fees and litigation costs. The coverage includes (i) coverage of $5 million provided by an Israeli insurer, which initially insured us for $10 million beginning in March 2014 and then reduced the coverage to $5 million in July 2014 (the "first layer"), (ii) additional coverage of $5 million (the "second layer") in excess of the first layer, and (iii) an additional excess layer of $10 million in excess of the first layer and second layer, starting from July 2014 (the "third layer"). Our product liability insurance policy is effective until March 31 2015. Our current product liability insurance policy includes a double-rate premium compared to our prior year insurance and a deductible of $125,000 per claim that was applied within the renewed policy term, instead of a $5,000 deductible applied previously. The second and third layers apply only for illnesses discovered after February 2010. Our first layer insurer has informed us that the first layer of coverage will not be renewed as of March 31, 2015. Although we will seek to renew our product liability insurance to cover silicosis related claims, there is no assurance that we will be successful.

We believe that our current insurance in Israel covers the pending individual product liability claims; however with respect to the claim brought in April 2014 where the plaintiff applied for class certification, our insurer has notified us that our product liability insurance covers such claim only partially. While we believe that

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such class action is fully covered by our product liability insurance policy, subject to the coverage amount limit, there is no certainty whether our insurance would also cover the class action. In addition, as discussed below, the amount claimed in the currently pending class action exceeds our insurance coverage by a material amount.

In the event that we are unable to renew our insurance at all or in part, we are unable to obtain coverage from other insurance providers, we cannot obtain insurance on as favorable terms as previously, our insurance is terminated early, our insurance coverage is decreased, our insurance coverage inadequately covers damages for which we are found liable, or we become subject to silicosis claims excluded by our employer liability insurance policy, we may incur significant legal expenses and become liable for damages, in each case, that are not covered by insurance, and our management could expend significant time addressing such claims. Such events might have a material adverse effect on our business and results of operations.

Our employer liability insurance excludes silicosis damages and, therefore, in case that we are found liable for any of our employees' illness with silicosis, we will have to bear compensation for such damages, which might have adverse effect on our business and results of operations.

912. The information provided in Caesarstone's year-end 2014 annual report was known to the officers and directors of the company that are identified in the report as follows:

Officers

Yosef Shiran	Chief Executive Officer
Yair Averbuch	Chief Financial Officer
David Cullen	Chief Executive Officer Caesarstone Australia
Sagi Cohen	Chief Executive Officer Caesarstone USA
Giora Wegman	Deputy Chief Executive Officer
Michal Baumwald Oron 41	Vice President Business Development and General Counsel
Eli Feiglin	Vice President Marketing
Erez Schweppe	Vice President Sales
Harel Boker	Vice President of Operations
Tzvika Rimon	Israel Country Manager
Erez Margalit	Vice President Research and Development
Lilach Gilboa	Vice President Human Resources

Directors

Maxim Ohana	Chairman
Yonatan Melamed	Director
Moshe Ronen	Director
Shachar Degani	Director
Irit Ben-Dov	Director
Ofer Borovsky	Director
Belinkov	Director
Avner Naveh	Director
Ofer Tsimchi	Director
Or Gilboa	Director
Amihai Beer	Director

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12. Caesarstone's Knowledge of the Silicosis Epidemic From 2015 to 2020

913. In 2015 Spruce Point Capital Management issued an Investment Research Report regarding Caesarstone (CSTE), with a *"Strong Sell"* recommendation, the Executive summary of which stated:

> **Unquantifiable Product Liability for Silicosis-Related Deaths:** CSTE is a party to a growing number of lawsuits related to death and injury as it relates to injuries suffered by workers and fabricators of its products in Israel (from 14 in 2012, to 60 today). A single plaintiff and motion for class action certification alleges a $56m damage. CSTE's insurer said it would only be partially covered, thus exposing CSTE to a material risk. CSTE is also in the process of opening its new facility in the U.S. and OSHA has recently warned about the dangers of silicosis, specifically highlighting issues in Israel. Increasing regulatory scrutiny could drive up its cost of doing business.

914. In 2015, Caesarstone opened a new facility in the United States with an investment of about 100 million dollars. The plant was built in Richmond Hill, Georgia, and provides Caesarstone® mainly to markets in North America, and other countries as well.

915. By 2015, another 15 Israeli workers occupationally exposed to Caesarstone had developed silicosis, bringing the total number of silicosis cases attributed to Caesarstone to 40 cases. Of the 40 cases, 16 were lung transplant recipients (an additional 6 transplants above the 10 that the Israeli researchers had report three years earlier). Of the 40 workers who had silicosis from occupational exposure to Caesarstone, 9 also had specific diagnoses of autoimmune diseases, which are also known to be caused by occupational exposure to crystalline silica. The Israeli physicians observed that "[a]ll 40 patients included in the study were male and had substantial occupational histories of silica exposure while working with a high-silica-content synthetic stone material. They all did similar work that included drycutting and polishing the stone for end use, predominantly for kitchens and other countertop applications." The researchers "identified nine patients with a specific diagnosis of autoimmune disease among the 40 persons with silicosis evaluated at our lung transplantation centre, representing 23% of the cohort." Straichman O, et al., "Outbreak of autoimmune disease in silicosis linked to artificial stone," *Occup. Med.* 2015; 65:444-450. The results of this study were known to Caesarstone's officers and directors at the time of publication.

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916. By November 2016, the Israeli physicians had identified 82 workers who had been exposed to artificial stone dust (Caesarstone) and had been diagnosed with silicosis, of whom 13 patients underwent lung transplantation. This was more than double the number of workers exposed to Caesarstone that they had identified in 2015 as having silicosis. The Israeli researchers reported progressive massive fibrosis, indicating advanced and complicated silicosis in 85% of the lung transplant patients. Additionally two patients had silicoproteinosis diagnosed within the resected lung, indicating an acute or accelerated form of silicosis. The researchers concluded that "[t]his silicosis current outbreak is important because of the worldwide use of this and similar high-silica-content artificial stone products, which can cause progressive severe forms of silicosis." Grubstein A, et a., "Radiological Evaluation of Artificial Stone Silicosis Outbreak: Emphasizing Findings in Lung Transplant Recipients," *J. Comput. Assist. Tomogr.* 2016; 40(6):923-927. The findings and conclusions of this study were known to Caesarstone's officers and directors at time of publication.

917. In 2016, an abstract by Israeli researchers was presented at the 2016 annual meeting of the International Society for Environmental Epidemiology and published the following year in the journal *Environmental Health Perspectives*. The Israeli researchers reported that "Israel's stone industry is witnessing a drastic rise in silicosis" and that "a total of 203 new cases were identified since 2009 alongside with an increase in use of artificial quartz surfaces at ~ 500 enterprises [in Israel]." The abstract further stated that "[t]hese high-end and durable countertops Israeli-made surfaces, introduced in 1987, consist of up to 93% of crystalline silica (SiO2)" and that "[a]nalyses of registered cases (2012-2014) indicate a short latency period (65% ≤20 years; 37%≤10 years), as compared to former registry." Raanan N, et al., "An Outbreak of Artificial Stone Silicosis in Israel – A Call for Worldwide Awareness," Abstract No. P3-208, presented at the 2016 Annual Meeting of the International Society for Environmental Epidemiology in 2016, published in *Environmental Health Perspectives* in 2017 at https://ehp.niehs.nih.gov/doi/abs/10.1289/isee.2016.4338.

918. In 2017, the Israeli researchers published a study in which they reviewed data for all patients who underwent lung transplantation for silicosis and a matched group undergoing lung transplantation for idiopathic pulmonary fibrosis (IPF) at the National Transplant Center from March 2006 and the end of December 2013. Survival was followed through 2015. They noted that a total

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of 17 lung transplantations had been performed for silicosis among 342 lung transplantations (4.9%) during the study period. They also observed a survival advantage that was not statistically significant (hazard ratio 0.6; 95% CI 0.24–1.55) for those undergoing lung transplantation for silicosis relative to idiopathic pulmonary fibrosis patients undergoing lung transplantation during the same period. Rosengarten D, et al., "Survival Following Lung Transplantation for Artificial Stone Silicosis Relative to Idiopathic Pulmonary Fibrosis," *Am. J. Ind. Med.* 2017; 60:248-254. This study This study showed that workers who receive lung transplants for silicosis resulting from occupational exposure to artificial stone (Caesarstone) generally fare well as lung transplant recipients. The study was known to the officers and directors of Caesarstone at or about the time of publication.

13. Caesarstone's January 2020 Safety Data Sheet

919. In January 2020, Caesarstone issued a new Safety Data Sheet for its Caesarstone® product. In Section 1 of this Safety Data Sheet, headed "Product and Company Identification," Caesarstone identified the "product name" as "Caesarstone® surfaces" and stated: "This Safety Data Sheet relates to Caesarstone Classico, Supernatural and Metropolitan collections." This section of the Safety Data Sheet listed five Caesarstone entities (Caesarstone Ltd., Caesarstone USA Inc., Caesarstone Canada Inc., Caesarstone Australia Pty Ltd., Caesarstone South East Asia Pte Ltd., and Caesarstone (UK) Ltd), and provided their addresses and telephone numbers. The next page of the Safety Data Sheet contains a statement that "In this SDS "Caesarstone® slabs are referred to also as 'products.'" Thus, this Safety Data Sheet clearly applied to Caesarstone® that was marketed and sold in the United States in slabs which required fabrication before installation in consumers' homes.

920. Section 2 of Caesarstone's January 2020 Safety Data Sheet, titled "Hazards Identification," began with the following statement: "The finished Caesarstone® is an inert, stable product that does not release hazardous materials in its fully intact form." This statement is misleading in two respects. First, Caesarstone® is not a "finished product," i.e., a product that can be used by consumers, but is instead an industrial product that requires extensive processing before it becomes a finished product that can be installed as countertops in consumers' homes. As explained in an article published in *Business of Home* that very month, "consumers - even designers -

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can't go to a stone supplier or a Caesarstone showroom and order the company's product" and Elizabeth Margles, Caesarstone's vice president of marketing was quoted in that article admitting "We sell to the fabricator." Second, and more importantly, the statement that the product "does not release hazardous materials in its fully intact form" does not identify hazards of the product, but instead misleads readers to believe that the product has no hazards because the of the language that the "product does not release hazardous materials."

921. Section 2 of Caesarstone's January 2020 Safety Data Sheet contains three "Hazard Statements":

- (H350) May cause CANCER (inhalation)
- (H372) Causes damage to lungs through prolonged or repeated exposure (inhalation)
- (H335) May cause respiratory tract irritation

Although silicosis is the major health hazard of Caesarstone®, the Safety Data Sheet does not mention silicosis at all in the Hazards Identification section of the Safety Data Sheet.

922. The three hazards identified in the Hazards Identification section of the Safety Data Sheet are all inadequate and misleading for several reasons. The statement that the product "may cause cancer" is misleading because it suggests that the product is not known to cause cancer, although it is comprised of more than 90% crystalline silica which for more than 20 years had been classified by the International Agency for Research on Cancer as a known human carcinogen. The statement that the product "causes damage to lungs through prolonged or repeated exposure" is inadequate and misleading for three reasons. First, it suggests that "lung damage" can only occur as a result of "prolonged" exposure which could mean exposure over a few decades. Second, it suggests that "lung damage" can occur as a result of "repeated exposure" which could mean hundreds or thousands of exposures. These statements wrongfully suggest to employers and workers that fabricators can use Caesarstone® safely as long as their use is not unduly "prolonged" or "repeated," although Caesarstone fails to quantify these terms, leaving workers to guess how "prolonged" or "repeated" their exposure to Caesarstone® must be to cause lung damage. Third, the language that Caesarstone® "causes damage to lungs through prolonged or repeated exposure" does not indicate that the lung damage caused by Caesarstone® is always permanent, irreversible, progressive

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(continuing after exposure to Caesarstone® ceases), and is often fatal. The statement wholly fails to convey the severity of the hazard to fabricators' respiratory health. This failure is compounded by the third hazard statement that Caesarstone® "may cause respiratory tract irritation," because respiratory tract irritation occurs frequently from such harmless activities as chopping an onion, thereby suggesting that the respiratory hazards of inhaling Caesarstone® may not be serious.

923. Caesarstone's Safety Data Sheet states, on page 3: "**PREVENTION:** Do not breathe dust generated during the Fabrication, installation and/or removing/demolishing processes." This is an inadequate and harmful instruction, because dust is always generated during the fabrication of stone products and were a worker to follow the instruction and hold his breath for a full 8 hour work shift, the worker could suffer asphyxia and other harm. The SDS also states: "Wear respiratory protection for particles (P3/N95 or higher)." This is also an inadequate use instruction, because the extremely high silica content of the product (>90% crystalline silica) renders it so dangerous that the instruction to wear a P3 or N95 mask assures harmful respiratory exposure rather than preventing harmful respiratory exposure, which require an air supplied respirator and other protection.

924. Section 8 of the Safety Data Sheet, which is titled "Exposure Controls/Personal Protection," has subheadings for Exposure Guidelines, Engineering Controls, Cleaning and Maintenance, Preventive Maintenance Programmes, and Personal Protective Equipment.

925. The section of the Safety Data Sheet regarding Exposure Guidelines has a subheading: "Permissible Exposure Limit (PEL)." This is misleading because it implies that exposure to crystalline silica dust is "permissible" although the instruction on page 3 of the SDS states: "Do not breathe dust generated during the Fabrication, installation and/or removing/ demolishing processes." The Safety Data Sheet then states: "There is no provision for any risk associated with the finished Caesarstone® product in the CLP (EC) regulation no. 1272/2008." This is misleading because it implies an absence of risk associated with the "finished" product simply because the EC [the European Commission] has not decreed the existence of risk associated with the "finished" product. The Safety Data Sheet then states: "[I]n Fabrication Processes of the product, dust containing crystalline silica (SiO_2), other minerals, and titanium dioxide may be generated. USA OSHA determined a total dust PEL of 15 mg/m^3, a respirable fraction PEL of 5 mg/m^3, and a

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titanium dioxide (total dust) PEL of 15 mg/m^3." This information is misleading because, total dust exposure limits refer to dust that is not toxic (commonly called "nuisance dust") - not to crystalline silica dust. Employers that kept exposures to dust from Caesarstone below 15 mg/m^3 would be exposing their workers to respirable silica dust approximately 200 times greater than the regulatory limit.

926. The Safety Data Sheet then states: "Threshold Limit Value (TLV) for crystalline silica α-quartz and cristobalite (ACGIH 2019): 0.025 mg/m^3." However, it does not explain what a TLV is or how it differs from the PEL. The SDS then states: "Check the PELs applicable under the regulations of each country where you handle the product. PELs for respirable crystalline silica and cristobalite, measured in mg/m^3, 8 hours, TWA are as follows: (These limits may be changed from time to time; you are required to follow local safety announcements.)" The SDS then provides a long list of countries, and for USA OSHA, PEL for respirable crystalline silica states: "0.05 - general industry/maritime" and "10÷(%SiO_2 + 2) - construction*." A footnote explains the asterisk: "Fabricators who work at construction sites (for example, installers) should apply the PEL for construction; others should apply the PEL for general industry." This is unintelligible, leaving workers and employers to speculate what exposure level is "permissible" when all exposure to respirable crystalline silica is prohibited by the instruction on page 3: "Do not breathe dust generated during . . . fabrication, installation."

927. The Personal Protective Equipment section of the Safety Data Sheet has a subsection titled "**RESPIRATORY PROTECTION**" that states: "Properly fitted respiratory protection equipment approved by the National Institute for Occupational Safety and Health (NIOSH; USA) for protection against organic vapours and dusts is necessary to avoid inhalation of crystalline silica during the Fabrication Process of the product, and other processes that generate dust. The appropriate respirator selection depends on the type and magnitude of exposure. Use a positive pressure air supplied respirator if there is a potential for an uncontrolled release, exposure levels are not known, or under any other circumstance where air purifying respirators may not provide adequate protection." This information is inadequate and confusing for several reasons. First, the Safety Data Sheet does not specify the types of respiratory protection equipment that are approved by NIOSH

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for protection against organic vapors and dusts that are "necessary to avoid inhalation of crystalline silica during the Fabrication Process." Second, the Safety Data Sheet does not explain how the employer or worker can determine whether the unspecified respiratory protection equipment is "properly fitted." Third, it is grossly inadequate to state that "the appropriate respirator selection depends on the type and magnitude of exposure," because the product contains more than 90% crystalline silica, which results in excessive airborne exposures to respirable crystalline silica dust from virtually all fabrication processes, which are defined in Section 2 of the SDS as "cutting, grinding, chipping, sanding, drilling, polishing, etc. manufacturing processes, including during installation or removal of the product." Given the extremely high concentration of crystalline silica in the product (which is many times greater than the silica concentration of natural stone) and the consequent extremely high concentrations of respirable silica dust generated by fabrication processes, the highest level of respiratory protection is necessary to use the product safely, i.e., an independent air supply respirator with full body protection like that typically used by sandblasters, which prevents toxic dust from contacting the body while the worker breathes fresh air from a tank rather than from contaminated workroom air. The language in the Safety Data Sheet that one should "use a positive pressure air supplied respirator if there is a potential for an uncontrolled release, exposure levels are not known, or under any other circumstance where air purifying respirators may not provide adequate protection" is inadequate, because (1) an "uncontrolled release" indicates an extraordinary release of dust as in an industrial accident, whereas all fabrication processes result in the "uncontrolled" release of respirable crystalline silica; (2) exposure levels are never known unless real-time air monitoring is done throughout the workday (which is grossly impractical); and (3) the extremely high concentrations of silica dust generated by fabrication processes of the product containing more than 90% crystalline silica are such that air purifying respirators never provide adequate protection against silicosis.

928. Section 11 of the Safety Data Sheet regarding Toxicological Information also provides misleading and inaccurate information. This section of the Safety Data Sheet begins with the statement in boldface type: "**No acute or chronic effects are known from exposure to the intact product.**" This information is misleading because there is no respiratory exposure, ocular

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exposure, or exposure by ingestion to Caesarstone as a slab of synthetic stone, and the stone slab is so solid and hard that dermal exposure to the slab would not result in any detectable transfer of silica to human skin. Thus, for all practical purposes, there is no exposure "to the intact product." Including this language is therefore unnecessary at best and misleading at worst.

929. The Safety Data Sheet then provides the following information regarding **PRIMARY ROUTES OF EXPOSURE:** "None for intact product. Inhalation and potential exposure to eyes, hands, lungs or other body parts if contact is made with dust emitted from the Fabrication Process." This information is misleading, because fabrication processes invariably result in the inhalation of crystalline silica dust and contact exposure to eyes, hands, lungs and other exposed body parts.

930. Regarding **RESPIRATORY EFFECTS** of Crystalline Silica (SiO_2), the SDS states: "Safety measures including wet processing and the use of effective respiratory protection will reduce the burden of inhaled dust and prevent the disease." This is a false statement, because (1) wet silica dries and becomes airborne by the movement of people, forklifts, other equipment and air currents in fabrication areas, and (2) wet processing does not prevent silicosis. Indeed, silicosis cases have been reported in artificial stone fabricators who regularly used wet processing methods and wore masks full shift. While these precautions reduce exposure to crystalline silica, they do not prevent silicosis. The Safety Data Sheet therefore lulls workers who do their work using wet processing methods and who face masks into a false sense of safety.

14. Caesarstone Mounts Public Relations Campaign

931. In the Fall of 2019 National Public Radio reported that almost 20 fabrication workers had fallen ill with silicosis after working with engineered stone. As a result of adverse press, Caesarstone commenced a public relations campaign by announcing an educational initiative, whose real purpose was to inform workers of the hazards of silicosis so Caesarstone could claim that they assumed the risk of silicosis when they were later diagnosed with the dreadful disease.

15. Judgment Against Caesarstone

932. In 2021, Caesarstone was found liable in Yigal Rozman's lawsuit against the company for causing his silicosis and was ordered to compensate Mr. Rozman for his injuries.

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16. Caesarstone's Health & Safety Webpage

933. As part of this public relations campaign, in 2022 Caesarstone created a webpage titled "Caesarstone® Health & Safety" that stated: "As part of our ESG commitment, we are committed to developing environmentally friendly and low-silica products. We launched our low-silica based product into the market in 2022." Caesarstone® Health & Safety webpage, https://www.caesarstone.com.au/caesarstone-health-safety/.

17. Caesarstone's Silicosis Statement

934. On February 20, 2023, Caesarstone issued a Silicosis Statement in the form of a letter addressed to "Dear Valued Customer," responding to the company's negative press coverage regarding engineered stone. Caesarstone posted the statement on its website: https://e925c66phkg.exactdn.com/wp-content/uploads/2023/02/Caesarstone-Silicosis-Statement_Feb-2023.pdf.

935. After paying lip service to victims of the silicosis epidemic it caused, Caesarstone wrote: "Silicosis is an avoidable occupational disease and we are absolutely committed to playing our role in its eradication." Both of these statements are false. First, silicosis is not avoidable from the fabrication of artificial stone, because rigorous use of wet processing methods and wearing air purifying respirators are incapable of preventing silicosis in artificial stone workers. Second, Caesarstone has never shown commitment to eradicating silicosis, but has always blamed the victims of this horrific disease and their employers who have been unable to protect their workers from silicosis due to misinformation and inadequate, harmful use instructions provided by Caesarstone.

936. Caesarstone wrote that "we take issue with a number of claims made in the recent news coverage regarding the safety of engineered stone," asserting: "Engineered stone is entirely safe to consumers in its installed form and silica only presents a risk to workers if stone is handled incorrectly." In the first statement Caesarstone once again seeks to deflect the lethal hazard of silicosis to workers by claiming that "engineered stone is entirely safe to consumers" although Caesarstone is not a consumer product, but is an industrial product and is only sold to consumers as finished countertops after being fabricated. Caesarstone's statement that "silica only presents a risk to workers if stone is handled incorrectly" is false, because studies have shown that artificial stone

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fabricators who use wet processing methods and wear air purifying respirators still get silicosis.

937. Caesarstone then asserts: "Efforts to improve safety standards have been hampered historically by some non-compliance with product handling requirements, a lack of regulatory enforcement and the absence of a national standard. This is the role of employers and work safety bodies." These statements are also false. The major impediment to improving safety standards for silicosis has not been a lack of regulatory enforcement, but has always been opposition by affected industries to lowering occupational exposure standards for respirable crystalline silica, resulting in the absence of adequate national standards and the perpetuation of standards that do not prevent silicosis. Equally false is Caesarstone's assertion that the silicosis epidemic is due to employers and governmental bodies that try to protect workers from the lethal hazards caused by Caesarstone. Thus, Caesarstone once again blames everyone for the epidemic it caused except itself.

938. Caesarstone then asserts that its "response to the issue has been to provide clear warnings and guides for safe handling of stone, to actively work with government and regulators on improved safety regimes and to invest heavily in fabricator education to improve safety standards." Of course, all of these statements are false, because Caesarstone has always failed to provide use instructions that could actually prevent silicosis, as demonstrated by the innumerable false, misleading, and harmful statements in its Safety Data Sheets over the years. Caesarstone did not work with government regulators to improve safety regimes and did not invest in fabricator education until its product had caused thousands of illnesses and deaths and Caesarstone decided to adopt a fabricator education program so that it could claim in defense of lawsuits that artificial stone fabricators knew of the hazards of silicosis, having been belatedly apprised of them by Caesarstone.

939. Caesarstone then advocates a licensing program with rigorous auditing and enforcement, so that when fabricators get silicosis, Caesarstone could blame governmental officials who license the fabricators and could blame the fabricators themselves for causing their own deaths.

940. Lastly, Caesarstone argues that natural stone can also cause silicosis although the epidemic is largely driven by artificial stone, rather than lower silica-containing safer products.

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18. Caesarstone's "Opening Statement"

941. In early 2023, Caesarstone responded to a series of questions by Australian regulators in an "Opening Statement" for a public hearing that the company published on its website.

942. One of the questions posed to Caesarstone was: "What level of silica was in the engineered stone in 1987? 95 per cent?" Caesarstone responded to this question: "At that time, the silica content was in the vicinity of 90%." Whether the silica content of Caesarstone was 90% or 95%, this is an extremely high and very dangerous silica content.

943. Another question posed to Caesarstone was: "When Caesarstone started selling artificial stone slabs in 1987 did it know that it contained high levels of silica, a level that is vastly higher than natural stone such as granite and marble and considered carcinogenic to humans if the crystalline silica dust is inhaled?" Caesarstone responded to this question: "Engineered stone has traditionally contained 60-97% silica." Thus, Caesarstone did not answer the simple question whether it knew its product contained silica levels that are much higher than those of natural stone.

944. Another question posed to Caesarstone was: "Workers in Israel and men who owned businesses and bought the product claim Caesarstone representatives told them the product was natural and did not mention they had to take precautions. Any comment?" Caesarstone responded: "Caesarstone cannot provide a response in the absence of being told any particulars of these discussions." This was an evasive response because Caesarstone must have some knowledge of how its employees marketed the company's product. Even if Caesarstone somehow did not know how its employees marketed its product, Caesarstone could have asked them whether the company's sales representatives told customers that the product was natural and did not mention they had to take precautions, so as to be able to answer the regulators' question.

945. Another question posed to Caesarstone was: "When did Caesarstone first learn that people working with the product were getting sick as a result?" Caesarstone answered this question: "2010." Thus, Caesarstone admitted that at least as early as 2010 it knew that people were getting sick as a result of working with the company's product.

946. Caesarstone was also asked: "In response to a series of questions from Safework NSW as to the alleged first findings of silicosis among artificial stone workers following tests of

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patients, Caesarstone said it became aware in 2010 as part of the first lawsuit filed against it. How does this correspond with your 2021 annual report which says the first court case was filed in Israel in 2008?" Caesarstone responded to this question as follows: "A single action filed in 2008 does not give rise to a more serious issue in the industry. Caesarstone was not aware of a number of cases of silicosis until 2010." Although the 2008 lawsuit alleging exposure to Caesarstone caused a worker's silicosis was just one case, it put Caesarstone on notice of the harmful nature of its product.

947. The next question posed to Caesarstone was: "Is Caesarstone suggesting that it never heard about an outbreak of workers being diagnosed with silicosis before the 2008 legal action in Israel?" Caesarstone responded to this question as follows: "A single action filed in 2008 does not give rise to a more serious issue in the industry. Caesarstone was not aware of a number of cases of silicosis until 2010." Notably, Caesarstone did not deny that before 2008 it heard about the outbreak of silicosis in workers who used Caesarstone in Israel.

948. Another question posed to Caesarstone was: "In 2010 Caesarstone started putting so-called warning stickers on the slabs it was selling. Why did it wait until 2010?" Caesarstone responded to this question as follows: "Caesarstone placed warning labels on slabs of stone when it became aware that workers were contracting silicosis in 2010." Caesarstone's response constitutes an admission that from 1987 when Caesarstone began making the product until 2010 (a period of 23 years), Caesarstone did not put any warnings on slabs of the product.

949. Another question posed to Caesarstone was: "How big was the warning sticker in Feb 2010 on the slab? – can you provide the measurement? How big is the slab? What part of the slab was the sticker put - on top, the bottom or was there no specific place?" Caesarstone responded: "The warning label is affixed to the back of each slab. The labels started in 2010 at approximately 14cm x 14cm. The 'standard' current [slab] size is 3050mm v 1440 mm." Converting from metric to American measurements, the sticker was about 5½ square inches and the slab was about 10 feet by $4^{3}/_{4}$ feet. Thus, the sticker covered less than a half of 1 percent of the surface area of the slab.

950. Another question posed to Caesarstone was: "In early 2010 a documentary in Israel aired which exposed workers dying of silicosis due to engineered stone. The documentary had been in the works months before it aired. Is that what triggered the decision by Caesarstone to start

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attempting to put warning labels on the products?" Caesarstone answered this question, "Yes," thereby admitting that it only began putting warning labels on the product *after* deaths of Israeli workers were publicly aired on Israeli television.

951. Another question posed to Caesarstone was: "When did Caesarstone start putting hazard warning symbols on the labels to Australia? Why did it take so long? Why didn't it do it from 2010?" Caesarstone responded: "While the first labels did not include the warning symbols, they clearly included the word: "WARNING." Notably, Caesarstone avoided answering the question and did not explain why the company did not put hazard warning *symbols* on labels for the product in 2010 – why it took the company another 10 years to do this.

952. Another question posed to Caesarstone was: "In 2010 a study was released with the titled Caesarstone and silicosis. Why did Caesarstone send legal letters to the publisher threatening legal action if it wasn't changed? At the time more than 90 per cent of the products sold in Israel were Caesarstone. It is claimed by one of the authors it was an attempt to cover up the role of Caesarstone products in the surge in silicosis cases in Israel?" Caesarstone responded to this question as follows: "The objection to the article was on the basis that it targeted Caesarstone. The article was entitled "Caesarstone® Silicosis: Disease resurgence among Artificial Stone". The invented name "Caesarstone® Silicosis" did not (and still does not) exist in the World Health Organization's International Classification of Diseases (ICD)." Notably, Caesarstone did not deny that it sent letters to the publisher of the medical journal threatening legal action of the titled of the article "Caesarstone® Silicosis" were not changed.

953. The next question posed to Caesarstone was: "Did Caesarstone ever offer one of the authors of the report a donation to the lab?" Caesarstone responded: "In the short time provided to respond, we have been unable to find any evidence of this." Notably, Caesarstone did not deny that it offered on the authors of the report a bribe.

954. Another question posed to Caesarstone was: "When the Israeli study . . . was finally published in 2012 it was based on a study of workers from 1997 to 2010 who had been diagnosed with silicosis and they all used the Caesarstone product. What did caesarstone do in Australia to warn customers about the study?" Caesarstone responded: "Caesarstone first became aware of this

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issue in 2010. In terms of customer warnings, see responses to Q5, Q6, Q8 and Q10." Caesarstone did not answer the question; the referenced "customer warnings" don't mention the 2012 Israelis study at all.

955. Another question posed to Caesarstone was: "Caesarstone told Safework reps it visited Stoneworx from 2007 to discuss dust and silicosis. Did Caesarstone ever report any factories to the regulator relating to concerns over dust and safety given workers at these sites have been diagnosed with silicosis. In the case of Stoneworx almost half the workforce was diagnosed with silicosis. If you could provide details." Caesarstone responded: "Caesarstone Ltd did not have representatives in Australia in 2007. Caesarstone Australia started trading on 1 April 2008. Caesarstone is involved in litigation with Stoneworx in the Dust Diseases Tribunal, and it is not appropriate to comment in the context of ongoing litigation." Caesarstone did not deny that it did not report to the regulator factories where almost half the workers were diagnosed with silicosis.

956. Another question posed to Caesarstone was: "Does Caesarstone admit it is selling a product that is killing people?" Caesarstone answered this question: "No." However, this response seems inconsistent with Caesarstone's prior statement admitting that it first learned in 2010 that people working with the product were getting sick as a result. In denying that it is selling a product that is killing people, is Caesarstone claiming that none of the many workers who got silicosis from Caesarstone died of silicosis, or is Caesarstone denying that it sells the product?

957. Another question posed to Caesarstone was: "Does Caesarstone agree the product should be banned? If not, what is the company's rationale for not banning it?" Caesarstone responded to this question as follows: "Caesarstone does not support a ban on engineered stone. A ban on engineered stone would not solve the issue of silicosis. There is no logic in banning one product that must be handled in exactly the same manner as all similar products, with almost half of silicosis cases reported in the year to 30 June 2021 occurring in industries outside engineered stone." Thus, Caesarstone argued that engineered stone should not be banned, because engineered stone is *only* responsible for about half of the industrial cases of silicosis.

958. Another question posed to Caesarstone was: "Workers in Israel and Australia, medical specialists and lawyers claim that Caesarstone covered up or underplayed the dangers of the

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stone for more than a decade after its release, how do you respond?" Caesarstone responded: "Caesarstone notes that the sources of these serious allegations are not cited. Caesarstone utterly rejects the notion of covering up or diminishing the seriousness of silicosis." Notably, Caesarstone did not answer the question whether it covered up or underplayed the *dangers* of its product for more than a decade. Instead, Caesarstone denied that it has covered up or diminished the seriousness of the *disease.*

959. Another question posed to Caesarstone was: "Given so many workers have been diagnosed with silicosis from engineered stone products, including Caesarstone which is the market leader in Australia, do you think there should be a public campaign about the dangers? Should the dangers be mentioned on TV shows that use the product?" Caesarstone answered this question as follows: "No. In terms of engineered stone, there are no cases of silicosis outside manufacturers and fabricators of the stone. Engineered stone is safe in situ, so there is no risk to consumers. It is an occupational disease that exclusively affects workers who cut, drill, grind or shape the stone without proper precautions." Thus, Caesarstone responded that the dangers of its product should not be made public because it is only manufacturing workers and fabricators who get silicosis - not consumers. Apparently, Caesarstone only values the lives of consumers, not workers.

960. Another question posed to Caesarstone was: "How many court cases in Australia is Caesarstone involved with either directly or as a third party? How many since the first legal case in Australia?" Caesarstone responded: "This is a matter of public record." The question arises why Caesarstone would not even say how many cases it is involved with in Australia. Doesn't Caesarstone know how many cases there are? Doesn't it care? Are there so many cases that it cannot accurately count them all?

961. Yet another question posed to Caesarstone was: "On average, what is the cost difference to produce and also the price sold for a product with less silica?" Caesarstone's response to this question was: "No comment." Thus, Caesarstone refused to state the cost difference to produce low-silica product and its price. Caesarstone's refusal to answer this question precluded regulators from determining whether low-silica product is an economically feasible alternative.

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19. Caesarstone's Submission to Safe Work Australia Regarding the Public Consultation on the Prohibition on the Use of Engineered Stone

962. In April 2023, Caesarstone submitted its position statement to Safe Work Australia regarding that governmental agency's proposed prohibition on the use of engineered stone. In this document Caesarstone responded to the question "do you support a prohibition of engineered stone that contains more than certain percentage of crystalline silica?" as follows: "Yes. Caesarstone supports . . . prohibition on the use of engineered stone containing 40% or more crystalline silica ...."

963. In responding that "Caesarstone supports ... prohibition on the use of engineered stone containing 40% of more crystalline silica," Caesarstone abandoned the position that it expressed in its "Opening Statement" earlier that year in which Caesarstone stated: "Caesarstone does not support a ban on engineered stone. A ban on engineered stone would not solve the issue of silicosis."

964. Apparently, Caesarstone concluded it could no longer defend its position that there should be no artificial stone ban, because Cosentino had conceded that the high-silica products are too dangerous and that artificial stone products of more than 40% crystalline silica should be banned.

965. Whatever the reason that Caesarstone abandoned its position that high-silica content artificial stone products should not be banned, its new position that the company "supports . . . prohibition of engineered stone . . . containing 40% or more crystalline silica" establishes that its >90% crystalline silica product is a defectively designed product that should be taken off the market.

966. In its statement to Safe Work Australia regarding that agency's proposed prohibition on the use of engineered stone, Caesarstone also commented: "When orders are placed, Caesarstone distributes the slabs to ... fabricators, who cut, shape and polish the slabs to the required specification. In most cases, the slabs are installed in homes and other buildings by the fabricators or sub-contractors connected to them." These comments are noteworthy, because Caesarstone acknowledged (1) that its artificial stone slabs are industrial products distributed to fabricators - not to consumers, and (2) that Caesarstone knew its slabs were being fabricated by "contractors" who were not employees of fabrication companies who would not receive training that employers are required to provide their employees and would not be covered by workers' compensation insurance.

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20. Caesarstone's Disgraceful October 2023 Advertisements

967. Caesarstone has feared that regulators would ban artificial stone in Australia because of the severe health risks it presents to fabricators and the large number of fabricators in Australia who suffer from silicosis. To deter Australian regulators from banning artificial stone, Caesarstone mounted a desperate advertising campaign in October 2023, taking out newspaper ads in Australian newspapers that sought to scare people into believing that banning artificial stone would harm Australian "tradies," i.e., fabricators and scare consumers. The advertisement said:

> **Banning benchtops won't solve silicosis.**
>
> **This incomplete solution puts workers at risk.**
>
> **The Issue**
> The government is currently reviewing a piecemeal ban targeting engineered stone benchtops and ignoring thousands of other products that contain silica. The engineered stone industry employs an estimated 8,000-10,000 Australians, however, they only represent an estimated 0.7% of workers exposed to silica and silicosis. It's clear that this issue isn't motivated solely by the safety of workers and will instead throw the construction industry into chaos.
>
> **The Facts**
> **Engineered stone is safe in our homes**
> As with other common materials that contain silica like bricks, concrete, tiles and sandstone that are not covered by this potential ban, it's the cutting process that requires safety measures to protect workers from silicosis. Like these other materials, engineered stone can be cut and handled safely when safety standards are followed. It's only when these standards aren't followed that there is a risk, as with all stone products containing silica.
>
> **Banning engineered stone will not solve silicosis**
> Substitute products including granite, quartzite and porcelain all contain high levels of silica. Alternate products such as laminate and artificial stone made of bauxite and acrylic binder also contain potentially harmful materials and chemicals. Banning one product does nothing to ensure the safety of the 99.3% of workers who are potentially exposed to other products containing silica that are being ignored by this potential ban.
>
> **A ban would cause chaos for homebuilding and renovations**
> With an estimated 1 million new bathrooms and kitchens built or renovated every year, households and builders will be scrambling to find substitute products that, even then, are likely to contain some level of silica. The construction industry, already under pressure, has warned this will create significant disruption.
>
> **Education, uniform standards and regulations can successfully protect workers**

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> There is generally a long latency period for silicosis, which means many current cases are from the past, prior to better education, practices and reduced silica content, which are all improving worker safety.
>
> **The Solution**
> There is a better, less disruptive path forward that will deliver a safer workplace for all stone workers. This includes a ban on engineered stone above 40% silica levels from next year and a transition to even lower levels of silica in the future.
>
> This must be coupled with continued worker education, uniform standards, monitoring, a licensing regime and robust enforcement by regulators for work on engineered stone and all products containing silica.
>
> AESAG caesarstone QUANTUMQUARTZ stoneAMBASSADOR smartstone

968. This advertisement prompted New South Wales Treasurer Daniel Mookhey to accuse Caesarstone of spinning deception and spreading misinformation. Mookhey compared the current advertising push to the tactics used by concrete manufacturer James Hardie before the nationwide prohibition of asbestos 20 years ago. Angus Thompson, "Ads over deadly engineered stone labelled disgrace and misinformation by state treasurer," *The Sydney Morning Herald* (October 25, 2023).

969. "Can I say in my own personal capacity that having seen that ad yesterday, I thought it was a disgrace, and an attempt at misinformation and misdirection worthy of James Hardie and the worst of their tactics as they fought to stop the regulation of asbestos," Mookhey said. James Hardie was the manufacturer associated with asbestos after using the substance in many of its building products. In 2005, the company signed an agreement with the NSW government to pay $4.5 billion for asbestos victims. Angus Thompson, "Ads over deadly engineered stone labelled disgrace and misinformation by state treasurer," *The Sydney Morning Herald* (October 25, 2023).

970. Construction, Forestry, Maritime, Mining and Energy Union national secretary Zach Smith described the ads as "the most blatantly evil corporate campaign I have ever seen." "No one needs Caesarstone. It is a product that kills people. And it kills them young," he said, adding he would be pushing federal Workplace Relations Minister Tony Burke to ignore the company's

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"bullshit letters" after it wrote to the minister. Angus Thompson, "Ads over deadly engineered stone labeled disgrace and misinformation by state treasurer," *Sydney Morning Herald* (Oct. 25, 2023).

971. Caesarstone Australia chief executive David Cullen denied there was anything misleading about the advertising campaign, which was run on behalf of several manufacturers under the banner of the Australian Engineered Stone Advisory Group. "Despite the rhetoric from the unions, the reality is that a ban on only one product containing silica will not solve silicosis," Cullen said. "There is a genuine concern that focusing on only one product containing silica may increase risks to workers by creating the impression that other forms of stone are 'safe' and do not require the same level of caution." Angus Thompson, "Ads over deadly engineered stone labelled disgrace and misinformation by state treasurer," *The Sydney Morning Herald* (October 25, 2023).

972. Dubbed the new asbestos, engineered stone contain up to 95 per cent crystalline silica and is responsible for a surge in irreversible lung disease in stonemasons. Asbestos was banned nationwide in 2003. Angus Thompson, "Ads over deadly engineered stone labelled disgrace and misinformation by state treasurer," *The Sydney Morning Herald* (October 25, 2023).

973. Calls for a blanket ban were taken up by the Australian Council of Trade Unions, which vowed to ban the material from the nation's building sites by next July if state governments had not acted by then. Angus Thompson, "Ads over deadly engineered stone labelled disgrace and misinformation by state treasurer," *The Sydney Morning Herald* (October 25, 2023).

21. Caesarstone's Response to Australia's Ban of Artificial Stone

974. In response to Australia's ban of artificial stone, which went into effect July 1, 2024, Caesarstone prepared a new page for its website titled "Is Engineered Stone Banned in Australia?" https://www.caesarstone.com.au/is-engineered-stone-banned-in-australia/#:~:text=Come%201st%20July%202024%2C%20engineered,any%20of%20the%20Caesarstone%20collection). It says:

> **Understanding the engineered stone ban in Australia**
>
> *With recent changes in regulations, many of our customers are asking if Caesarstone is banned in Australia, as well as if engineered stone has been banned in Europe and other regions.*

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It is important to understand that Caesarstone is the brand name and engineered stone is the product. Caesarstone the company is not banned it is those products defined as 'engineered stone' which has been banned irrespective of the supplier's brand name.

Caesarstone has a number of beautifully designed substitute products for selection that are the ideal solution for applications such as kitchen benchtops, bathrooms, laundries and more.

At Caesarstone, we have been proactively working on making stone production and processes safer and have anticipated and advocated for restrictions around the engineered stone industry, so we have been preparing for this change.

Come 1st July 2024, engineered stone will no longer be sold in Australia.

(Subject to final government decisions we believe contracts entered into prior to December 13th, 2023, will be able to be supplied any of the Caesarstone collection).

Leading up to this date, the sale and installation of engineered stone will continue and post July 1, Caesarstone will offer Caesarstone Mineral™ Crystalline Silica Free surfaces for applications such as kitchen benchtops. Along with the Caesarstone Porcelain collection of surfaces ideal for a variety of applications within your home including kitchen benchtops, bathrooms, laundries and outdoor dining areas.

Our response to the engineered stone ban.

The engineered stone industry is evolving, and so are we.

Since 1987, Caesarstone has been Australia's leading supplier of engineered stone for over 30 years. Over this time, we have heavily invested in the research and development of safer products and processes, we are proud to be leaders in innovation and change in our industry and excited about the evolution of our products.

As part of our commitment to continuous innovation, we have replicated 34 of our most loved market-leading colours and designs to a new crystalline silica-free material blend which will retain the same ease of fabrication and functional performance characteristics as current materials. Same designs, new material blend, Caesarstone Mineral™ Crystalline Silica Free surfaces are the ideal surface solution for kitchen benchtops, splashbacks and applications in bathrooms, laundries, furniture and commercial interiors.

In addition, Caesarstone® have introduced new designs into our Porcelain collection.

Our Porcelain brings additional functional performance to kitchen benchtops as well as being UV resistant and suitable for both indoor and outdoor applications.

Every Caesarstone® surface has a lifetime warranty, which is not impacted by these changes.

The Caesarstone Mineral™ design collection will only be available in the new crystalline silica free material blend from July 1st 2024.

Caesarstone is well advanced in transitioning from our previous low silica formula to the new crystalline silica free material blend, with many of our most loved colours and designs already available; with the full collection concluding latter in 2024.

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These products offer the same high-quality aesthetic and durability that Caesarstone is known for, while aligning with the new safety standards. They are developed with cutting-edge technologies and are produced with a unique blend of natural minerals, advanced innovative materials, and recycled materials, such as recycled glass.

Because our commitment to innovation and safety drives us to develop materials that meet the highest standards of environmental sustainability, our transition to crystalline silica free products is a natural progression towards more sustainable products that ensure safer working conditions for our industry.

The future of engineered stone in Australia and beyond

The trend is clear: there is a move towards safer, more sustainable materials used in industries; and we are at the forefront of this shift to ensure that our products meet not only Australian standards but also global expectations.

We are leading the way in safe and stylish surfaces

We understand that our customers want surfaces that are sustainably beautiful and pose no risk of harm to workers during the manufacturing and fabrication of their benchtops. Our crystalline silica free mineral surface is designed with this in mind.

Whether you're renovating your kitchen, designing a new bathroom, or working on a commercial project, you can trust Caesarstone to provide surfaces that are as safe as they are beautiful.

22. First Verdict Against Caesarstone in the United States

975. The first stone fabricator silicosis case in the United States to be heard by a jury is the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs, et al.,* Los Angeles Superior Court Case No. 22STCV31907, which was filed on September 29, 2022. On August 7, 2024, the jury in that case found Caesarstone USA, Inc. liable for causing the Mr. Reyes-Gonzalez's silicosis under all three theories of liability presented to the jury: negligence, strict liability for failure to warn, and strict liability for defective product design. The jury's verdict, which was rendered against Caesarstone and two other defendants, totaled $52,437,366 for Mr. Reyes-Gonzalez's compensatory economic and non-economic damages. The question whether Caesarstone's conduct warranted the imposition of punitive damages was not addressed by the jury.

976. The day after the jury rendered its verdict, Caesarstone Ltd. filed a Form 6-K Report of Foreign Private Issuer with the Securities and Exchange Commission, stating:

> As previously disclosed, Caesarstone USA, Inc. is one of a number of defendants in a series of lawsuits alleging that fabricators contracted illnesses, including silicosis, through exposure to silica particles while fabricating the defendants' products.

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> On August 7, 2024, the jury rendered a verdict in one such case brought in the Los Angeles County Court, *Gustavo Reyes-Gonzalez vs. Aaroha Radiant Marble & Granite Slabs, et al*. The jury found all defendants liable and awarded the plaintiffs $52.4 million in damages. Caesarstone USA was apportioned 15% of this amount, or $7.9 million, if assessed without modification.
>
> The Company strongly disagrees with the jury's verdict. It believes the verdict is not supported by the facts of the case, such as its failure to acknowledge the proactive measures the Company has taken over the years to warn and educate about safe fabrication practices. The Company intends to pursue its various post-trial remedies, including but not limited to overturning the verdict on appeal.
>
> The Company does not expect the outcome of this claim to have a materially adverse effect on its consolidated financial statements due to the amount involved and the fact that the Company has insurance coverage. The Company is subject to over 45 other product liability claims in the U.S. alleging silica exposure causing silicosis that are in an early stage. While we plan to vigorously defend all these claims, we are unable to provide an estimate of their potential exposure, if any, at this time.

977. Based on Caesarstone's representation to investors that the company does not expect the outcome of the *Reyes-Gonzalez* case "to have a materially adverse effect on its consolidated financial statements due to the amount involved," Caesarstone can withstand punitive damages.

23. Caesarstone's New "Silica-Free" Sustainable Mineral Surfaces

978. Sometime in 2024, Caesarstone posted a new webpage on its website titled "Sustainable Mineral Surfaces: Pioneering the *Crystalline Silica-Free* Revolution." Available online at https://www.caesarstone.com.au/crystaline-silica-free/#care-faqs. This webpage states:

> Since 1987 Caesarstone has combined design creativity and expertise in crafting beautiful, high-quality, durable and unique surfaces that empower you to create spaces that reflect your style and individuality.
>
> Caesarstone Mineral surfaces are the ideal surface solution for kitchen benchtops, splash backs and applications in bathrooms, laundries, furniture and commercial interiors.
>
> Pioneering, advanced technology.
> Same designs, new material blend.
>
> Caesarstone Mineral™ crystalline silica-free sustainable surfaces are developed by our pioneering expertise and advanced technology, and crafted from a unique blend of distinctive minerals, recycled materials, and other innovative materials.
>
> Utilising cutting-edge technology, they adhere to Caesarstone's highest quality and fabrication standards, surpassing the most rigorous industry and safety testings and complying with strict regulatory requirements, including XRD tests and the Hazard and Human Health Risk Assessment (HHRA) conducted by certified Australian

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laboratories.

These surfaces deliver exceptional longevity with minimal maintenance, confirming Caesarstone's renowned quality and outperforming other surface materials, backed by our famous Lifetime Warranty.

Caesarstone is well advanced in transitioning our Mineral designs from the previous low silica formula to the new crystalline silica-free material blend with many of our most popular Mineral designs already available in the new crystalline silica-free blend, with the full collection transition concluding latter in 2024.

979. The webpage included a series of FAQs, as follows:

Q Does the regular Warranty still apply to Caesarstone Mineral™ surfaces?

A Each of our surfaces is carefully inspected to ensure that it meets the highest level of international quality standards and is backed by professional customer service and support. For added peace of mind, Caesarstone products come with a lifetime Warranty. Visit caesarstone.com.au/warranty for more information.

Q What is the difference between Caesarstone Mineral™ crystalline silica-free and the recently banned engineered stone?

A Both of these products are manufactured in the same way, the major difference being in the raw material, engineered stone is classified as an artificial product that: a) is created by combining and heat curing natural stone materials that contain crystalline silica (such as quartz or stone aggregate) with chemical constituents (such as water, resins or pigments). Our Caesarstone Mineral™ material blend is made from recycled glass, polymer resins and pigment.

Q What is the Caesarstone Mineral™ Crystalline Silica-Free Collection?

A The collection is a curated range of our most loved designs, which will be transitioning to a crystalline silica-free material blend in line with the new government regulations. View the designs transitioning throughout 2024.

Q Is there any change to the size of the new crystalline silica-free slabs?

A Moving forward our complete range of Caesarstone Mineral™ surfaces will be available in Grande size slabs 3,240 x 1,640mm x 20mm.

Q Will the new product formulation retain the same look and finishes?

A Same designs and finishes, new material blend. Developed by our pioneering expertise and advanced technology, creating a crystalline silica-free material that delivers high resistance, durability, aesthetics, and exceptional design versatility.

Q What does this new product composition include?

A The new composition combines unique minerals and recycled materials such as glass developed especially for this use. This unique composition uses the materials to create a synergetic effect, bringing forward the best

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characteristics of each material, resulting in a world-class product that is safer for stonemasons to work with when taking the necessary safety measures.

Q How was this product created?

A Our dedicated efforts are geared towards seamlessly transitioning our most beloved designs to crystalline silica-free alternatives by the end of the year. These endeavours involve continuous investments in research and development, resulting in cutting-edge technologies that leverage specific minerals and advanced materials. This not only upholds our product's durability, strength, versatility, and aesthetics but also ensures that our offerings are free of crystalline silica, reinforcing our commitment to the safety and well-being of our workforce.

Q Do the new crystalline silica-free surfaces have any differences in durability?

A No. Developed by our pioneering expertise and advanced technology, creating a crystalline silica-free material that delivers high resistance, durability, aesthetics, and exceptional design versatility. Retaining the same properties of heat, stain and scratch resistance.

Q Will the range remain the same?

A We have edited our current range of 48 designs back to a curated collection of 33 designs which is reflective of current and importantly future design directions. With many exciting new innovative designs planned for future introduction.

Q When will the crystalline silica-free range be available?

A We are currently working through the transition on our range, with some colours having arrived, and continuing to do so in the months leading up to the end of the year. (availability in crystalline silica-free will vary by state, due to shipping times and stock levels). You can be confident in your choice, backed by our lifetime warranty. We're always here for you, let us know how we can help.

980. Regrettably, Caesarstone's advertising of its "Sustainable Mineral Surfaces" as "[p]ioneering the *Crystalline Silica-Free* Revolution" is yet another fraud by the company, because this new product is not "crystalline silica-free" as Caesarstone is advertising the product. Contrary to the statements on the company's websites and in its promotional material, Caesarstone's Safety Data Sheet dated May 2024 for the "Caesarstone Mineral™ Crystalline Silica-Free Surfaces" states that "[t]he product may contain <1% crystalline silica, of which some or all may be respirable when dust from Fabrication of the product is created." In addition to containing some crystalline silica, the product contains 80-90% recycled glass by weight, consisting primarily of amorphous silica which, although not as toxic as crystalline silica, is still toxic to the human lungs. Like its high-silica

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content product that has been banned in Australia, this new product also contains a polyester resin at a concentration of 10-15% by weight, which, when cut or ground with electric-powered tools, releases toxic volatile organic compounds (VOCs), including styrene, phthalic anhydride, benzene, ethylbenzene, and toluene. These chemicals are all respiratory irritants and cause various toxic effects to the human lungs, the most serious of which are asthma, bronchiolitis obliterans, decreased lung function, sclerosis and fibrosis when styrene and phthalic anhydride (which are respiratory sensitizers) are generated when polyester resin is cut or fractured under heat and pressure. Caesarstone's Safety Data Sheet for its"Caesarstone Mineral™ Crystalline Silica-Free Surfaces" does not disclose these toxic hazards and effects of its new supposedly "crystalline silica-free" product. The Safety Data Sheet for the new product also states that the product contains various pigments at a concentration of <0.5%, without identifying any of the chemical constituents of the pigments, although they are metals likely include aluminum, antimony, arsenic, chromium, cobalt, copper, iron, manganese, nickel, titanium, tungsten, and vanadium, some of which cause an immunologic lung disease called hypersensitivity pneumonitis characterized by granulomas in lung tissue.

24. Knowledge of the Silicosis Hazard by Caesarstone Officers and Directors

981. Throughout the time that Caesarstone manufactured and sold its artificial stone products, exposing fabricators and installers to crystalline silica from its products, Caesarstone's officers and directors were aware that its artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that it provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by its defective artificial stone products. Among Caesarstone's officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators were the following officers and directors of the company:

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Officers

Yosef Shiran	Chief Executive Officer
Yair Averbuch	Chief Financial Officer
David Cullen	Chief Executive Officer, Caesarstone Australia
Sagi Cohen	Chief Executive Officer, Caesarstone USA
Arik Tendler	President and Chief Executive Officer, Caesarstone USA
Giora Wegman	Deputy Chief Executive Officer
Michal Baumwald Oron	Vice President Business Development and General Counsel
Eli Feiglin	Vice President Marketing
Erez Schweppe	Vice President Sales
Harel Boker	Vice President of Operations
Tzvika Rimon	Israel Country Manager
Erez Margalit	Vice President Research and Development
Lilach Gilboa	Vice President Human Resources
Maxim Ohana	Chairman of the Board of Directors

Directors

Yonatan Melamed	Director
Moshe Ronen	Director
Shachar Degani	Director
Irit Ben-Dov	Director
Ofer Borovsky	Director
Avner Naveh	Director
Ofer Tsimchi	Director
Or Gilboa	Director
Amihai Beer	Director

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D. Cambria Company LLC

982. Cambria was founded in 2000 in Le Sueur, Minnesota; it is a privately held company owned by members of the Davis family. According to information on Cambria's website, "Cambria President and CEO Marty Davis realized the magic of quartz on one day" and "[i]t all began when Marty Davis' friend put him onto this new investment opportunity." The website states: "The Davises studied the opportunity and ultimately Mark Davis, Marty's father, made a personal investment in a northern Minnesota business start-up in the late '90s. They loved the company's technology and quartz product, but didn't know much more than that about the operation. But taking risks was something the Davis family was familiar with." That Cambria takes risks is undoubtedly true; every time it sells its lethal product Cambria risks the health and lives of countertop fabricators.

983. A Cambria YouTube video boasts that "now Cambria is one of the largest state-of-art quartz processing facilities in North America."

1. Cambria's January 5, 2001 Material Safety Data Sheet

984. On January 5, 2001, Cambria issued a Material Safety Data Sheet for a product that it identified as "Quartz Surfaces." In Section II of this document Cambria provided false and misleading information by identifying the product as a "Non Hazardous- Quartz Surfacing Product" and by stating that "exposure limits may be applicable . . . when cutting or grinding of the product is performed" because of its crystalline silica (quartz) content. The latter statement is false and misleading, because exposure limits for crystalline silica ***always apply*** when it is cut or ground.

985. Section VI of Cambria's January 5, 2001 Material Safety Data Sheet, regarding Health Hazards, began with the misleading statements that "this product is not hazardous as shipped," and that "grinding and cutting may generate dust containing crystalline silica." The former statement is misleading because the product is extremely hazardous when used as intended; the latter statement is false and misleading, because dust containing crystalline silica is ***always generated*** when the material is ground or cut. This section states that "continued overexposure to respirable crystalline silica can cause silicosis, a chronic and progressively debilitating disease, created by the silica-containing scar tissue which forms in the lungs." This statement is also false and misleading,

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because it indicates that only "continued overexposure" to respirable crystalline silica can cause silicosis, even though exposure to crystalline silica within occupational exposure limits (which is not an "overexposure") likewise causes silicosis. In this section of the Material Safety Data Sheet, Cambria also misrepresented the carcinogenicity of the product by stating that "this product is not considered to be a carcinogen as shipped, only when dust containing crystalline silica is produced." This statement is false, because the product is almost 100% crystalline silica and is therefore, by definition, carcinogenic to humans, the risk of harm depending on the nature and extent of exposure.

986. Section VII of the January 5, 2001 Material Safety Data Sheet, titled "Precautions for Safe Handling," is the most important section of the Material Safety Data Sheet, because it is this section that must provide clear, specific, and detailed instructions how to use the product safely, i.e., so that it will not cause silicosis. However, this section of the Material Safety Data Sheet only contains two sentences. The first sentence was "Recover material for reuse and reclamation when possible," which does not inform workers how to handle the product safely. The second sentence stated: "For silica dust, use a vacuum or wet down to prevent causing airborne particles." This use instruction is not merely incomplete and inaccurate; it is dangerous because use of a vacuum and "wet down", does not prevent the generation of airborne particles and does not prevent silicosis. Critically, this section for precautions for safe handling does not inform workers that to prevent silicosis they must always wear an air-supplied respiratory when fabricating the material.

987. In section VIII of the January 5, 2001 Material Safety Data Sheet for the product, regarding Control Measures, Cambria provided the following information on the form in the space for "Respiratory Protection *(Specify Type)*: "NIOSH approved respirator during cutting or grinding. Respirators should be used in accordance with OSHA Respiratory Protection Standard CFR 1910.134." This is an inadequate control measure because it does not specify the ***type*** of respirator that is necessary to prevent silicosis. There are numerous "NIOSH approved respirators." However, only one type of NIOSH-approved respirator is adequate to prevent silicosis when cutting or grinding the product - a NIOSH-approved ***air-supplied*** respirator. Following the instruction and wearing a NIOSH-approved respirator (i.e., a NIOSH-approved air purifying respirator) will not prevent silicosis, but actually contributes to silicosis. Thus, Cambria concealed this critical information.

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988. The last paragraph of the January 5, 2001 Material Safety Data Sheet contains a disclaimer that improperly attempts to shift responsibility for Cambria's false and misleading statements in the document to others (another company and the users of the product themselves): "The opinions expressed herein are those of qualified experts within Davisco Foods Int'l, Inc. We believe that the information contained herein is current as the state of MSDS sheet. Since the use of this information and these conditions of use of this product are not wihin the control of Davisco Foods, Int'l, Inc., it is the users obligation to determine the conditions of safe use of this product."

2. Cambria Starts Doing Business in California

989. On January 12, 2011, Defendant, Cambria Company LLC filed an application to Register a Foreign Limited Liability Company to do business in California.

3. Cambria's Response to the Artificial Stone Silicosis Epidemic in 2019

990. On December 2, 2019, Nell Greenfield-Boyce of National Public Radio interviewed Marty Davis regarding Cambria at its artificial stone factory in LeSuere, Minnesota. She observed: "It turns out about 30 thousand slabs of quartz countertop material every month. That means every day 20 to 30 trucks unload large white sacks full of quartz. Some of it's a powder, almost like flour, while some is like little pebbles." Marty Davis acknowledged: ""It's about 30 million pounds of quartz a month - so about 1 million pounds a day." He said this place has millions of dollars worth of air handling systems to control dust. Pointedly, he acknowledged: "There's no good dust. Zero." Ms. Greenfield-Boyce explained the production process: "We put on white disposable respirators and go past a sign warning of silica, into a huge room with mechanical mixers. Here, quartz gets combined with pigments plus a binder to make it stick together. The mixture gets spread out onto a giant baking sheet. It goes through a machine that vibrates and kind-of thumps it. The result is a compressed slab that, at first, is soft. The slab hardens when it gets heated, then cooled and polished." She asked Marty Davis "what responsibility does he have for making sure that people he sells it to will cut all this material safely?" He answered: "You know, how do you police your customers?" He said that the dangers of silica have been known for decades. He claimed that "there's clear regulation and clear guidance and governance on how to process materials safely to control dust and respiratory inhalation of dust." He said he can't follow his products to thousands

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of countertop shops -- that cutting is safe when companies obey worker protection laws." Thus, Mr. Davis, the Chief Executive Officer of Cambria, disclaimed any responsibility of Cambria to monitor the use of its lethal product by its customers, any responsibility of Cambria to protect the health of customers' employees and other workers injuriously exposed to its lethal product, and any responsibility to cease selling Cambria's lethal product to customers who fail to use Cambria safely.

4. Cambria's Letter to the Los Angeles County Board of Supervisors

991. On July 28, 2023, Marty Davis, CEO of Cambria, signed a letter to the Los Angeles County Board of Supervisors, urging the Board of Supervisors not to ban the importation and use of artificial stone in Los Angeles County. This letter stated: "Stone products are safely handled and worked on every day, including in Los Angeles County . . . ." This statement is false, because artificial stone products are not "safely handled and worked on every day, including in Los Angeles County," as is shown by the epidemic of accelerated silicosis among stone countertop fabricators which has its epicenter in Los Angeles County.

992. The letter by CEOs of artificial stone manufacturers seeks to foist blame on the owners of the small fabrication shops that fabricate artificial stone, rather than accepting personal responsibility for the deadly effects of their defectively designed artificial stone products. Thus, the letter states that "fabrication employers must provide necessary training, air monitoring and adherence to air quality requirements, engineering air handling controls, personal protective equipment (PPE), and medical surveillance in compliance with OSHA regulations." While multi-billion dollar manufacturers and importers like Cambria, M S International, Dal-Tile, and of course, Caesarstone and Cosentino, have the financial resources to spend millions of dollars to make their manufacturing facilities safe for their workers, fabrication shops (most of which are small mom-and-pop businesses that have 2 to 10 workers and generate annual revenues of a few hundred thousand dollars) lack the financial resources to implement the necessary protective measures, which cost a few million dollars in capital costs per shop, with annual maintenance costs of a few hundred thousand dollars. Thus, it is facetious for the multibillion dollar manufacturers and importers to attempt to blame the fabrication shop owners for their inability to protect workers from the deadly hazards of their artificial stone products.

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993. The letter also states: "Stone products, including engineered stone, have been manufactured and fabricated safely for decades . . . ." This statement is false. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the letter that "engineered stone ha[s] been manufactured and fabricated safely for decades is clearly and indisputably false.

5. Cambria's Endorsement of Misrepresentations by The Stone Coalition

994. In October 2023, a Paid Advertisement titled "Illegal Cutting Processes, Not Stone Products, can Cause Silicosis," was published in the Los Angeles Times. The advertisement states that it was "Paid For By The Stone Coalition," info@stonecoalition.org, which is described as "a collaborative effort between the quartz surface and natural stone industries."

995. The Stone Coalition is an industry trade association that was apparently formed in 2023 to defend the Stone Countertop Fabricator Silicosis Cases by mounting a public relations campaign to deflect liability from stone slab manufacturers, distributors and suppliers, by attempting to foist blame for the new stone fabricator silicosis epidemic on the victims, their employers, and regulatory and enforcement agencies – all to avoid accepting personal responsibility for the massive (ultimately fatal) harm that they have inflicted on thousands of young immigrant workers.

996. The home page of the new website of The Stone Coalition bears the name and logo of the Natural Stone Institute, implicating that industry trade association with the new trade association. The home page states: "The Stone Coalition is dedicated to promoting safe, wet processing technology in stone-cutting facilities while prioritizing compliance with OSHA air monitoring standards and other silica rules. Safety is our unwavering commitment." That is quite a statement by stone companies that for years opposed OSHA's adoption of the Silica Standard.

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997. A webpage titled "About" describes "Our Organization" as follows: "The Silica Safety Coalition is a collective of dedicated stone fabricators, manufacturers, stone distributors, and industry professionals united by a shared commitment to promoting workplace safety within the stone cutting and fabrication sector. Our mission is to promote and maintain the highest standards of safety, supporting the well-being of workers throughout every stage of stone processing." These statements are at best mere industry propaganda and at worst blatant falsehoods. The Coalition is actually a collective of multibillion dollar stone manufacturers and distributors that have been sued for causing the new stone fabricator silicosis epidemic – companies that for years failed to prepare any Safety Data Sheets or labels for their stone products or prepared Safety Data Sheets and/or labels that were so deficient that they caused, rather than prevented, the new fabricator silicosis epidemic.

998. The website of The Stone Coalition does not identify its members, but the "About" webpage contains a section titled "Workplace Safety" that informs readers to "Click the button to read our letter to the Los Angeles County Board of Supervisors." Clicking on the button reveals a letter dated July 28, 2023 to the Los Angeles County Board of Supervisors in which the authors of the letter attempt to persuade the Los Angeles County Board of Supervisors not to ban the importation and use of artificial stone products in Los Angeles County. The letter is signed by executive officers of four artificial stone companies: Marty Davis, CEO of Cambria; Rupesh Shah, Co-CEO of M S International, Inc.; Matthew Kahny, President of Dal-Tile; and Nate Kolenski, President of Block Tops, Inc.; and James A. Hieb, CEO of the Natural Stone Institute. The first three of these companies are among the most culpable defendants in the Stone Fabricator Silicosis Cases.

999. The title of the Paid Advertisement is itself misleading and false, for two reasons. First, it states that stone products do not cause silicosis, although most silicosis cases over the millennia and at the present time have been and continue to be caused by crystalline silica dust from stone products. Second, it states that only "illegal cutting processes . . . can cause silicosis," although cutting stone slabs can cause silicosis whether the cutting process is performed "legally," i.e., in compliance with OSHA requirements, or "illegally," i.e. in violation of OSHA requirements.

1000. The Paid Advertisement begins with the following statement: "Silicosis, a rare lung disease resulting from the inhalation of crystalline silica dust from dry-cutting or grinding concrete,

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brick or stone, has been found in illegal and unregulated stone fabrication across California, with a significant concentration in the San Fernando Valley." This statement is at best misleading and at worst false, for a few reasons. First, silicosis is not a rare lung disease. It is the oldest lung disease known to humankind and has killed more workers over the millennia than any other lung disease, including all lung diseases caused by exposure to asbestos. Additionally, recent epidemiological studies have reported a prevalence of silicosis among stone fabricators in the range of 30% to 40%, making it an especially common occupational lung disease that is of great public health concern. Second, the statement falsely suggests that silicosis is only caused by dry-cutting or grinding, although many workers who regularly used water-dispensing powered tools to reduce the amount of dust in fabricating stone countertops now suffer from silicosis and the National Institute for Occupational Safety and Health (NIOSH) has done studies which show that wet processing methods are inadequate to prevent silicosis among workers who fabricate artificial stone countertops. Third, silicosis among countertop fabricators and other workers exposed to crystalline silica has been shown to occur even at exposure levels below limits adopted by the Occupational Safety and Health Administration (OSHA), i.e., "legal" stone fabrication.

1001. The Paid Advertisement then states: "Yet, this disease is preventable through wet processing techniques and strict adherence to existing OSHA regulations." This statement is also false, because studies by NIOSH show that even fabrication workers who regularly use water-dispensing tools and wear particulate filter respirators at all times they are in the fabrication shop still develop silicosis from exposure to artificial stone dust.

1002. The Paid Advertisement then states: Despite Federal and State regulations to prevent the use of 'drycutting,' or cutting of stone or tile without water, and requiring personal protective equipment (PPE), many noncompliant facilities continue to put their employees at risk by failing to implement these basic safety precautions." This statement is also misleading and false, because most stone countertop fabrication shops have followed the recommendations of artificial stone manufacturers to use powered tools that dispense water to suppress dust generated by the fabrication of artificial stone, as well as the manufacturers' recommendations to have their employees wear particulate filter masks. However, both of these precautionary measures recommended by stone slab

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manufacturers are inadequate to prevent silicosis among stone countertop fabricators, which recommendations misled both employers and fabrication workers to believe that following the manufacturers' recommendations would prevent fabrication workers from developing silicosis. The use of water-dispensing tools is inadequate to prevent silicosis in artificial stone fabricators because at most it merely reduces the amount of lethal crystalline dust to which fabrication workers are exposed, and particulate filter masks do not prevent the extremely small particles of crystalline silica from cutting artificial stone from being inhaled and causing silicosis. In fact, the recommendation of the artificial stone manufacturers to wear a "NIOSH-approved" mask has caused many workers to develop silicosis, because NIOSH-approved particulate filter masks do not prevent harmful silica exposure, the only type of respirator that is effective in doing so is an air-supplied respirator, which the manufacturers of artificial stone have not recommended as necessary protection for workers.

1003. The Paid Advertisement then states that Jim Hieb, CEO of the Natural Stone Institute, knows this doesn't have to happen and quotes him saying: "Silicosis is preventable. Any contractor that follows Cal/OSHA's guidelines ensures that any cutting of any stone product is done safely." This statement is also misleading and false for a few reasons. First, while silicosis from exposure to natural stone dust may be preventable, silicosis from exposure to artificial stone is not preventable, because unlike natural stone, the fabrication of artificial stone generates massive amounts of ultrafine and nanosized crystalline silica particles that penetrate through particular cartridge respirators and are inhaled by fabricators and cause progressive massive fibrosis, because they are extremely toxic to the lungs - much more so than larger silica particles from natural stone. Second, while it may theoretically be possible to prevent silicosis in artificial stone fabricators, in the real world it is not possible to prevent silicosis in artificial stone fabricators, because the cost of installing state-of-art ventilation systems, respiratory protection programs, exposure monitoring programs, administrative industrial hygiene programs, and medical monitoring programs necessary to prevent silicosis, the capital cost of implementing these programs is a few million dollars per shop with annual costs of several hundred thousand dollars, which small fabrication shops that generate annual revenues of a few hundred thousand dollars cannot afford. Third, OSHA's guidelines were developed to protect against respirable crystalline silica particles in the micron size range - not ultrafine and nanosized

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crystalline silica particles that are uniquely generated from the fabrication of artificial stone and present extraordinary fibrotic hazards to the human lung and while compliance with OSHA's exposure limits for respirable crystalline silica may reduce fibrotic lung disease or delay its occurrence among stone fabricators, multiple studies have shown that compliance with OSHA's exposure limits is inadequate to prevent all silicosis. It is therefore irresponsible for the CEO of the Natural Stone Institute to state that compliance with OSHA guidelines "ensures that any cutting of any stone product is done safely," especially because exposure to respirable crystalline silica not only causes silicosis which may be dose-dependent, but also causes lung cancer and there is no level of exposure to crystalline silica that does not increase workers' risk of lung cancer later in life.

1004. The Paid Advertisement also states: "Almost all experts agree that what is being cut matters less than how the stone is cut and fabricated for placement within homes and offices." While this statement may generally be true for natural stone products, it is not true for artificial stone products which present unique respiratory hazards to stone countertop fabricators because artificial stone is manufactured by crushing and pulverizing quartz (crystalline silica) and then adding a polymeric resin, pigments and other additives and curing the mixture, so that when the finished slab is cut, the ultrafine and nanosized particles that are in the plastic matrix are released and are inhaled by fabricators even though they wear particulate filter respirators. Indeed, the extreme hazard of artificial stone is due not only to the extremely high crystalline silica content of the product (much higher than marble and granite), but is also due to the extremely small size of the crystalline silica particles that are released into the air when fabricators use powered tools to cut artificial stone.

1005. The Paid Advertisement also states: "Despite studies and regulations that show that the type of product matters significantly less than the method of cutting, plaintiffs' attorneys have been trying to blame engineered stone for recent cases of Silicosis among stone workers." It is true that attorneys who represent the ever-increasing number of young male Hispanic immigrants who have developed silicosis with progressive massive fibrosis and are terminally ill unless they receive lung transplants, primarily blame artificial stone for causing the workers' fatal lung disease, so too do knowledgeable pulmonologists, occupational medicine specialists, epidemiologists, and public health experts. Indeed, the new occupational disease epidemic of accelerated silicosis among stone

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fabricators is largely attributable to artificial stone, because it is an inherently dangerous and defective product whose purported benefits which are merely aesthetic in nature, are outweighed by the severe lung and other diseases that this product causes at with such a high disease prevalence. The Paid Advertisement then states: "Engineered stone products including Quartz, have been manufactured and fabricated safely for decades." This statement is a blatant lie. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the Paid Advertisement that "[e]ngineered stone products, including Quartz, have been manufactured and fabricated safely for decades" is absolutely false.

1006. The Paid Advertisement quotes Mr. Hieb as stating: "The biggest problem our industry faces is enforcement. Without efforts to stop those who are unaware of or unwilling to comply with current regulations, cases of Silicosis are going to keep increasing." This statement is also false and misleading. The biggest problem the stone industry faces is that artificial stone is the cause of a worldwide epidemic of accelerated silicosis among stone countertop fabricators. Stating that the biggest problem the industry faces is enforcement is merely an attempt by manufacturers of deadly artificial stone products to foist blame on OSHA due to its inability to prevent the disease and death that are primarily due to artificial stone products. OSHA is extremely underfunded and lacks the resources to initiate enforcement actions against the thousands of small fabrication shops nationwide and enforcement actions do nothing to prevent silicosis among the tens of thousands of countertop fabrication workers who have already been exposed to crystalline silica from stone products and who already have silicosis even though many of them have not yet exhibited symptoms of this disease. Moreover, many fabrication shops are unaware of the silicosis hazard because the

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manufacturers of artificial stone for many years did not prepare or provide customers with Safety Data Sheets or product labels informing them of the silicosis hazard and none of the manufacturers provided their customers with use instructions adequate to prevent silicosis among fabricators.

1007. The Paid Advertisement also states: "Industry leaders provide resources to support smaller businesses in the industry." This statement is at best misleading and at worse false. For years the manufacturers of artificial stone concealed the nature and severity of the toxic hazards of their products from their customers and only provided them training on how to improve profitability. Only after the new silicosis epidemic was well under way did the manufacturers of artificial stone initiate any programs to "support smaller businesses in the industry," and those programs were public relations programs to deflect responsibility from the manufacturers of deadly artificial stone products to blame the epidemic on the victims, the owners of small fabrication shops that employed them, on regulators and governmental enforcement agencies – anyone except themselves for causing the harm.

6. Knowledge of the Silicosis Hazard by Cambria Officers and Directors

1008. Throughout the time that Cambria manufactured and sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, Cambria's officers and directors were aware that Cambria's artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that Cambria provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by Cambria's defective artificial stone products. Among Cambria's officers and directors who had this knowledge and who nevertheless consciously disregarded the health and safety of fabricators and installers were the following: Marty Davis, President and Chief Executive Officer; Mark Davis, Chairman of the Board; Jim Ward, Chief Operating Officer; Brian Scoggin, Executive Vice President of Operations; Summer Kath, Executive Vice President of Product Development; Tripp Parker, Executive Vice President of Sales; Arik Tendler, Chief Sales Officer; Ben Davis, Executive Vice President and Chief Information Officer; Sarah Ministrelli, Vice President of Operations; Adam Sura, Director of Corporate Safety.

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E. C & C North America, Inc.

1009. "The Cosentino Group is a family-owned business which was founded in Cantoria, Almeria (Spain) in 1979 that produces surfaces marketed as Silestone®, Dekton® and Sensa®, as well as natural stone marketed as Scalea®. The Group currently employs over 4,500 individuals worldwide in locations throughout, among others, Spain, Portugal, France, the United Kingdom, the United States, Canada, Mexico, Brazil, Argentina, Scandinavia, Turkey, South Africa, Malaysia, Australia and New Zealand. . . . The Cosentino Group is the largest supplier of engineered stone product throughout the world." Letter dated November 29, 2019 to the Hon. Niall Blair, Committee Chair of the Legislative Council Standing Committee on Law and Justice in Sydney, Australia.

1010. In 1990 Cosentino began manufacturing artificial stone under the brand name Silestone in Almeria, Spain, in Andalusia in southeastern Iberia on the Mediterranean Sea.

1011. "In 1997, Cosentino brought Silestone to a new market by forming a subsidiary called Cosentino North America. And its appeal caught on quickly. Silestone's durability and resistance to stains was huge for kitchen designers, and it was featured in *Time* and *Good Housekeeping*. After that, business grew rapidly, and the company partook in promotional videos through groups like Home Depot and even Super Bowl advertisements." See "US Countertop Workers Falling Sick from Silica Dust," *Occupational Health & Safety* (Dec. 5, 2019).

1. Cosentino Enters the United States Market

1012. In an interview with Surface Magazine in 2017, Eduardo Cosentino was asked "How did Cosentino enter into the U.S. market?" He answered: "We started our operation here in 1998 with four or five people. Then we signed a deal with Home Depot and started a fabrication business. Kitchen countertops and things like that. Now we have fifty distribution centers in the U.S." Charles Curkin, "The Spanish marble scion has led his namesake company to conquer the U.S. market," *Surface* (June 26, 2017).

1013. Cosentino also operated its own network of shops called Stone Systems, and it came to have dozens of locations around the U.S." See "US Countertop Workers Falling Sick from Silica Dust," *Occupational Health & Safety* (Dec. 5, 2019).

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2. Current Cosentino Entities in Spain

1014. According to Registradores de Espana, there are three current Cosentino entities in Almeria, Spain: Cosentino SA, Cosentino Industrial SA, and Cosentino Global Sociedad Limitada. These three entities and their predecessors collectively acted in concert to design, manufacture, market, export, distribute and sell their deadly products, causing the new countertop fabricator silicosis epidemic which has claimed the health and lives of so many workers.

3. Cosentino History

1015. A webpage on the Cosentino website is titled "Cosentino, 40 Years of International Growth and Expansion: COSENTINO 1980-2020." [See webpage available online at https://www.cosentino.com/usa/news/cosentino-40-years-of-international-growth-and-expansion]

1016. This webpage states: "Last April 14th was the 40th year since the creation of the commercial company "Mármoles Cosentino S.A.", genesis of what ended up being Cosentino S.A. and finally Cosentino Group."

1017. This webpage provides the following chronology of the company:

1980	Mármoles Cosentino is born
1985	For the first time, products are exported
1990	Launching Silestone
1997	First warehouse in the USA
2000	Cosentino Latina (Vitória, Brazil) is born
2005	The new antibacterial Silestone The first Spanish firm to advertise in the Super Bowl
2006	Expansion throughout Europe
2009	Launching Sensa by Cosentino®
2009/10	Acquisition of 100% subsidiaries in the USA
2013	Launching Dekton
2014	Cosentino reaches five continents. First Cosentino City: Sydney
2016/19	Cosentino has more than a dozen Cosentino City in the world (London, Madrid, Miami, Los Angeles . . .)
2020	Cosentino celebrates 40 years with 5,000 employees worldwide.

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4. Cosentino Industrial SA

1018. According to Registradores de Espana, Cosentino Industrial SA commenced doing business December 15, 1989 and has its registered office at C/ Francis Martinez 2 Macael 04-Almery, Spain and is business entity No. A04117297.

1019. According to Registradores de Espana, the business of Cosentino Industrial SA includes "the extraction, manufacturing, processing and marketing of natural stones, and development and innovation for the production and marketing of artificial stone . . . ; research and development of mining deposits, drilling work, cutting, projects and blasting work," "exploitation and extraction for al; mining resources (rocks and industrial minerals), . . . "Artistic representation" management and transfer of intellectual property rights, image rights, works and pre-existing rights."

1020. According to Registradores de Espana, Cosentino Industrial SA's business is in sectors 2399, 2399, 0811, and 0990 - Manufacture of other non-metallic mineral products nec; manufacture of other non-metallic mineral products nec, extraction of ornamental and construction stone, limestone, gypsum, chalk and slate; support activities for other extractive industries."

1021. According to Registradores de Espana, Cosentino Industrial SA's internet domain is www.cosentino.es.

1022. According to Registradores de Espana, Cosentino Industrial SA is a "sole proprietorship", its sole owner being Cosentino SA.

1023. According to Registradores de Espana, among Cosentino Industrial SA's Directors and Legal Representatives is Eduardo Martinez-Cosentino Ramos, who was appointed on September 27, 2012.

1024. According to Bloomberg Markets, Cosentino Industrial SA produces quartz surfaces and "the company provides design, production, and distribution of surfaces such as kitchens and bathrooms worktops, cladding, and other products, as well as offers marble and granite products.

1025. According to Bloomberg Markets, Cosentino Industrial SA operates throughout Spain.

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5. Cosentino Global Sociedad Limitada

1026. According to Registradores de Espana, Cosentino Global Sociedad Limitada (Cosentino Global Limited Company) commenced doing business September 24, 2020, and has its registered office at CTRA A-334 Baza-Huercal Overa, Salida 60, Poligono Industrial (Edificio Oficinas) Km Cantoria 04850-Almeria, Spain and is business entity No. B01966597.

1027. According to Registradores de Espana, the business of Cosentino Global Sociedad Limitada is "the production, distribution and marketing, both in national and foreign territory, of feature films and short films of cinematographic and audiovisual works in general, series and television programs and the exploitation of said works . . . , and the artistic representation, management and transfer of intellectual property rights, image rights, works and pre-existing rights, of service to the industrial sector such as industrial design, engineering and design of machinery, materials, industrial processes, industrial plants and others related to technical advice."

1028. According to Registradores de Espana, Cosentino Global Sociedad Limitada's business is sector 4673 "Wholesale trade in wood, construction materials, and sanitary appliances."

1029. According to Registradores de Espana, Cosentino Global Sociedad Limitada is a "sole proprietorship, its sole owner being Cosentino SA."

1030. According to Registradores de Espana, included among Cosentino Global Sociedad Limitada's Directors and Legal Representatives are Eduardo Martinez-Cosentino Ramos, who was appointed Joint Administrator on January 20, 2022 and Francisco Martinez Cosentino Justo.

1031. The United States Trademark for SILESTONE was filed by Cosentino SA with the U.S. Patent and Trademark Office and was subsequently transferred by Cosentino SA to Cosentino Global Sociedad Limitada, which is currently the owner of the SILESTONE trademark, such that Cosentino Global Sociedad Limitada is in the chain of distribution of SILESTONE and is hence subject to strict products liability for the defective design and defective warnings of SILESTONE.

1032. Cosentino Global Sociedad Limitada has imported stone products manufactured by Cosentino Industrial SA to California, including to the Port of Oakland (4th largest port of unlading), Los Angeles (5th largest port of unlading), and Long Beach (10th largest port of unlading).

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6. Cosentino SA Subsidiaries

1033. According to Cosentino SA's website, Cosentino SA (formerly known as Cosentino Group SA) has the following subsidiaries:

Blanco Almenas S.L.

C&C North America Inc.

Carrara Stone Systems of Chicago, LLC dba Stone Systems of Chicago

Cosentino Canada Inc.

Cosentino Research & Development

Cosentino Ireland Ltd.

Cosentino Malaysia Sdn. Bhd.

Cosentino South Africa Pty Ltd

Cosentino Poland Sp. Z O. O.

Cosentino New Zealand Ltd

Cosentino Denmark Aps

Cosentino Finland Oy

Cosentino South East Asia Pty Ltd

Cosentino Center Israel Ltd

Cosentino Austria Gmbh

Cosentino Japan K.K.

Cosentino Norway A.S.

Cosentino UK Ltd.

Cosentino Latina Ltda.

Cosentino the Netherlands B.V.

Cosentino Deutschland Gmbh

Cosentino Scandinavia A.B.

Cosentino Portugal Unipessoal Lda.

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Cosentino Italia S.R.L.

Cosentino Australia Pty Ltd.

Cosentino Swiss A.G.

Cosentino Belgium Bvba

Cosentino Milano S.r.l.

Cosentino Turkey Yapi İthalat İhracat Ve Ticaret Limited Şirketi İmza Sirküleri

Entorno Del Faro S.L.

Grupo Cosentino S.L.

Jardines La Tejera S.L.

Stone Suppliers Mexico S. De R.l. De C.v.

Stone Services of France Sarl

Stone, Systems & Services, Inc. dba Stone Systems of Minnesota

Stone Systems of South Florida, LLC

Stone Systems of Raleigh, LLC

Stone Systems of New Mexico, LLC

Stone Systems of New Jersey, LLC

Stone Systems of New England, LLC

Stone Systems of Houston, LLC

Stone Systems of Central Texas, LLC

Stone Systems of Atlanta, LLC

Stone Systems of Arizona, LLC

Stone Systems of North Texas

Stone Made Products, Inc. Dba Superficies De Piedra Innovadoras S. De R.l. De C.v.

Surister Del Arroyo S.L.

Vigia Del Valle S.L.

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7. C&C North America's Liability for the Acts of Cosentino

1034. At all material times hereto, Defendant, C & C North America, Inc., has been a subsidiary of Cosentino Group, a Spanish corporation; Defendant, C & C North America, Inc. has been wholly owned and controlled by Cosentino Group; and Defendant, C & C North America, Inc. has acted in the capacity of an agent, co-conspirator, and alter ego of Cosentino Group, and within the course and scope of its authority as Cosentino Group's agent, co-conspirator, and alter ego, and with the permission, consent, knowledge, authorization, ratification and direction of Cosentino Group. The liability of Defendant, C & C North America, Inc. as an agent, co-conspirator, and alter ego of Cosentino Group, for the acts of Cosentino Group is evidenced and established by the following facts:

8. Cosentino Group Executive Officers

1035. Francisco Martinez-Cosentino Justo is the Chairman, Chief Executive Officer, and President of Cosentino Group.

1036. Eduardo Martinez-Cosentino Alfonso is the Executive Vice President for Global Sales of Cosentino Group.

1037. Francisco Martinez-Cosentino Justo and Eduardo Martinez-Cosentino Alfonso are also members of the Executive Committee of Cosentino Group.

9. Eduardo Martinez-Cosentino Alfonso

1038. Eduardo Martinez-Cosentino Alfonso is commonly known as Eduardo Cosentino.

1039. Since 2005, Eduardo Cosentino has held the position of Executive Vice-President of Global Corporate Sales for Cosentino Group. ["Eduardo Cosentino on Cosentino" published in 2020 in the journal *Slippery Rock Gazette, the Beacon of the Stone Industry,* at https://www.slipperyrockgazette.net/index.cfm/pageId/3892/Eduardo%20Cosentino%20on%20Cosentino/.]

1040. In addition to his global sales responsibility, in 2010 Eduardo Cosentino was named CEO of C & C North America, Inc., where he has overseen the company's growth in the U.S. market.

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["Eduardo Cosentino on Cosentino" published in 2020 in the journal *Slippery Rock Gazette, the Beacon of the Stone Industry,* available online at https://www.slipperyrockgazette.net/index.cfm/pageId/3892/Eduardo%20Cosentino%20on%20Cosentino/.]

1041. In addition to these duties, Eduardo Cosentino has also been a member of Cosentino Group's Steering Committee, its Executive Committee, and a member of Cosentino Group's Board of Directors. ["Eduardo Cosentino on Cosentino" published in 2020 in the journal *Slippery Rock Gazette, the Beacon of the Stone Industry,* available online at https://www.slipperyrockgazette.net/index.cfm/pageId/3892/Eduardo%20Cosentino%20on%20Cosentino/.]

10. Cosentino Centers in the US and California

1042. Cosentino Group has about 110 Centers around the world, 50 of which are located in 16 countries in Europe, 42 in North America, 4 in Canada, 7 in Brazil, 5 in Australia, 1 in New Zealand, and 1 in Mexico. [https://www.cosentino.com/usa/cosentino-center/]

1043. A Cosentino website lists the following Cosentino "Centers" in California, the name of each being preceded by a distinctive white blockish C in a grey circle:

Anaheim Center 611 East Cerritos Avenue - Anaheim

Los Angeles Center 12822 Rangoon Street - Los Angeles

Sacramento Center 10015 Foothills Boulevard Suite 150 - Roseville

San Diego Center 9020 Activity Road Suite C - San Diego

[Cosentino webpage at https://www.cosentino.com/usa/cosentino-center/].

1044. Each of these Cosentino Centers has links for "Call," "How to get there," "View store detail" and "Virtual Visit." [Cosentino webpage]

1045. Clicking on the Los Angeles Center link brings one to a webpage with a heading "Cosentino » Where to buy » Los Angeles Center" and provides the following contact details: 12822 Rangoon Street 91331, Los Angeles, **Email** orders.la@cosentino.com, **PHONE** +1 (818) 381-8220.

1046. There are more Cosentino Centers in the United States than any other country.

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11. First Cosentino Center in North America

1047. The first Cosentino Center in North America opened in 2010 in Anaheim, California.

1048. An article titled "First North American Cosentino Center opens in Anaheim" was published in *Stone World* on September 8, 2010. [https://www.stoneworld.com/articles/86034-first-north-american-cosentino-center-opens-in-anaheim].

1049. The article stated: "Cosentino, a global leader in natural stone, quartz and recycled surfacing, recently opened its first Cosentino Center in North America in Anaheim, CA. More than a showroom, the Cosentino Center is designed to support, promote and educate trade professionals by integrating distribution facilities, exhibition areas, workspaces for designers to bring clients, classrooms for continuing education, and fully functioning kitchens and event space for demonstrations." https://www.stoneworld.com/articles/86034-first-north-american-cosentino-center- opens-in-anaheim.

1050. The article further stated: "Officially opening with a reception for industry leaders on Wednesday, September 15th, the new Anaheim center aims to enhance both the trade and consumer experience, and marks the launch of a greater plan to significantly expand Cosentino's presence in the U.S. market over the next year." [https://www.stoneworld.com/articles/86034-first-north-american-cosentino-center-opens-in-anaheim.]

1051. The article stated: "'We are thrilled to be introducing the Cosentino Center to the U.S. market by unveiling the first in Anaheim, CA,' said Lorenzo Marquez, Vice President of Marketing for Cosentino. 'This is the next evolution of the Cosentino brand -- offering a new take on the showroom experience, design innovation and demonstration.' The first Cosentino Center is located in central Anaheim, CA, a region known for its rich history in the natural stone industry, and only a 20-minute drive from downtown Los Angeles. The facility includes over 50,000 square feet of warehouse space and distribution center as well as a state-of-the-art showroom." [https://www.stoneworld.com/articles/86034-first-north-american-cosentino-center-opens-in-anaheim]

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12. Cosentino City Los Angeles

1052. A Cosentino webpage says that a Cosentino City is "a space for design and architectural professionals to get inspired, connect, and create." This webpage shows pictures of buildings with Cosentino signage in Atlanta, Chicago, Los Angeles, New York, Miami, San Francisco, Montreal, Toronto and Washington. [https://www.cosentino.com/usa/professional/cosentino-city/]

1053. A building which bears the name "COSENTINO®" is presently located at 8764 Beverly Blvd., West Hollywood, California 90048. [Picture of the Cosentino Los Angeles building on the Cosentino website at https://www.cosentino.com/usa/professional/cosentino-city/los-angeles/]

1054. The building located at 8764 Beverly Blvd., West Hollywood, California 90045 is called "Cosentino City Los Angeles."

1055. The website LinkedIn has a webpage for Cosentino City Los Angeles which has a picture of a storefront with signage stating "COSENTINO" with the distinctive white blockish C in a tan square. [Exhibit "O": LinkedIn webpage for Cosentino City Los Angeles.]

1056. The webpage states: "Located in the design district of West Hollywood, Cosentino City Los Angeles is the perfect environment for architects and designers to interact with the latest innovations in hard surface installation. Spread across 2,200 square feet, Cosentino City Los Angeles has an Atelier Lab, a central space featuring a library of materials where you can find inspiration and develop all kinds of projects. It also has several social areas, digital design tools and a patio that showcases the limitless possibilities Dekton provides for outdoor spaces. Schedule your appointment: Phone: +1 (310) 620-6084. We are waiting for you!" The page then states: Website: https://www.cosentino.com/usa/professional/cosentino-city/los-angeles/; Phone +1 (310) 620-6084; Industry: Architecture and Planning; Company size: 1,001-5,000 employees; Founded 1979; Specialties: #Dekton, #Silestone, #Sensa, #Architecture, #Design, and #Interiorism. [LinkedIn webpage for Cosentino City Los Angeles.]

1057. Clicking on the website link takes one to a Cosentino webpage that states: "Welcome to Cosentino City Los Angeles: A Space for design and architecture professionals to get inspired, connect, and create." This webpage then has a picture of a building with signage that says:

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"COSENTINO®" with smaller signage stating "Silestone," "Dekton," and "Sensa." [Cosentino webpage https://www.cosentino.com/usa/professional/cosentino-city/]

1058. The opening of Cosentino City Los Angeles was attended by Eduardo Cosentino, Executive Vice President for Global Sales of Cosentino Group.

1059. An April 15, 2019 article in *KBB* [Kitchen & Bath Business] was titled "Cosentino Group Announces $1.1 Billion in Sales in 2018 and Celebrates LA City Center Grand Opening." [https://www.kbbonline.com/news/business/cosentino-group-announces-1-1-billion-in-sales-in-2018-and-celebrates-la-city-center-grand-opening/].

1060. This article contains a photograph of five people, one of whom is Eduardo Cosentino (Executive Vice-President of Global Sales of The Cosentino Group), who is depicted holding a ribbon bearing the name "COSENTINO." Standing next to him in the photograph is Cindy Crawford. Another photograph in the article includes Santiago Alfonso (Marketing Director of the Cosentino Group). The photographs show these individuals in front of a backdrop that bears the blockish C and wordmark COSENTINO followed by "CITY" and also bears the tradenames and trademarks for Cosentino' Silestone® amd Dekton®. [https://www.kbbonline.com/news/business/cosentino-group-announces-1-1-billion-in-sales-in-2018-and-celebrates-la-city-center-grand-opening/].

1061. The opening of Cosentino City Los Angeles is not the first Cosentino event that Eduardo Cosentino attended in Los Angeles County with Cindy Crawford.

1062. On May 16, 2017, photographs of Eduardo Cosentino and Cindy Crawford were taken in front of signage showing the blockish C and "COSENTINO" and were published with an announcement tiled "Cindy Crawford and Eduardo Cosentino NA Launch Silestone's 'Eternal Beauty and Eternal Style' Collection." The announcement also stated: "LOS ANGELES, CA - May 16: Cindy Crawford attends Cindy Crawford and Eduardo Cosentino's New Design Alliance and launch of Silestone's latest collection 'Eternal Beauty and Eternal Style' at Milk Studios on May 16, 2017 in Los Angeles California. (Photo by Emma McIntyre/Getty images)." [https://www.gettyimages.com/detail/news-photo/cindy-crawford-attends-cindy-crawford-and-eduardo-news-photo/683986976?adppopup=true]."

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13. Cosentino Trade Name and Word Mark

1063. **C COSENTINO** is a word mark for "non-metallic building materials, namely stone slabs and blocks for building and construction, slabs and blocks not of metal, for building and construction, rock materials used in countertops, worktops, cladding and tiles, rigid pipes, not of metal, for building, asphalt, pitch and bitumen; transportable buildings, not of metal; monuments, not of metal; marble, silica, namely, quartz, building glass, xylolith, gypsum, stone, slate, granite, sandstone, concrete, brick, ballast, namely, sand, limestone, lime building materials, rock crystal, quartz, asbestos cement, clay sold in powdered from for use in the manufacture of wallboard and plastics, ceramic tiles, alabaster." [Cosentino Trademark IC 019. US 001 012 033 050, filed February 25, 2016 with the U.S. Patent and Trademark Office].

1064. The registrant of the **C COSENTINO** trademark is Cosentino S.A.U. Sociedad anónima unipersonal SPAIN Ctra. A-334, Km. 59 E-04850 Cantoria (Almeria) Spain." [Cosentino Trademark IC 019. US 001 012 033 050, filed February 25, 2016 with the U.S. Patent and Trademark Office].

1065. The last listed owner of the **C COSENTINO** trademark is Cosentino Global, S.L.U Sociedad Limitada Unipersonal Carretera A-334, Baza-Huércal-Overa, Salida 60, Polígono Industrial (Edificio Oficinas), E-04850 Cantoria (Almeria) Spain. [Cosentino Trademark IC 019. US 001 012 033 050, filed February 25, 2016 with the U.S. Patent and Trademark Office].

14. Cosentino Product Tradenames and Trademarks

1066. SILESTONE BY **COSENTINO** S is a word mark for "non-metallic building materials, namely, agglomeration stones." [Cosentino Trademark IC 019. US 001 012 033 050, G & S, filed June 26, 2008 with the U.S. Patent and Trademark Office].

1067. DEKTON BY **COSENTINO** is a word mark for "non-luminous, non-metallic, and non-mechanical coverings for facades; non-metallic tile coverings for walls and floors; non-metallic floor, wall, facade and ceiling building materials, namely, bathroom tiles and kitchen tiles; and non-metallic kitchen countertops and bathroom countertops for further installation; [clay slabs,] ceramic slabs, and slabs composed of ceramic surfaces; [asphalt, pitch and bitumen; transportable buildings,

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not of metal;] monuments, not of metal; non-metallic building materials, namely, marble, quartz, [glass; xylolith, gypsum,] stone, slate, granite, concrete, [brick,] limestone [asbestos, clay, and alabaster]." [Cosentino Trademark IC 019. US 001 012 033 050, G & S, filed April 25, 2013 with the U.S. Patent and Trademark Office.]

15. C & C North America, Inc.

1068. On March 21, 2003, C & C North America, Inc. was incorporated in the State of Delaware.

1069. On July 9, 2008, C & C North America, Inc. filed a Statement and Designation by Foreign Corporation with the California Secretary of State, which stated that it will do business in California as SMDS East Coast, that its principal executive office was 13124 Trinity Drive, Stafford, Texas 77477, that the address of its principal office in the State of California is 2980 Red Hill Avenue, Costa Mesa, California 92626, and that its agent for service of process is CT Corporation System. [Statement and Designation by Foreign Corporation with the California Secretary of State]

1070. The building at 2980 Red Hill Avenue in Costa Mesa had signage that consisted of the blockish C and the word COSENTINO in white on a dark square, followed by the following italicized text: *Silestone & Marble Distribution Services.*

1071. The blockish C and the word COSENTINO in white on a dark square is the same word mark that was filed with the U.S. Patent and Trademark Office on February 25, 2016 identifying COSENTINO. S.A.U. Sociedad anónima unipersonal SPAIN Ctra. A-334, Km. 59 E-04850 Cantoria (Almeria) Spain as the Registrant and Cosentino Global, S.L.U Sociedad Limitada Unipersonal Carretera A-334, Baza-Huércal-Overa, Salida 60, Polígono Industrial (Edificio

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Oficinas), E-04850 Cantoria (Almeria) Spain as the last listed owner. [Cosentino Trademark IC 019. US 001 012 033 050, filed February 25, 2016 with the U.S. Patent and Trademark Office].

16. Cosentino's 1999 Material Safety Data Sheet for Silestone

1072. On February 22, 1999, Cosentino issued a Material Safety Data Sheet for its Silestone® product which it identified as "Agglomerated stone slabs, tiles and fabricated items." Section 2 of this document, regarding "Hazardous Ingredients" has a table with five columns for Hazardous Ingredients, % by wt., % by vol., CAS #, and Other Limits. However, the table is blank; i.e, it does not identify any hazardous ingredients, even though the product contained as much as 95% crystalline silica, which causes silicosis, lung cancer and other occupational diseases. By failing to disclose crystalline silica as a hazardous ingredient of the product, Cosentino concealed this hazard from customers, their employees, and workers exposed to its lethal product.

1073. Section 7 of the Material Safety Data Sheet concerns "Preventative Measures." The first part of this section concerns "Personal Protective Equipment." In this action Cosentino stated: "RESPIRATOR: Use respirator or particulate mask when cutting or abrading material." This instruction was inadequate and harmful, because the use of an air-purifying respirator or particulate mask is inadequate to prevent silicosis from cutting or abrading the product and misled workers to believe that they would be safe if they wore an air-purifying respirator or mask when cutting or abrading the product. The instruction failed to inform workers that because of the very high crystalline silica content of the product and the high exposures to respirable crystalline silica dust that result from cutting or abrading the product, the only type of respirator that could prevent workers from getting silicosis from cutting or abrading the product was an air-supplied respirator.

1074. Section 7 of the Material Safety Data Sheet next contains information regarding "Procedures and Controls. Regarding "Engineering Controls." It states: "ASTME-1132-86 'Standard Practice for Health Requirements Relating to Occupational Exposure to Dust.'" This information was grossly inadequate, because the document to which it refers was not readily accessible, could only be purchased through the American Society for Testing Materials, and the document related to industrial dust, i.e., a nuisance dust, rather than respirable crystalline silica.

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1075. The next section regarding Procedures and Controls" was "Handling Equipment & Procedures" and stated: "Observe local safe handling procedures. Handle with care." This was a totally inadequate and meaningless instruction to workers how to handle Silestone safely. The instruction fails to tell workers to always use wet processing methods, to wear an air-supplied respirator, to wear full body protection to prevent all exposure to respirable crystalline silica dust, and fails to prescribe any engineering, ventilation, or administrative controls to prevent silicosis.

1076. Section 8 of the Material Safety Data Sheet, regarding First Aid Procedures, states that the International Agency for Research on Cancer (IARC) [has] determined that crystalline silica is a probable carcinogen. This is a false statement, because two years earlier, in 1997, IARC determined that crystalline silica is a Group 1 (known human) carcinogen.

17. Early Cases of Artificial Stone Silicosis from Silestone

1077. Occupational disease cases of Cosentino employees who worked in stone extraction at the Cosentino, S.A. facility in Almeria have been documented since as early as 2001 and 2002.

1078. A document by the Ministry of Labor and Occupational Safety of Almeria dated August 7, 2002 refers to occupational disease claims of three Cosentino workers. The document concerns the Work Violation Act and states that an inspector from the Ministry made an inspection visit to Cosentino, S.A. in Cantoria regarding the occupational diseases of two workers: D. Miquel Centas Antolin and Francisco Azor Vargas. The document notes that a third worker, D. Manuel Gea Martinez, had earlier been diagnosed with occupational disease on May 3, 2001. The document refers to stone extraction work at the Cosentino facility in Almeria and states that the inspection visit was attended by Francisco Martinez Cosentino, Manager of Cosentino S.A., and Antonio Rubio Ruiz, head of the company's Occupational Risk Prevention Service. The occupational disease claims of the three workers at Cosentino's Almeria facility may be the earliest cases of silicosis attributable to occupational exposure to Cosentino's Silestone artificial stone product.

1079. A document dated December 3, 2002, on letterhead of the Ministry of Employment and Technological Development, Occupational Hazard Prevent Center, Almeria, provides details regarding the occupational disease of a fourth Cosentino employee, Jose Araque Martinez. Following is a translation of this document:

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BOARD OF ANDALUCIA **Ministry of Employment and Technological Development**
Occupational Hazard Prevent Center, Almeria

3 DEC. 2002 2811

TECHNICAL REPORT REGARDING

INVESTIGATION OF OCCUPATIONAL DISEASE

1. **DATE EXTRACTED FROM THE REPORT**

1.1 About the Worker

- Name and Surname: Jose Araque Martinez
- D.N.I.: 36-508-347
- Social Security Number: 07/47446686
- Date of Birth: 01-5-57
- Residence: C/ Obispo Rodenas, 50
- Location: Otula del Rio
- Province: Almeria
- Job: Operator Exp
- Category: Official 1
- Date of first employment: 02-5-79
- Duration of employment: 23 years
- Job when the disease was diagnosed: Freight forwarding
- Job previously done: Rework and finish parts

1.2 About the Employer

- Business Name: Costentino, S.A.
- Registered Office: C/ Fto. Martinez, 2- MACAEL
- Workplace: Ctra. Buza - Huercal-Overa, Km 59 - CANTORIA
- Activity: Industrial Natural Stone
- N.I.S.S.: 04/45683/07
- Location: CANTORIA
- Province: Almeria
- Telephone: 950-44-41-75
- Template: 373

1.3 About the Disease

- Date of diagnosis: 24-09-02
- Date of Receipt of Report: 14-10-02
- Type of Occupational Disease: Pneumoconiosis
- Diagnosis: Silicosis
- Symptoms of the disease: Cough, expectorate and dyspnea
- Degree of disease: Serious
- Nature of diagnosis: Of certainty
- Work that is considered to have caused the disease: Working with "Silestone"
- Time in months of exposure to the hazard: 8 years
- Date of previous medical examination: ------
- Date of last medical examination: 23-04-00

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18. Cosentino's 2006 Material Safety Data Sheet for Silestone

1080. In August 2006, Cosentino issued a Material Safety Data Sheet for its Silestone® product which it described as a "Solid quartz surface." Section 2 of this document contains a table (Table 1) that identified the components of the product as Orthophthalic polyester resin (5-25%), Pigments (<5%), Micronized silica (<0.1 mm) (5-50%) Grounded silica (0.1-10 mm) (10-90%), Grounded quartz (0.1-10 mm) (5-50%), Grounded Glass/Mirror (0.1-10 mm) (5-50%), and Grounded granite (1-10 mm) (5-50%). The Material Safety Data Sheet also contains a table (Table 2) that identified three additives by CAS and EINECS numbers rather than chemical names, so workers could not know what the additives were without reference books to look up code numbers. The additives so mysteriously identified are (1) Cobalt, C5-23-branched carboxylate naphthenate octanoate complexes, (2) tert-Butyl peroxybenzoate, and (3) 3-(Trimethoxysilyl)propyl methacrylate.

1081. After identifying the product's components, the Material Safety Data Sheet states: "This product does not contain free substances that involve a risk for the health in accordance to the Regulation of Dangerous Substances R.D. 255/2003 and according to the European Norms 67/548/EEC, 199/45/EE and its corrections 93/112/EEC, 2001/58/EEC y 2001/60/EEC." This statement, which suggested that Cosentino's Silestone did not entail a risk for health was false, because the expected and intended use of the product generates extremely hazardous respirable crystalline silica that causes silicosis and death. Cosentino made this statement even though EU Directive 67/548/EEC classifies as "dangerous" "substances and preparations" that are "very toxic," "which if they are inhaled ... may involve extremely serious ... chronic health risks and even death."

1082. The next sentence of the Material Safety Data Sheet states: "The finished product does not contain any of the substances described in Table 2 since, once completed the production process, these are part of the three-dimensional structure of the polyester, included and immobilized in it. Therefore, this product is not classified as dangerous substance or product that involves a risk for the health according to the Regulation of Dangerous Substances R.D. 255/2003, and according to the European Norms 67/548/EEC, 199/45/EE and its corrections 93/112/EEC, 2001/58/EEC y 2001/60/EEC by means of which the present Security Data Sheet (MSDS) has been written up." This statement is also false because the additives in the product are toxic via inhalation and are

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known to cause lung disease, including fibrotic lung disease, and when Silestone is cut or ground these components of the product do not remain "immobilized" in the product, but become airborne and are inhaled by workers exposed to dust from Silestone, thereby causing respiratory tract damage.

1083. Section 3 of the Material Safety Data Sheet is titled "Risks Identification and General Safety Measures." This section begins with the following statement: "This product presents no type of risks for the human health or environment in accordance to the Regulation of Dangerous Substances R.D. 255/2003, and according to the European Norms 67/548/EEC, 199/45/EE and its corrections 93/112/EEC, 2001/58/EEC and 2001/60/EEC." This is a false statement, because the product contains extremely high concentrations of crystalline silica as well as the other and components and additives that are toxic to the respiratory tract and can cause silicosis and other fibrotic lung disease and death, and because EU Directive 67/548/EEC classifies as "dangerous" "substances and preparations" that are "very toxic," "which if they are inhaled . . . may involve extremely serious . . . chronic health risks and even death."

1084. Section 3 of the Material Safety Data Sheet also states: "A prolonged exposure to the dust derived from the dry cutting and polishing treatments can cause serious health problems as pneumoniosis, silicosis, as well as a worsening of the people affected by pulmonary diseases as bronchitis, emphysema, etc." This statement is false because silicosis occurs from wet cutting Silestone and polishing treatments, and is misleading because the statement does not quantify the duration of "prolonged exposure" that can cause silicosis, leading workers to believe it would take decades of exposure to cause silicosis, although exposure to Silestone and other artificial stone products causes acute silicosis in less than 5 years and accelerated silicosis in less than 10 years.

1085. Section 3 of the Material Safety Data Sheet then states: "In order to reduce a casual [sic] exposure it is always recommended to use water as dust reducer. It is advisable the use of tools cooled by water and to perform the operations of dry cutting, milling and polishing of this product in a suitably ventilated place. Otherwise, it is essential to use respiratory personal protection for dust and particles type FFP1 according to norm UNE-EN 143:2001 and its revisions UNE-EN 143/AC 2002, UNE-EN 143/AC 2005." This instruction is inadequate because it merely recommends the use of wet processing methods to reduce dust, rather than stating that wet processing methods must

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always be used with all saws, and cutting, grinding and polishing tools to prevent silicosis. It is also inadequate because it doesn't specify the types of ventilation that provide a suitably ventilated space. The last sentence is also inadequate, because it refers to a European Standard that is not available online and is only available for purchase, the referenced standard appears not to be applicable for extremely high exposures to respirable crystalline silica, and the instruction suggests that particle air-purifying respirators are adequate to prevent silicosis, although air-purifying respirators do not prevent silicosis in workers exposed to respirable crystalline silica from fabricating artificial stone. The instruction is harmful because it does not inform workers that the only type of respirator that can prevent silicosis from exposure to high levels of respirable crystalline silica is an air-supplied respirator and it instead suggests that air-purifying respirators provide adequate protection.

1086. Section 4 of the Material Safety Data Sheet, titled "First Aids" begins with the following statement: "This product is not hazardous in normal use, but not using the right equipment during fabrication operations as cutting, drilling, etc can cause a situation of emergency." This sentence is false and harmful, because Silestone is indeed hazardous in normal use, because the normal use of the product causes silicosis and death. To the extent that the statement constitutes a use instruction, it is also inadequate, because it indicates that "the right equipment" must be used for fabrication operations, but does not specify what that equipment is.

1087. Section 6 of the Material Safety Data Sheet, titled "Manipulation and Storage" Aids" begins with the following statement regarding "Manipulation": "It is not necessary special measures for the manipulation of this product, but it is recommended to follow the next precautions." This statement is false and harmful, because manipulating the product as designed, intended, and expected results in the generation of respirable crystalline silica that causes silicosis and other occupational diseases, such that special measures for "manipulation of this product" are always required.

1088. Section 7 of the Material Safety Data Sheet, titled "Control of Exposure/Personal Protection," begins with a subsection titled "Limit Values of Exposure," which states: "In accordance to the previously exposed and relying to the norm 2000/39/CE, as well as to the R.D. 274/2001 which it sends us to the values published by the National Institute of Health and Hygiene at Work (INSHT), the limit of the daily exposition to the dust resulting of the elaboration of Silestone® is

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2 mg/m3. It appears in Table 1 for the y ear 2006 published by the mentioned INST in the line "Silica, vapor. Breathable fraction"." This statement is unintelligible and is therefore inadequate. Assuming that the statement means that the exposure limit for Silestone dust is 2 mg/m3, the statement is incorrect, because as of 2006, the permissible exposure limit and all recommended exposure limits for respirable crystalline silica in the United States were many times lower than 2 mg/m3. Indeed, by 1991 OSHA had adopted a Permissible Exposure Limit for respirable crystalline silica which was 10 / (% quartz + 2) mg/m^3. Since the percentage of quartz in Silestone was approximately 90%, the OSHA permissible exposure limit for the product was approximately 0.1 mg/m^3 - 20 times less than that stated in the Silestone Material Safety Data Sheet. The statement was therefore not merely false; it was extremely dangerous because it overstated the permissible exposure limit to the product by a factor of 20 – a level of exposure that causes silicosis.

1089. Section 7 of the Material Safety Data Sheet then has a subsection for "Exposure Controls" that provides the following information regarding "Respiratory protection": "Respiratory personal protection for dust and particles type FFP1 according to norm UNE-EN 143:2001 and its revisions UNE-EN 143/AC 2002, UNE-EN 143/AC 2005, even working with water as dust reducing agent during the elaboration of this product." This instruction is not only inadequate, but is extremely dangerous and harmful, because the type of respirator prescribed is the least filtering mask of the FFP series of masks that only filters 80% of airborne particles and allows inward leakage up to 22%, which is wholly inadequate to protect workers from respirable crystalline silica exposure and actually causes silicosis rather than preventing silicosis.

1090. Section 10 of the Material Safety Data Sheet, titled "Toxicological Information" states: "As another product of natural stone that contains quartz or quartz dust as quartz, marble or granite, the operations of dry cutting, milling or any other treatments of this product can generate dust susceptible to produce irritation in eyes, nose and respiratory tract. A prolonged exposure can cause serious health problems, including pneumoconiosis." This statement is false and misleading, because Silestone is an artificial stone (engineered stone product), is not a natural stone product and has toxicological properties that are much different than natural stone. These include the extremely high crystalline silica content of Silestone (which is much higher than the crystalline silica content

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of natural stone), the extremely small size of the particles of crystalline silica that are generated from cutting and grinding Silestone (most of the particles generated being in the ultrafine to nano-sized range unlike crystalline silica particles from natural stone), and the toxicological properties of the resin, metallic pigments and other additives of the product that are produced during fabrication processes as particles and probably metal fumes, thereby increasing the respiratory toxicity of the product. None of these toxicological properties of Silestone are mentioned and the information that is provided, which suggests that Silestone is no more toxic than natural stone, is false and misleading. The statement that "a prolonged exposure can cause serious health problems, including pneumoconiosis," is misleading because the duration of exposure that constitutes "a prolonged exposure" is not specified, so workers are left to speculate whether the "prolonged exposure" that can cause harmful effects is days, weeks, months, years, or decades. The word "pneumoconiosis" is also vague and confusing, because it is not a commonly used word and readers would unlikely know that it refers to a plethora of occupational dust diseases of the lungs, the most relevant of which is silicosis, which is not mentioned by name in this section even though it is the lung disease most strongly associated with occupational exposure to respirable crystalline silica dust.

1091. The last paragraph of Section 10 of the Material Safety Data Sheet states: "In accordance to RD 363/1995, regulation about notification of new substances and classification, packed and labeled of dangerous substances, the sample put under test is not considered classifiable within any group of risk on the basis of its acute toxicity by ingestion." This statement is false and misleading, because the referenced regulation requires notification and warnings for new hazardous substances in commerce that companies market and sell, including substances specified in subdivision 2 of Article 2 of the regulation, which includes dangerous substances, including those that are "very toxic," which is defined in subsection (f) of Article 2, subdivision 2 of the regulation as "substances and preparations that, by inhalation, ingestion or skin penetration in small quantities, can cause acute or chronic effects and even death."

1092. Section 15 of the Material Safety Data Sheet, regarding Regulatory Information," states: "Silestone is not classified as dangerous substance or product that involves a risk for the health in accordance to the Regulation of Dangerous Substances R.D. 255/2003 and according to

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European Norms 67/548/EEC, 199/45/EE and their corrections 93/112/EEC, 2001/58/EEC and 2001/60/EEC." Once again, this is a false statement, because the product contains extremely high concentrations of crystalline silica as well as the other and components and additives that are toxic to the respiratory tract and can cause silicosis and other fibrotic lung disease and death, and because EU Directive 67/548/EEC classifies as "dangerous" "substances and preparations" that are "very toxic," "which if they are inhaled . . . may involve extremely serious . . . chronic health risks and even death."

1093. Section 16 of the Material Safety Data Sheet, regarding "Other Information," contains three paragraphs, the first of which states: "The information contained in this document is, in accordance to all our actual acknowledges, true and exact. However any recommendation or suggest formulated here are out of our guarantee, because the conditions of use of our product are out of our control. Besides, nothing of contains here can be interpreted like a recommendation to use any product breaking the laws and trials of security or patents come into effect about any subject or its use." This paragraph appears to constitute a representation that the information in the Material Safety Data Sheet is true and correct, although most of the information provided is either, false, misleading or unintelligible, and could not have been genuinely believed by Cosentino to be "true and exact."

1094. The second paragraph of Section 16 of the Material Safety Data Sheet states: "The receiver of our product will have to observed, under its responsibility, the corresponding regulations and norms. In any case the data contained in this Security Data Sheet constitute a guarantee of specific properties or generate any contractual relation." Although this paragraph appears to constitute an attempt by Cosentino to disclaim all responsibility for its dangerous and lethal product and to shift all such responsibility to those who receive the product, the language actually states that "the data contained in this Security Data Sheet constitute a guarantee of specific properties" of the product and therefore actually constitutes a guarantee by Cosentino of safety.

1095. The last paragraph of the Material Safety Data Sheet repeats the previous false statements that the MSDS is in accordance with the aforementioned European laws.

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19. Silicosis Cases in Spanish Workers Exposed to Cosentino's Silestone

1096. The first cases of silicosis in Spanish artificial stone workers were published in 2010 by researchers at the National Institute of Silicosis at the University Hospital in Asturias, Spain. They reported 3 cases in workers who had been employed for 17 years by a small ornamental stone company that fabricated and installed in homes and buildings. The workers were all young: 32, 34, and 37 years old. Chest x-rays of all 3 workers showed nodular opacities with diffuse bilateral distribution and more profuse localization in the upper lobes, with a slight increase in mediastinal and/or hilar nodes. In case 1, a cluster of nodules was observed with progressive massive fibrosis; this worker was diagnosed with complicated silicosis. Martínez C, et al., "Silicosis, a Disease With an Active Present," *Arch. Bronconeumol.* 2010; 46(2):97-100 [in Spanish with English abstract]. These cases were apparently of workers who were exposed to Cosentino's Silestone product.

1097. In 2011, researchers at Galdakao Hospital in Bizkaia, Spain published a study of 11 workers who were exposed to different types of quartz surfaces since 1995. Four of the subjects worked in the cutting workshop; the rest of the workers worked in assembly (i.e. fabrication), without any specific respiratory protection apparatus. They diagnosed 6 of the 11 workers with silicosis, which equated to a disease prevalence in this work environment of 54.5%. Of the 6 workers affected, 5 (83.3%) were assembles (fabricators). The investigators attributed silicosis in these workers to quartz conglomerates (artificial stone). Pascual S, et al., "Prevalence of silicosis in a marble factory after exposure to quartz conglomerates," *Arch. Bronconeumol.* 2011; 47(1):50-51 [in Spanish with English abstract]. These workers were exposed to Cosentino's Silestone.

1098. On May 29, 2011, an article appeared in Diario de Cadiz titled "Silicosis has affected almost twenty Pelagatos workers." The article noted that this irreversible fibrotic-pulmonary disease is contracted through Silestone, a material used to manufacture countertops. A conference on occupational health organized by Comisiones Obreras (CCOO) in San Fernando brought to light information that affects workers in the Pelagatos industrial estate. From the Occupational Health Secretariat of that union, Manuel García Túnez, confirmed that a total of 19 workers from that industrial zone who are engaged in the manufacture of Silestone have suffered from silicosis. The union official pointed out that this disease is contracted through prolonged contact with a material

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used in countertops, Silestone (a quartz agglomerate), but that this condition is due to the fact that few measures are taken to prevent occupational hazards. Thus, he said that among the twenty people affected by silicosis there are already people with absolute disability and others who are able to work. In the same way, he criticized the functions of the mutuals that, in his opinion, "are more interested in their business than in the worker." He also pointed out that the health authority, in terms of occupational health, "is a real disaster in the entire Andalusian community, but much more in the province of Cádiz."

20. Cosentino's 2013 Material Safety Data Sheet for Dekton®

1099. In April 2013, Cosentino issued a Material Safety Data Sheet for its product DEKTON®, which described the product as an "Ultra-compact surface designed for use indoors and outdoors, particularly kitchen and bathroom worktop, flooring, cladding and facades."

1100. Section 2 of this Material Safety Data Sheet, regarding "Hazards Identification" states: "There is no provision for any risk associated with the finished DEKTON® material in the CLP (EC) regulation n^{0}. 1272/2008. However, respirable crystalline silica dust can be generated in manufacturing operations. Respirable crystalline silica causes harm to the lungs, such as silicosis, through prolonged or repeated exposure (Hazard H372). A series of preventative measures should be adopted to prevent or minimise exposure." This statement is false and misleading for the following reasons: First, the purpose of the referenced regulation "is to ensure a high level of protection of human health" and to provide "an obligation . . . for suppliers to label and package substances and mixtures placed on the market," suppliers being defined as including "any manufacturer, importer, downstream user or distributor placing on the market a substance, on its own or in a mixture, or a mixture." Second, crystalline silica is specifically identified in Annex 1 of the regulation as a hazardous substance. Third, the regulation requires suppliers (including manufacturers) of a hazardous substance or mixture to "ensure that the substance or mixture is labelled and packaged in accordance with [the regulations] before placing it on the market." Because DEKTON® is a chemical mixture that is not a finished, end-use product sold to consumers, but is rather an industrial product sold to companies that fabricate countertops for installation in kitchens

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and bathrooms, the ordinary, intended and expected use of the product is for it to be cut, ground, and polished, thereby releasing respirable crystalline silica dust. Accordingly, contrary to Cosentino's assertion, there is risk associated with DEKTON® and the referenced regulation does require health hazard and other disclosures for the product.

1101. The Material Safety Data Sheet then states: "Contens [sic] crystalline silica < 11%" and provides the following warning: "HAZARD: H372 Causes damage to lungs through prolonged or repeated exposure (inhalation)." This is information is vague and misleading, because it does not specify how many days, weeks, months, years or decades constitutes "prolonged" exposure or the number of exposures that constitute "repeated exposure" that causes such damage.

1102. The Material Safety Data Sheet then provides four instructions under a heading "Prevention": P260 Do not breathe dust generated in the cutting, grinding, and polishing processes; P264 Wash face and hands thoroughly after handling; P270 Do not eat, drink or smoke when using this material; P284 Wear respiratory protection for particles (P3)." The first instruction is meaningless and impossible of performance, because dust is always generated in cutting, grinding and polishing DEKTON®, and workers cannot hold their breath an entire workshift so as not to breathe dust generated in the cutting, grinding, and polishing processes. The second instruction, although a useful general hygiene instruction, not a means of prevention, i.e., washing one's face and hands after handling DEKTON® cannot prevent silicosis. The third instruction is also not a means of preventing silicosis and is a rather useless instruction, because DEKTON® is too hard to eat (one cannot eat stone), DEKTON® dust does not present an appreciable ingestion hazard, so that there is no appreciable risk to one's health of eating or drinking when using DEKTON®, and there is no risk of fire or explosion from smoking when using DEKTON®, because it is not flammable. The fourth instruction, to "wear respiratory protection for particles" (which is accompanied by a pictograph of a worker wearing a particulate filter respirator) is inadequate, because air-purifying respirators are inadequate to prevent silicosis from inhaling DEKTON®, and the only type of respirator that is adequate to prevent silicosis from inhaling DEKTON® is a NIOSH-approved air-supplied respirator. Thus, this preventive instruction is actually harmful, because it prescribes the wrong type of respirator to prevent silicosis from inhaling respirable crystalline silica dust from

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DEKTON®, and would thereby mislead workers to believe that wearing a particulate air-purifying respirator would prevent silicosis and thereby preserve their health and safety.

1103. Section 8 of the Material Safety Data Sheet is titled "Exposure Controls/Personal Protection" and contains a section regarding "Exposure Controls (Manufacturing and installation)" that states: "The manufacturer recommends methods that involve the use of water in the manufacturing of this material. Dust derived from the manufacturing processes could contain respirable crystalline silica (SiO_2)." The first sentence is an inadequate use instruction, because wet processing methods ***must*** be used whenever DEKTON® is cut, ground or polished, to prevent silicosis, although wet processing methods alone are insufficient to prevent silicosis. The second sentence is misleading because it suggests that dust from manufacturing processes may not contain respirable crystalline silica, although respirable crystalline silica is generated whenever DEKTON® is cut, ground, drilled, millers, polished, or otherwise fabricated.

1104. The section of the Material Safety Data Sheet regarding "Exposure Controls" then says: "Long term exposure to dust derived from the cutting and manufacturing processes without the use of suitable protection may cause serious deseases [sic] including pneumoconiosis such as silicosis, as well the deterioration of other lungs diseases such as bronchitis, emphysema, etc." This statement does not constitute an "exposure control," i.e., a means of controlling exposure. It is also a vague and inadequate description of health hazards, because it indicates that only "long term exposure" to dust from the product can cause silicosis, which could well be understood to be decades of exposure that results in chronic silicosis, although fabricating artificial stone countertops has most strongly been associated with acute silicosis (typically following exposure of less than 3 years) and accelerated silicosis (following exposure between 5 and 10 years). The sentence is also vague and misleading, because it does not define "suitable protection," which workers would typically understand to be the use of a particulate filter (air-purifying) respirator, which is inadequate to prevent silicosis in artificial stone fabricators, because the only type of respirator that can prevent silicosis in such workers is an air supplied respirator.

1105. Section 8 of the Material Safety Data Sheet states: "Always use respiratory protection for P3 type particulates according to EN 143:2001 and its revisions EN 143/AC 2002, EN 143/AC

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2005 . . . during the preparation of Dekton®." While this type of air-purifying respirator will reduce exposure to crystalline silica, it will not eliminate such exposure and will not prevent silicosis, as will a NIOSH-approved air supplied respirator. The instruction to use this respirator is thus harmful.

1106. Section 11 of the Material Safety Data Sheet is titled "Toxicological Information." This section provides little toxicological information regarding the product. Although Section 3 of the Material Safety Data Sheet identifies silicoaluminates, amorphous silica, crystalline silica, zircon and inorganic pigments as the ingredients of DEKTON®, no toxicological information is provided regarding any ingredients of the product other than crystalline silica, and the information provided regarding crystalline silica throughout the Material Safety Data Sheet is inadequate, incomplete, misleading and false. Especially because Cosentino did not disclose the cancer hazard that exposure to DEKTON® presents in the Hazards Identification section of the Material Safety Data Sheet, that information should be disclosed in Section 11 of the Material Safety Data Sheet. In particular, this section of the Material Safety Data Sheet should state that crystalline silica is a known human carcinogen, because the International Agency for Research on Cancer classified crystalline silica as a Group I (known human) carcinogen in 1997. The only statement regarding cancer in the entire document is the last sentence of Section 11 which states: "Persons affected by silicosis have a higher risk of suffering from lung cancer." Although true, this statement is misleading, because it suggests that silicosis causes cancer. However, silicosis does not cause cancer; it is crystalline silica that causes cancer. Persons who have been diagnosed with silicosis typically have a greater cumulative exposure to crystalline silica than do persons who have not been diagnosed with silicosis, so persons who have silicosis have an increased risk of developing lung cancer because of their greater exposure to crystalline silica. Cosentino's failure to disclose the carcinogenic hazard of DEKTON® due to its crystalline silica content not only violates the Hazard Communication Standard, but also violates California's Safe Drinking Water and Toxic Enforcement Act ("Proposition 65"), which requires manufacturers of carcinogenic products to warn individuals (including workers) exposed to such products that they contain a chemical (crystalline silica) known to the State to cause cancer.

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21. Cosentino Denies Responsibility for Silicosis Cases of Workers in Andalusia

1107. In July, 2015, Younes Nachett authored an article regarding silicosis among Spanish workers in Andalusia who had been occupationally exposed to crystalline silica from Cosentino's Silestone. On July 28, 2015, Santiago Alfonso Rodriguez, Cosentino's Director of Communications sent a letter to the newspaper, denying Cosentino's responsibility for the silicosis cases in Andalusia:

> We are contacting you regarding the publication in the newspapers that you direct of the articles titled "The deadly dust of kitchen countertops with a Quartz base," Viva Sevilla, July 28, 2015, and Viva Caldiz, July 28, 2015, authored by journalist Younes Nachett and published in the digital edition of the media.
>
> In the aforementioned publications, false and misleading statements are made regarding Cosentino and products such as Silestone, that are attributed to causing illnesses and even deaths. Extensive documentation and statements from the company were provided to the journalist, Younes Nachett, at his request, which we shared for his knowledge as an attached document.
>
> The materials that we produce are harmless to health and, as the author who signed the report explained in detail, improper handling is the cause of these diseases, but your newspaper insists that our material is especially harmful to health.
>
> We ask you to attend to this communication by proceeding to rectify the information in everything related to Cosentino and Silestone, both in the aforementioned article and in any other of your publication in which it may be replicated.
>
> In the legitimate defense of the good name of our company and our interests, we reserve the right to take any legal action that may be appropriate.
>
> Sincerely, Santiago Alfonso Rodriguez
>
> Director of Communications, Cosentino

1108. Cosentino stated that according to the National Institute of Silicosis, the measures to control dust in the cutting and polishing process are based on irrigation with water so that the particles settle, and that adequate controls are used that do not return them to the atmosphere and remove them from the environment with aspiration and ventilation. To the extent that these procedures fail, personal protection measures must be used. Devices can be used to filter and prevent the inhalation of these materials when carrying out work such as mining. It is important to avoid

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tobacco, in any case, but especially in workers who handle the stone and take the appropriate measures to prevent tuberculosis." Cosentino claimed that "Silestone® is a safe product, that exposure to the material is not harmful in any case . . . , what happens is that these marble factories lacked safety measures of any kind, both for granite and for quartz countertops," which "cannot be attributed" to Cosentino. Cosentino insisted that "neither was the risk unknown to the marble workers, nor to the mutual companies, nor were the safety measures and health surveillance protocols that had to be adopted different from those of other materials with silica content." Cosentino also claimed that "since the start of marketing Silestone® products, the company printed commercial catalogs in which it was indicated that their composition contains more than 90% quartz, the composition of Silestone® could not be unknown to the marble workers and in fact it was not, which is why they could have applied safety measures from the beginning that were none other than those that they should already be applying for the handling of granite. Cosentino also claimed that "already in 2005, coinciding with the entry into force of the European directive that regulates the labeling of products, Cosentino began to include an eye-catching label that warned of the health risks of handling these products without protection and in 2009, this information was expanded with much more explicit labeling. Cosentino argued that responsibility for the silicosis epidemic among Spanish workers exposed to its product was with the workers' employers rather than Cosentino: "Knowing that the focus of the problem is clear, it is essential that those responsible for companies that cut, polish and install stone materials assure compliance with safety measures because they are the ones who must supervise compliance with requirements are also responsible for incorrect actions."

22. The First Silicosis Lawsuit Against Cosentino in the United States

1109. Ublester Rodriguez was a Mexican immigrant who came to the United States at age 14. He spoke no English, did not receive a formal education, and worked in restaurant kitchens until changing jobs and working with countertop cutting. Since 2000, Rodriguez has worked on cutting and polishing slabs of an artificial stone to make kitchen and bathroom countertops." "Just 10 years after beginning work with Cosentino, Rodriguez noticed serious health problems that affected his

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day-to-day. He had to stop playing soccer for fun because he got tired very easily. He developed a persistent cough, and after getting some X-rays done, the doctor told him he had severe silicosis at 33 years old. Rodriguez had never heard the terms before." "His lungs are so damaged that he is on oxygen about six hours a day. Unfortunately, he will likely need a lung transplant." "The shop Rodriguez worked for is run by Cosentino . . . ." "His employer [Stone Systems] did not explain anything about Silestone's makeup, the fact that it's made from mostly quartz, and it contains a lot of silica. Silestone can be as much as 90 percent crystalline silica – twice as much as natural granite. The only thing his employer warned him about was injuries related to cutting, for example. He explained that no mention of potential lung disease was ever communicated." "Around the time of Rodriguez's diagnosis, the company had just begun to issue warnings around the shop of risk of silicosis, and it had not tested the workplace air until just the year previous. The 2009 inspection fo the air showed that silica exposure levels were well above the legal limit in three of seven workers who wore monitoring devices to assess the air quality around them. Still, a 2011 round of air tests had the same results: three of seven monitored workers above the permissible exposure limit, and employees still at risk. This was the case even though all the processes including cutting and grinding were using water to keep down the dust. The company says it believed it was taking the necessary measures to protect employees, especially since the early 2000s. Travis Dupre, the current vice president of sales for Stone Systems, testified and said the following: "We felt like we were doing what was reasonable. We had switched everything to wet grinding. We had moved into a facility with better ventilation. We'd enforced no dry cutting. We felt like we were taking the reasonable steps." Mr. Rodriguez filed a lawsuit against his employer Stone Systems and against Cosentino, which settled in 2016. The lawsuit "was settled confidentially, with no admission of liability. Neither Cosentino nor Stone Systems made public statements regarding the legal proceeding or the documents associated." "US Countertop Workers falling Sick from Silica Dust: More and more cases of countertop workers getting sick indicates the hazards are cutting Silestone, a material made of quartz that releases dangerous silica," *Occup. Health & Safety* (Dec. 5, 2019).

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23. Martin Mendiola Sues Cosentino in Los Angeles for Causing His Disease

1110. On August 1, 2017, Martin Mendiola, who was a lifelong never-smoker, filed a lawsuit in Los Angeles Superior Court (Case No. BC 670691), alleging that his exposure to silica in the course of his employment with Sistone, Inc. and Realstone, Inc. from 1981 to August 2016 caused him to suffer disabling lung disease, at which time he was determined to be disabled and could no longer work. He alleged that he was diagnosed with chronic obstructive pulmonary disease (COPD) on August 1, 2015 and that "his latest breathing test returned with a 64% spirometry reading."

1111. Mr. Mendiola alleged that "Defendants intentionally, deliberately, callously, and/or with willful and wanton disregard exposed workers [to] highly toxic pulmonary dust and material know[n] to cause silicosis," that Defendants "concocted a fraudulent scheme to deceive workers as to the nature of such hazards, and they fraudulent concealed from workers data on actual workplace conditions that would have caused the workers to cease working . . . ." Mr. Mendiola further alleged that "[t]his fraudulent concealment continued for years until exposed and in the discovery of medical testing it conf[i]rmed that indeed PLAINTIFF had and has silicosis."

1112. Mr. Mendiola alleged that "for years DEFENDANTS did next to nothing to protect the health and safety of the [ ] PLAINTIFF" and that "DEFENDANTS kn[ew] that the workers were using and working with material that was . . . known by DEFENDANTS to cause diseases such as silicosis, lung cancer . . . , chronic obstructive pulmonary disease (COPD), renal disease, and tuberculosis." Mr. Mendiola alleged that "DEFENDANTS fraudulently concealed this information from workers deliberately so as to avoid the added costs . . . and inconvenience of providing adequate respiratory protection [to] PLAINTIFF, knowing that the actual, [p]articulate levels were certain to cause harm." He further alleged that "[t]he workers so impacted would have refused to work with said products and or materials[] without at least adequate [r]espiratory protection and protective clothing had DEFENDANTS disclosed the facts to them."

1113. On or about September 4, 2018, Mr. Mendiola named Cosentino S.A. as a doe defendant in the case.

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1114. On October 26, 2018, Cosentino S.A. filed a motion to quash service of the summons and complaint, arguing that "the Court lacks personal jurisdiction over [Cosentino S.A.] because the Summons and Complaint served are substantially defective and the Court lacks personal jurisdiction of . . . Defendant due to improper service." Cosentino S.A. also claimed that the Los Angeles Superior Court "lacks personal jurisdiction over . . . Defendant because the allegations noted in Plaintiff's Complaint did not arise out of any contacts that . . . Defendant COSENTINO, S.A., might have had with the State of California; and . . . did not purposefully avail itself of any benefits of doing business in the State of California."

1115. In support of this motion, Cosentino S.A. submitted a Declaration of Jorge Cuervo Vela, Legal Director of Defendant COSENTINO, S.A., acknowledging that on or about September 19, 2018, he was sent a copy of the doe amendment naming COSENTINO S.A. as a defendant in the case and that the "Amendment to Complaint, Summons, and Complaint . . . were left at the reception desk of Cosentino Center Los Angeles." Although the signage on that building at the time bore word marks, tradenames, and trademarks of Cosentino and some of its products, Mr. Vela nevertheless declared that "COSENTINO, S.A. does not operate Cosentino Center Los Angeles." On November 14, 2018, Plaintiff's counsel filed his declaration in support of Plaintiff's opposition to the motion, attaching as an exhibit a press release dated November 12, 2015 on Cosentino's website titled "Cosentino Unveils Innovative 'Cosentino Center' in Los Angeles." This press release showed a photograph of Cosentino Center Los Angeles which bore a blockish "C" and the word "COSENTINO," which constitutes a word mark (a type of trademark) owned by the Cosentino Group S.A. The press release stated: "The new state-of-the-art Cosentino Center in Los Angeles is an interactive showroom and warehouse that will enhance the kitchen and bath design experience for architects, designers, fabricators, distributors and consumers in the region. The center officially opened today. As a family owned business headquartered in Spain, Cosentino has long been the trusted surfacing brand in Europe. The Los Angeles opening is part of the company's larger strategic plan to underscore its position as the surfacing leader in the U.S. market with increased availability and distribution of its products. The Center will create jobs in the area and allow architects and designers to regionally source their favorite surfacing materials. The new Los Angeles

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location boasts a 29,000 square-foot warehouse and distribution space that displays the full portfolio of Cosentino brands: **Dekton®**, . . . **Silestone® Natural Quartz** . . . . 'The Southern California design community is an integral market for Cosentino,' said Lorenzo Marquez, VP of Marketing for Cosentino North America. 'The opportunity to greatly strengthen our presence in the region is a testament to Cosentino's growth in North America, and the value of the area to the A&D world. We are excited to partner with architects, designers and consumers in Southern California through our showroom experience, design knowledge and resources. . . . The Los Angeles Cosentino Center is located in the heart of Los Angeles County's stone and tile distribution district at 12822 Rangoon St., Los Angeles, CA 91331. Phone: 818-381-8220. © Cosentino S.A. All rights reserved."

1116. The judge in the case granted Cosentino's motion to quash, apparently due to technical defects in the proof of service of the complaint on Cosentino. Nevertheless, as acknowledged by the Declaration of Jorge Cuervo Vela, Cosentino, S.A.'s Legal Director, the complaint in the *Mendiola* case clearly was received by Cosentino S.A. and put Cosentino on notice that its artificial stone products were causing lung disease, including silicosis and chronic obstructive lung disease among workers in Los Angeles County who were occupationally exposed to respirable crystalline silica from Cosentino's deadly products.

24. More Spanish Workers Get Silicosis from Silestone and Sue Cosentino

1117. On February 19, 2019, the Spanish newspaper Eldiario published an article by Nestor Ash. It was titled "Andalusian silicosis reaches the courts: a court investigates a complaint against the manufacturer of Silestone." This article noted that silicosis is the main occupational disease in Andalusia, according to a report from the Ministry of Health, which attributes it to quartz agglomerate (artificial stone). The article noted that the highest incidence had been registered in Cádiz, although all the production of quartz agglomerate comes from Almería. The article reported that several workers afflicted with the disease had filed a complaint. It related the story of one worker: José Araque spent the last two years of his life on a sofa, lying on his side to avoid the hemorrhages that every so often flooded his right lung, the only one that barely worked. His lungs

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had been filled with small silica stones twenty years before, while he was handling the quartz conglomerate that is manufactured in the complex that the Cosentino Group has in Cantoria (Almería) and whose star product is Silestone countertops. Araque died in 2015, a victim of silicosis, which today is the main occupational disease in Andalusia. Several afflicted with silicosis filed a complaint against those responsible for the company. They believe that the lack of adequate safety measures caused the death of Araque and injuries to other workers. "He knew he had little chance of life, but the last few years were spent waiting for death. He was very afraid, he was exhausted, and at the moment he began to bleed . . . he said that he was worthless," recalls his widow, Paqui Silva. He started suffering from respiratory problems in 1998. "He had a fever. We would go to the emergency room, antibiotics and work again. He was always very tired." In 2002, a biopsy confirmed that he suffered from silicosis and two years later they removed a large part of his left lung, eaten away by the disease. For years he suffered more and more frequent hemorrhages, which forced him to travel urgently from Huércal-Overa to Granada, intubated to avoid drowning in his own blood. The last years of his life, Araque spent suing his company. In 2004, he started a legal battle to determine the degree of disability that he suffered. A medical court deemed him disabled from work, but did not grant him absolute disability. In his mid-thirties, he was left without a job and with a salary of 800 euros. In 2015, thirteen years after he was diagnosed with silicosis, the labor inspectorate reviewed his case and acknowledged that Araque was completely unable to work. "Now that they know I'm dying, they give me this," lamented the man, as his widow recalled. He died a few months later. Araque's case is one of the few cases brought against Cosentino, the great marketer of quartz agglomerates in Andalusia and Spain. Cosentino employs around 1,500 workers at its factory in Cantoria (Almería). It is the great company of the marble region. It ended 2017 with revenues of 901 million euros and 57 million euros in profit. Last year some affected workers and relatives filed a complaint against the managers of the company, charging them with alleged crimes of reckless homicide and injuries. The article noted that silicosis accounts for 18.55% of occupational diseases in Andalusia and is the most common occupational disease in Andalusia, having displaced pathologies from exposure to asbestos as the most common occupational disease according to the monograph "Communications of suspected occupational diseases 2009-2016,"

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prepared by the surveillance and occupational health service of the Ministry of Health. The report, published in May 2018, links the rise in disease to quartz agglomerates, which became popular in the real estate boom years. The reported cases of silicosis, 279 in total, were concentrated in the provinces of Cádiz, Córdoba and Almería, with a maximum peak in 2011. From that year on, the cases in Almería decreased. The total number of cases reported in the period 2009-2016 was 122 in Cádiz, 37 in Almería and 37 in Córdoba, the most affected provinces. "If there is one, there must be more", thought Dr. Rabadán and his team, who began an active search that led them to 24 small workshops where compacted quartz countertops were cut. "Word spread and among those we searched for and those who turned up, we began to do tests and biopsies. The CT images [chest tomography] were shocking, you could see the white lungs," explains the doctor. The silicosis produced by the quartz agglomerate is especially virulent and evolves much more rapidly than the silicosis of the miners. The reason for the aggressiveness of this variant is the material that produces it. Silestone is a composite material that contains around 80% silica and cristobalite, which is crystalline silica derived from high temperatures. When dumped into a silo, the silica produces dust; when a hopper is cleaned, it produces dust; when a countertop is cut, dust is produced. "The silica particles are so small they are respirable, and masks are not effective in preventing inhalation of the small particles, explained the doctor. In total, 122 cases were reported in the province of Cádiz in the period 2009-2016 and those affected ended up formed the Association of Affected and Sick with Silicosis (ANAES), founded by Agustín Cebada shortly before undergoing a lung transplant that was not successful. Today the president of the association is Ismael Aragón, who suffers from silicosis like two of his brothers, his father and ten other relatives. They all worked in the marble shop. "We did the fine work, the adaptation to the home," he recalls. According to his account, they worked with Cosentino countertops. "A lot of cutting, a lot of sanding." In those *boom times,* no one in the marble shops took any safety measures. "They had not told us everything it contained: lead, arsenic, cadmium. . . . Some labor inspector has come to tell us that this must be worked with Ebola suits," laments Aragón, who noted that a case of the disease has already been detected in an office worker: "We pray that our wives, who worked in the offices, are not sick." The Cosentino company denied any responsibility in these cases, and emphatically claimed that the cutting, manufacturing and

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installation of the quartz agglomerate slabs could be done in a "totally safe" manner, following the measures indicated on the labels of each slab, the Safety Data Sheet and the Good Practices Guide. "Unfortunately, the implementation and continuity of existing safety measures in each marble shop is the exclusive responsibility of the owner of the same," said the company. According to his widow, Antonio signed a confidentiality agreement with Cosentino. Paqui, the widow of José Araque, also mentioned these clauses, supposedly signed by some workers in exchange for compensation or a new job away from silica dust. José Antonio López, president of the association of affected people from Almería, confirmed that it is a common practice in the company: "They wanted to deal with me, but they played with my life: I was about to die. I don't even want to go through the door. I can tell you about 15 or 20 people who are working in factories with silicosis." The company admitted the existence of confidentiality clauses. The existence of these contracts could explain the sharp drop in reports of silicosis in Almería, after the peak of 2011. Those affected would guarantee themselves a position in the company away, in theory, from the supposed source of contamination, and avoid a retirement with a pension that barely reached half of the worker's salary. "Some workers don't want us to do the examination, because they would be unemployed and they don't know how to do anything else," admitted Dr. Andrés Rabadán. For him, this refusal poses an "ethical" problem. Cosentino, however, claimed that the number of "relocated" workers did not exceed ten, out of the "less than 25 cases" of silicosis registered in his factory. Another possible explanation for the sharp drop in reports of silicosis in Almería is that, following the first cases detected, Cosentino adopted strict safety measures that it claimed was able to effectively protect its employees from silica dust. Cosentino claimed that it adopted comprehensive protective measures according to the work area (water nebulizers, localized exhaust ventilation, forced environmental ventilation) with the use of respirator masks, "thus guaranteeing that the worker does not have any exposure to dust from silica." Just over a year ago, Interviú magazine published some images that refuted this statement. In them you can see areas of the Cosentino factory in Cantoria wrapped in a cloud of dust that barely allows you to see what is a few meters away. Eldiario.es Andalucía has had access to two videos, supposedly made in 2017, and provided by one of the sources consulted for this report. In one of them a massive dust leak is observed in some facilities; in the other, dust is generated by various

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polishers. However, the place of the recording could not be verified, according to Cosentino. "The images published in the Interviú article did not represent the reality of the factory at all, nor has it been proven in any way that they had been taken in our production centers," the company claimed, attributes its publication to the interest in creating "an unjustified alarm." The company asserted that measurements of exposure to silica dust would "objectively" prove that workers can carry out their work safely. The last possible explanation is that doctors are not detecting the disease. This is what the report of the Junta de Andalucía suggests. For Doctor Rabadán, it would not be strange: "It is not an easy disease to detect. We have experience that no one else in the world has. We have seen more than a hundred cases." Those affected from Almería refer to several workers who were not diagnosed in Almería, and were in Cádiz. Dr. Rabadán believes an active search is necessary for cases of silicosis to surface: "If you wait, not many will appear, and if you do an active search they will."

25. Judgment By Spanish Court that Cosentino's Disclosures Were Deficient

1118. On February 20, 2019, Eldiario published the second in the series of articles by Nestor Ash, titled "A ruling established the responsibility of Silestone manufacturers for failing to warn of the risk of silicosis." This article stated that "The Provincial Court of Bilbao ruled in 2017 that Cosentino disclosures of the risks of handling quartz agglomerate was "late, insufficient and confusing." This article noted that the manufacturers and especially Cosentino denied all responsibility for how the material was handled in the marble factories to which it supplied the product. The Almeria-based company claimed that it currently conducts training courses for marble shops and issues information bulletins in which it explains the protective measures that must be adopted to cut, process and install its countertops. These measures are also outlined in the safety labels incorporated in each table, the Safety Data Sheet and the Good Practices Guide. "Unfortunately, the implementation and continuity of existing safety measures in each marble shop is the exclusive responsibility of the owner of the same," said the company. However, a sentence of the Criminal Court 1 of Bilbao, which was confirmed by the Provincial Court of Vizcaya in May 2017, questioned the thesis of the exclusive responsibility of the company fabricating the

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countertops. These rulings determined that Cosentino, as a manufacturer of quartz agglomerates, had joint responsibility for the illness of various workers at a Vizcaya marble factory, because Cosentino disclosed the hazards of the material they supplied "late, insufficiently and confusingly." Nevertheless, the heads of Cosentino and Levantina de Granitos (a company that imported a similar product from Israel) were acquitted due to the statute of limitations for the reckless injuries, the crime with which they were charged. Marmolerías Cid, where several patients with silicosis worked, was a family business that had been dedicated since 1984 to the fabrication and installation of granite countertops. Around 1999, Marmolerías Cid began to acquire and work on Silestone countertops, which at that time were expanding rapidly throughout Spain. From 1999 to 2008, Marmolerías Cid acquired Silestone countertops manufactured by Cosentino for a value of 1.8 million euros, in addition to a similar product, Caesarstone, worth around 250,000 euros. The judgments declared that it had been proven that up until 2004 neither Cosentino nor Levantina de Granitos disclosed the hazards of handling this product, despite the general duty established by the 1995 Occupational Risk Prevention Law. In 2004, Cosentino added a label to the slabs with a warning that equated the risks of dry cutting or grinding Silestone to the risks of fabricating "natural stone products such as marble or granite: Prolonged exposure . . . can cause serious health problems, including pneumoconiosis." However, the safety sheets did not begin to be produced until 2005-2006, and there was no record that they were delivered to the marble factory until 2009, according to the judgment, which added that "they gave rise to confusion" because they compared Silestone slabs to those of natural stone, and insisted that they are safe for the end user, obviating the risk for the intermediate handler. The court concluded that Silestone is a product that workers must handle with extreme safety measures. The court's ruling noted that the International Agency for Cancer Research has concluded since 1997 that silica is a carcinogenic substance, and that the slabs contain free crystalline silica in a percentage between 70% and 90%, "whose inhalation by minimal and continuous exposure for five years can cause silicosis." Neither the labor inspection, nor the risk prevention mutuals, nor the manufacturers warned of the composition of Silestone or the risks it entails, so the workers "performed the machining tasks without adequate protection, leaving them exposed . . . to respirable dust with a high silica content," the judgment concluded. The judgment considers that the heads of the marble factory

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could not be aware of the danger of this material, but that the manufacturers could be held responsible for the generation of silicosis in the workers, for failing to satisfy their "duty of disclosure" regarding the product that they were supplying. The judge reasoned that this omission resulted in no preventive measures being adopted, but ended up reducing the responsibility of the manufacturers because the legislation was imprecise, the product was new, and the manufacturers provided information, even if it was late, vague or deficient. In this way, the judge acquitted Francisco Martínez-Cosentino, president and general director of the company, for the offense. The sentence was appealed before the Provincial Court, which confirmed that "it is clear that there was a violation of the duty of disclosure by the manufacturing company" and affirmed the judgment.

26. Cosentino Falsely Claims its Products are Not Inherently Dangerous and that Silicosis from Exposure to its Products is Entirely Preventable

1119. In a letter dated November 29, 2019, to the Hon. Niall Blair, Committee Chair of the Legislative Council Standing Committee on Law and Justice in Sydney, Australia, Cosentino claimed that "Cosentino has been making continuous efforts to raise awareness amongst the companies and persons working with the engineered stone products, by way of holding on-site Occupational Health & Safety educational sessions to the industry during many years, worldwide." This statement is false, because Cosentino only initiated its educational program as a public relations effort to salvage Cosentino's reputation and to avoid liability for causing silicosis worldwide after news media reported the artificial stone fabricator silicosis epidemic in 2019, especially because Spanish courts had issued judgments finding that Cosentino had failed to adequately disclose the toxic hazards of its product and that the disclosures that it made were inadequate, confusing, and late. Whereas Cosentino had previously disclaimed all responsibility for the silicosis cases among Spanish workers who fabricated Silestone and blaming the epidemic on its customers for failing to provide a safe workplace, in its letter to the Chair of the Australian Legislative Council Standing Committee on Law and Justice, Cosentino "acknowledg[ed] its corporate social responsibilities" "for the benefit of employees and suppliers alike" to provide adequate warnings and use instructions for its products. In this letter Cosentino acknowledged that "Silicosis dust disease related illnesses is one of the main challenges to be addressed by the engineered stone industry." In the letter Cosentino claimed that

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in the last fiscal year, "the Cosentino Group has provided approximately 1,200 hours of training to suppliers [and] more than 30,000 hours of training directly to employees." Thus, Cosentino finally acknowledged its duty to make adequate health hazard disclosures and to train its customers' employees regarding the extreme silicosis hazard of its products and how to use Cosentino's products safely so that they would not develop and suffer from silicosis. This was a complete reversal of Cosentino's prior stated position that it had no responsibility to its customers' employees, that their health and safety was solely the responsibility of their employers, and that Cosentino could not protect the health of its customers' employees because it lacked control over their workplaces. The new position that Cosentino presented in its November 29, 2019 letter to the Chair of the Australian Legislative Council Standing Committee on Law and Justice, was expressed as follows:

> At the outset, it is important for Cosentino to emphasise that it shares the concerns expressed on behalf of the AESAG [Australian Engineered Stone Advisory Group] concerning the welfare of persons engaged in the use of engineered stone products. A safe working environment for everyone involved in the lifecycle of those products is of utmost importance to Cosentino and for many years has been accepted as integral component to the sustainability of not only the manufacturers and suppliers of those products, but the many downstream industries and employers which rely on manufactured stone product for their livelihood.

In its letter Cosentino then defended its products, asserting that "Cosentino quartz products (Silestone®) are produced according to very strict quality criteria and comply with all technical requirements of existing regulations." However, this statement was merely an effort by the company to deflect attention from the silicosis epidemic and deaths by urging legislators to instead focus on the product's manufacture being in compliance with regulatory requirements. After defending its compliance with regulatory requirements regarding the manufacture of its lethal products, Cosentino expressed its positions regarding those of the Australian Engineered Stone Advisory Group. The first position that Cosentino expressed was: "Engineered quartz products are not inherently dangerous. Silicosis associated with the use of those products is 100% preventable when manufacture, fabrication and installation occur in accordance with published OH&S guidelines." This assertion was false, because multiple scientific studies published in the peer-reviewed literature have shown that even when all precautions and protections that had been suggested by Cosentino (i.e., use of wet processing methods and air-purifying respirators) were implemented and rigorously

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followed, workers nevertheless developed silicosis, because the extremely high crystalline silica content of Silestone and other artificial stone products does render them inherently dangerous. In addition, Cosentino's assertion that "engineered quartz products are not inherently dangerous" because of their extremely high crystalline silica content is refuted by the company's own decision to begin manufacturing products that contained much less crystalline silica, e.g., its Dekton® and Dekton Xgloss® family of products which it reformulated to have a total crystalline silica content of just 5-11% according to Cosentino's October 2018 Safety Data Sheet for the product, its Dekton® LITE product which it formulated to contain just 3-9% crystalline silica according to Cosentino's May 2020 Safety Data Sheet for the product, its SILQ® product which Cosentino formulated to have a crystalline silica content of 51-92% according to Cosentino's May 2022 Safety Data Sheet for the product, and its Sensa® and Scalea® family of natural stone products which contain less crystalline silica than Costentino's traditional artificial stone products according to its September 2022 Safety Data Sheet for the product, although the range or typical crystalline silica content of this product is not stated in the September 2022 Safety Data Sheet for the product. In its November 29, 2019 letter to the Committee Chair of the Legislative Council Standing Committee on Law and Justice, Cosentino strongly opposed banning all artificial stone products, recommended by the Australian Engineered Stone Advisory Group, arguing that such a ban "would create enormous disadvantage to the countless businesses and households which rely on the trades that are closely aligned with the use of all those products, including the retail, marketing and distribution networks that have developed in parallel with the core trades." However, Cosentino's argument that "businesses and households which rely on the trades" would suffer "enormous disadvantage" is untrue, because the needs of consumers and business for stone countertops could readily be satisfied by natural stone countertops which contain much less crystalline silica than artificial stone countertops, as well as Cosentino's new artificial stone products, some of which it formulated to have lower concentrations of crystalline silica, such as its Dekton® and Dekton Xgloss® family of products which it formulated to have a total crystalline silica content of just 5-11% according to Cosentino's October 2018 Safety Data Sheet for the product, and its Dekton® LITE product which it formulated to contain just 3-9% crystalline silica according to Cosentino's May 2020 Safety Data Sheet for the product.

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27. Cosentino Admits Negligence

1120. On February 7, 2023, Reuters reported that Francisco Martinez, who owns Cosentino, "admitted in court that he covered up the dangers of his company's star product, which allegedly led to nearly 1,900 workers contracting the occupational lung disease silicosis, court documents showed on Tuesday." He "accepted a six-month suspended prison sentence for five counts of serious injury due to gross negligence in a plea bargain with the court in the northwestern region of Galicia." Reuters wrote: "Cosentino said in a statement the plea deal only admitted liability for insufficient technical information affecting five workers at a specific workshop and therefore could 'not be extrapolated to other past or future proceedings.'" Reuters noted that "Prosecutors had initially sought a prison term of two years and nine months." The Reuters report stated: "Cosentino, based in the southern province of Almeria, is planning an IPO that could be worth more than 3 billion euros. The company employs over 5,000 people worldwide and posted record sales of 1.4 billion euros in 2021. In the ruling, the judge said Martinez had failed to adequately label the 95% silica content of Cosentino's bestselling quartz agglomerate, branded as "Silestone", despite being aware of the safety and health risks its manipulation entailed." Reuters also reported that "the 71-year-old businessman also agreed to pay 1.1 million euros ($1.2 million) in compensation to the five stonemasons - one of whom has since died - who had sued him for failing to warn of the risk of silicosis linked to cutting and polishing Silestone countertops." Reuters further reported that "Cosentino said managers at stone-cutting workshops 'are responsible for ensuring that their workers have the necessary means of protection and that they implement them appropriately.' 'It is entirely incorrect that Cosentino has admitted to having concealed the fact that the handling of Silestone has caused the majority of cases of silicosis that have affected 1,856 workers,' it added." The Reuters report concluded, stating that "Martinez is set to return to the dock in July for a separate trial in the northern city of Bilbao. Prosecutors are asking for two and a half years' imprisonment on six counts of reckless injury." David Latona, "Owner of Spain's Cosentino admits negligence over silicosis in workers - documents," *Reuters* (February 7, 2023).

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28. Cosentino Calls for a Ban of High-Silica-Content Artificial Stone

1121. On February 22, 2023, WA today, a news agency from Western Australia reported: "One of the world's largest stone benchtop companies and a coalition of health experts have separately called for a ban on products blamed for a deadly silicosis epidemic. The push from manufacturer Cosentino and key health organisations, including the Lung Foundation Australia and Public Health Association Australia, came as a leading government voice on workplace relations also called for immediate action from state and federal governments to 'right a terrible wrong'. . . . Manufacturer Cosentino produces more than one in every five domestic kitchen benchtops sold in Australia and is facing international scrutiny over its safety record. It is now pushing for a nationally co-ordinated approach to reduce risks associated with products containing high levels of silica, ahead of a meeting of workplace safety ministers next week. 'We have an immediate solution without disrupting the construction and building market', a Cosentino spokesperson said. 'And prices won't increase.' Two weeks ago Cosentino was found guilty in a Spanish Court of negligence. Reuters reported that the company's owner accepted a six-month suspended prison sentence after admitting to covering up the dangers of the product. It is also facing legal action in Australia. A coalition of peak health groups, including the one writing a government action plan on silicosis, also backed a ban on high-silica-content products, and urged leaders to boost the policing of workplaces and overhaul compensation schemes for sick workers. The Cosentino spokesperson said restrictions should start tomorrow, not next year or in 18 months. 'The immediate solution is everyone buys products that are less than 40 per cent silica,' he said. . . . The spokesperson said Cosentino had developed a product containing between 10 per cent and 40 per cent silica which could be distributed at scale if products with higher levels of silica were stopped from entering the market." Adele Ferguson and Angus Thompson, "Benchtop giant, health groups demand dangerous-stone ban," Watoday (February 22, 2023).

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29. Second Criminal Trial Against Cosentino

1122. On July 8, 2023, elDiario published an article by Nestor Ash titled "Cosentino faces a year and a half in prison in his second trial for silicosis," with a subtitle "The judge considers it proven that Cosentino acted "grossly negligent" with the Silestone handlers suffering from silicosis." The article reported:

> The second criminal trial against Francisco Martínez-Cosentino, founder and owner of the Almeria multinational stone surfaces, has been seen for sentencing this Friday. The Prosecutor's Office accuses Cosentino and two former managers of Levantina, the other large Spanish manufacturer, of crimes against the health of eight workers at a Vizcaya marble factory, who contracted silicosis while handling quartz agglomerate countertops from both companies without their warning of its dangerousness. The prosecutor believes that serious injuries were caused recklessly.
>
> In addition, the doctor from the prevention service and the three owners of Novogranit, the marble factory where those affected worked, are accused. The trial was held before Criminal Court 5 of Bilbao. The Prosecutor's Office requests that Martínez-Cosentino and the owners of Levantina be sentenced to a year and a half in prison, the payment of 3,600 euros and that they be disqualified from managing companies for two years. It also asked that among all the defendants they assume the payment of compensation of between 25,000 and 102,000 euros to the workers, although Cosentino satisfied that responsibility in 2019 through private agreements.
>
> "We did provide information, regardless of the fact that the risks of working with stone are known to marble factories. We are confident that the courts will recognize that the company has acted correctly", says a company spokesperson, who explains that the case is similar to another that occurred in Bermeo, in which Cosentino was acquitted.
>
> **Prosecutor: the company did not prevent and the manufacturer did not warn**
>
> The facts contained in the indictment of the Prosecutor's Office, which this newspaper has been able to consult, include a common practice in hundreds of marble shops in Spain during the real estate boom, and that is what places Cosentino in the pillory, although authorized sources of the company clarify that there are no more open cases, nor do they expect them.
>
> As detailed in the Prosecutor's brief, workers from a small marble factory cut and polished Silestone (Cosentino) and Ceasarstone (Levantina) countertops for years, with a high content of crystalline silica, which when cut generates a respirable dust that causes a form of especially aggressive silicosis. Until 2012,

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Novagranit did not apply basic safety measures to prevent inhalation. And this, despite the fact that the Labor Inspectorate had demanded in 2009 about twenty measures in 2009, among which were working in the wet, installing nebulizers, providing FFP3 masks, preventive training, risk assessment...

Cosentino supplied around 85% of the countertops, and Levantina the rest, but neither was diligent in disclosing the risks of quartz agglomerates, according to the prosecutor. Until 2009, the Almería-based company did not provide any safety data sheet, and only from March of that year did it begin to report the risk of prolonged exposure to crystalline silica causing pulmonary fibrosis and pneumoconiosis such as silicosis. Before, Silestone was compared to natural stones such as quartz, marble or granite, which contain a maximum of 20% silica. Quartz agglomerates are around 90%. That is to say, nothing to do with the effects of risk.

In her brief, the prosecutor notes that Cosentino had already had an infringement report in 2002, in which the Labor Inspectorate verified that there had been patients with silicosis in its factory in Cantoria (Almería) since at least 2000. She deduces hence, Francisco Martínez-Cosentino knew about the risk at least since 2002, but he did not inform the marble works until 2009.

Neither did Levantina say anything about the dangers of handling Ceasarstone until 2009, and until December 2009 it did not prepare a safety data sheet or deliver a label, despite the fact that those responsible (Cipriano Gómez and Antonio José Pinos) "knew or had the obligation to know" the risks of the product.

The responsibility of the preventive physician

Finally, the Prosecutor's Office also points to the Novogranit doctor, whom it points out for failing to comply with the prevention protocol, which requires annual examinations in cases in which it is suspected that silicosis can be contracted, such as in marble shops.

In fact, the workers had to go to the National Silicosis Institute or other public centers to be diagnosed with the disease, since the prevention service did not perform a CT scan with which to observe the characteristic cystic nodules of silicosis. Despite the fact that they were already developing the disease, the first chest X-rays did not detect it and they were declared "fit" until 2012. This caused them to remain in the crystalline silica exposure posts after contracting the disease, " thus increasing the risk of aggravation of his ailment," says the prosecutor.

For the Public Ministry, the owners of the company, the manufacturers and the prevention service failed in their obligation to protect the health of the workers. As a result, eight of the ten workers at the marble mill contracted silicosis. Several have recognized absolute permanent disability or for their profession, almost all suffer respiratory distress, coughing and expectoration, and many report sleep problems, depression or anxiety.

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The sentence in February

This Friday, the Prosecutor's Office has reduced its request to sentence Martínez-Cosentino from two and a half years in prison to one and a half years, taking into account the delay in the procedure (it was opened in 2013) and that Cosentino has already paid compensation. "The company decided a long time ago not to leave the workers stranded, without waiting for the last minute and for criminal cases," explains a Cosentino spokesperson. The private prosecution withdrew in 2019, when the compensation was paid, but the case went ahead promoted by the Prosecutor's Office.

Unlike what happened last February, when Martínez-Cosentino was sentenced by a Vigo court to six months in prison after reaching an agreement with the Prosecutor's Office, in this case the trial has been fully completed in five sessions, in which the owners of the manufacturers, those of the marble works, witnesses and various experts have testified.

Quartz agglomerate silicosis is an epidemic of unknown magnitude . It has been the main occupational disease in Andalusia for some time. From 2007 to 2019, 1,856 reports of this disease were communicated to Social Security, but experts warn that the methodological limitations of this communication system mean that the real figure is probably around triple. During this time, the Junta de Andalucía allowed its plan against silicosis to expire without coming close to meeting its objectives.

The Vigo ruling caused a notable media, business and political uproar because, for the first time, the owner and architect of Cosentino, a key company in Andalusia, present in dozens of countries, with a turnover of 1,401 million euros, was criminally convicted amid prospects of going public. The ruling concluded that, "grossly negligent," he did not warn of the risks of manipulating his product despite knowing about them "at least since the year 2000".

Cosentino was satisfied with that sentence, but this time he has decided to fight to the end.

https://www.eldiario.es/andalucia/cosentino-afronta-ano-medio-prision-segundo-juicio-silicosis_1_10359970.html.

30. Knowledge of the Silicosis Hazard by Cosentino Officers and Directors

1123. Throughout the time that Cosentino manufactured and sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, Cosentino's officers and directors were aware that Cosentino's artificial stone

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products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that Cosentino provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by Cosentino's defective artificial stone products. Among Cosentino's officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers were the following officers and directors of the company:

Officers

Francisco Martinez-Cosentino	Justo, Chairman/CEO, President of Cosentino Group
Jose Martinez-Cosentino Justo	Vice President and General Treasurer
Pilar Martinez-Cosentino Alfonso	Executive Vice President. Deputy Chairman, Director
Eduardo Martinez-Cosentino Alfonso	Executive Vice President of Global Sales and Chief Executive Officer of Cosentino North America
Valentin Tijeras Garcia	Vice President Global Product and Research & Development
Angel Madariaga Alvarez	Vice President of Engineering & Projects
Alberto Quevedo Gonzalez	Vice President of Global Production
Santiago Alfonso Rodriguez	Vice President of Global Marketing & Communication
Brandon Calvo	Chief Operations Officer of Cosentino North America

Directors

Isabel Martínez-Cosentino Ramos	Director
Eduardo Martínez-Cosentino Ramos	Director
María del Mar Martínez-Cosentino Ramos	Director
Eduardo Martínez-Cosentino Rosado	Director
Isabel Martínez-Cosentino Rosado	Director

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F. Dal-Tile Distribution LLC, Dal-Tile LLC, and Dal-Tile Tennessee LLC

1124. According to the website of Mohawk Industries, Inc., the company is "the largest manufacturer, distributor and marketer of ceramic tile and natural stone in the world," whose products include "ceramic tile, stone floors, porcelain roof tiles and stone, quartz and porcelain slab countertops" which it markets as the following brands: Daltile®, American Olean®, Complete Countertops®, Panoramic Porcelain Surfaces™, One Quartz Surfaces®, Perennial Porcelain Roofing™, Marazzi®, Ragno®, Kai®, Emilgroup®, Grande: The Large Size, Vitromex®, Eliane®, Elizabeth® and Kerama Marazzi®.

1125. According to its website, Mohawk Industries, Inc. had worldwide sales of $11.1 billion in 2023.

1126. According to Exhibit 21 (Subsidiaries of the Registrant) of the 10-K Annual Report for the year ending December 31, 2023 that was filed by Mohawk Industries, Inc. on February 23, 2024 with the Securities and Exchange Commission, following are the Dal-Tile subsidiaries of Mohawk Industries, Inc. and the jurisdictions where they were formed: Dal Italia LLC (Delaware), Dal-Elit, LLC (Texas), Dal-Tile Administracion, S. de R.L. de C.V. (Mexico), Dal-Tile Chile Comerical Limitada (Chile), Dal-Tile Colombia S.A.S. (Colombia), Dal-Tile, LLC (Pennsylvania); Dal-Tile Distribution, LLC (Delaware), Dal-Tile Group Inc. (Delaware), Dal-Tile I, LLC (Delaware), Dal-Tile International Inc. (Delaware), Dal-Tile Mexico Comercial S. de R.L. de C.V. (Mexico), Dal-Tile Mexico, S. de R.L. de C.V. (Mexico), Dal-Tile of Canada ULC (British Columbia, Canada), Dal-Tile Peru SRL (Peru), Dal-Tile Puerto Rico, Inc. (Puerto Rico), Dal-Tile Services, Inc. (Delaware), Dal-Tile Shared Services, Inc. (Delaware), Dal-Tile Tennessee, LLC (Delaware).

1127. According to a Form 10-K that Dal-Tile International Inc. filed with the Securities and Exchange Commission for the fiscal year ending 2000 (before Dal-Tile was acquired by Mohawk Industries), "Dal-Tile International Inc., a Delaware corporation formed in 1987 . . . , believes that it is the largest manufacturer, distributor and marketer of ceramic tile in the United States and one of the largest in the world. . . . Dal-Tile International Inc. is a holding company and conducts all its operations through its subsidiaries." Among those subsidiaries is Dal-Tile

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Corporation and Dal-Tile Distribution, Inc. According to the Form 10-K that Dal-Tile International Inc. filed with the Securities and Exchange Commission for the fiscal year ending 2000, "Dal-Tile has three regional distribution centers strategically located in California, Maryland and Texas to improve customer service in each distribution channel . . . ."

1128. According to Dal-Tile's website, the company is 75 years old, dating back to 1947 when "Robert M. Brittingham founded the Dallas Ceramic Company while operating out of a simple Quonset hut in Dallas, TX."

1129. According to the company's website, in 1980 the "Dallas Ceramic Company change[d] its name to Dal-Tile Corporation."

1130. According to the Dal-Tile website, in 1999 "Dal-Tile unveil[ed] its eagerly anticipated Natural Stone Collection," opening "its first Tile & Stone Gallery in Dallas, TX."

1131. In a Form 10-K that Dal-Tile International Inc. filed with the Securities and Exchange Commission for the fiscal year ending 2000, Dal-Tile acknowledged that many of the company's "manufacturing processes . . . currently result in the accumulation of dust that contains silica, thereby requiring expenditures for capital equipment in order to comply with Occupational Safety and Health Administration ("OSHA") regulations with respect to potential employee exposure to such dust." Thus, Dal-Tile has been aware of the silica dust exposure hazard of its products since at least 2000.

1132. On November 20, 2001, Dal-Tile announced that it had entered into an agreement for Dal-Tile to be acquired by Mohawk Industries, Inc. The acquisition was completed in March 2002.

1133. According to the Dal-Tile website, in 2009 "Dal-Tile launche[d] its Manufactured Stone Collection and innovative partnerships with Microban and Dupont."

1134. According to the Dal-Tile website, in 2014 "Daltile open[ed] its newest Design Studio in San Francisco."

1135. Plaintiff is informed and believes and alleges that prior to 2017 Dal-Tile imported quartz surfaces and distributed them throughout the United States, but in 2017 Dal-Tile announced plans to open a plant in Tennessee to manufacture quartz surfaces domestically and thereafter began manufacturing artificial stone at its Tennessee plant and selling it throughout the United States.

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1. Dal-Tile Entities in the Chain of Distribution of Dal-Tile Branded Products

1136. Plaintiffs are informed and believe that in addition to Mohawk Industries, Inc., multiple Dal-Tile entities are in the chain of distribution of Dal-Tile branded stone products (slabs, blocks, and tiles), each of which is liable to Plaintiffs for its own role in producing, manufacturing, importing, distributing, marketing, branding, trademarking, licensing, and otherwise undertaking affirmative acts and omissions that caused Plaintiffs' silicosis and related and consequential injuries.

1137. Mohawk Industries, Inc. is itself in the chain of distribution of Dal-Tile branded stone products, because the Mohawk Industries website contains a webpage titled "Products" which, under a heading "Countertops," states: "Mohawk's countertops and extra-large slabs for floors and walls help to create perfect residential and commercial designs. In addition to a well-established U.S. natural stone slab business, the Company is offering durable and elegant engineered quartz countertops as well as innovative porcelain slabs that replicate granite or marble visuals and can be used for flooring, walls or countertops." https://mohawkind.com/products.php#countertops. This webpage then lists the following brands with logos: COMPLETE COUNTERTOPS®, ONE QUARTZ SURFACES®, PANORAMIC porcelain surfaces®, GRANDE, and THE TOP. Thus, Mohawk Industries, Inc. markets stone "countertops" and "slabs" as of Mohawk Industries itself.

1138. Plaintiffs are informed and believe and thereon allege that all of the Safety Data Sheets of Dal-Tile stone slab products from 2015 to 2020 identify the manufacturer of those stone products as Dal-Tile Corporation, and that all of the Safety Data Sheets of Dal-Tile stone slab products from 2023 and thereafter identify the manufacturer of those products as Dal-Tile, LLC.

According to the OSHA's Directive Number CPL 02-02-079:

> "The manufacturer or importer must provide the information required by the standard on any hazardous chemicals which they manufacture or import."
>
> "*Responsible party* means someone who can provide additional information on the hazardous chemical and appropriate emergency procedures, if necessary. This could be the manufacturer or importer or a company contracted to provide more information. The name and address of the responsible party MUST be the same on the SDS and the label."
>
> "The information supplied on the SDS must be accurate."

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1139. On March 29, 2022, Dal-Tile Corporation filed a Statement of Conversion with the Pennsylvania Secretary of State whereby it converted its entity type from that of a corporation to a limited liability company under the name Dal-Tile, LLC.

1140. Plaintiffs are therefore informed and believe and thereon allege that Dal-Tile Corporation was the manufacturer of Dal-Tile branded stone slabs and other stone products, including its artificial stone slabs, up to March 29, 2022 and that Dal-Tile, LLC became the manufacturer of those stone products and bears responsibility as the manufacturer of those products.

1141. Despite the foregoing evidence that Dal-Tile, LLC is the manufacturer of Dal-Tile branded stone slabs and other stone products including its artificial stone slabs branded"One Quartz," in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite, et al.,* Los Angeles Superior Court Case No. 22STCV31907, Roy Viana, Dal-Tile's Director of Product, who had given a deposition as the person most qualified to testify on Dal-Tile LLC's behalf, provided "errata" to his deposition testimony stating that the manufacturer of Dal-Tile artificial stone slabs was Dal-Tile of Tennessee, LLC rather than Dal-Tile, LLC. While it appears that the change in Mr. Viana's testimony may have been to persuade the court in the *Reyes-Gonzalez* case that the plaintiff in that case had sued the wrong party and that Dal-Tile, LLC should therefore be dismissed from that case, based on Mr. Viana's errata to his deposition testimony, Plaintiff alleges that Dal-Tile of Tennessee, LLC is also a manufacturer of Dal-Tile natural and artificial stone slabs and other stone products to which Plaintiff was occupationally exposed and that caused Plaintiff's silicosis and other injuries.

1142. On April 5, 2024, In the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite, et al.,* Los Angeles Superior Court Case No. 22STCV31907, Cathleen Smith, a Sustainability and Compliance Engineer of Dal-Tile LLC, who was designated to testify on Dal-Tile LLC's behalf, testified that Dal-Tile Distribution, LLC is the Dal-Tile entity that distributes Dal-Tile branded stone products, including tile, natural stone and artificial stone products. Ms. Smith also testified that Dal-Tile International, Inc. is the parent company of all the Dal-Tile subsidiaries.

1143. Plaintiff is informed and believes and thereon alleges that prior to the formation of Dal-Tile Distribution, LLC, Dal-Tile Distribution, Inc. was the distributor of Dal-Tile branded stone products, including tile, natural stone and artificial stone products.

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2. Dal-Tile's Knowledge of the Silica Dust Hazard as of 2000 and 2001

1144. In its Form 10-K Annual Report for the fiscal year ended December 29, 2000, filed with the Securities and Exchange Commission, Dal-Tile International Inc. acknowledged:

> Numerous aspects of the manufacture of ceramic tile currently require expenditures for environmental compliance. For example, the mixing of raw materials, preparation of glazes, and pressing, drying and firing of tile all are sources of air emissions that require expenditures for compliance with laws and regulations governing air emissions, including the purchase, operation and maintenance of control equipment to prevent or limit air emissions. Many of these manufacturing processes also currently result in the accumulation of dust that contains silica, thereby requiring expenditures for capital equipment in order to comply with Occupational Safety and Health Administration ("OSHA") regulations with respect to potential employee exposure to such dust.

https://www.sec.gov/Archives/edgar/data/906611/000091205701007653/a2041503z10-k.txt.

1145. In its Prospectus filed on May 17, 2001 with the Securities and Exchange Commission, Dal-Tile International acknowledged:

> Many of our manufacturing operations result in the processing of raw materials that contain silica. These manufacturing processes require expenditures for capital equipment in order to comply with Occupational Safety and Health Administration regulations with respect to potential employee exposure to dust which may contain silica generated by such processes.

1146. On November 20, 2001, Dal-Tile announced that it had entered into an agreement for Dal-Tile to be acquired by Mohawk Industries, Inc. The acquisition was completed in March 2002.

3. Dal-Tile Begins Manufacturing Artificial Stone

1147. According to the company's website, in 2009 "Dal-Tile launche[d] its Manufactured Stone Collection and innovative partnerships with Microban and Dupont."

1148. According to the company's website, in 2014 "Daltile open[ed] its newest Design Studio in San Francisco."

1149. Plaintiff is informed and believes and alleges that prior to 2017 Dal-Tile imported quartz surfaces and distributed them throughout the United States, but in 2017 Dal-Tile announced plants to open a plant in Tennessee to manufacture quartz surfaces domestically and thereafter began manufacturing artificial stone at its Tennessee plant and selling it throughout the United States.

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4. Dal-Tile's 2019 Safety Data Sheet for its One Quartz™ Collection

1150. In 2019, Dal-Tile issued a Safety Data Sheet for its One Quartz™ Collection. In Section 1 of this Safety Data Sheet ("Product Identification") Dal-Tile described its slabs as "environmentally preferable building materials" and "one of the most environmentally friendly building materials you can buy today." However, in Section 3 of the Safety Data Sheet, Dal-Tile states that the product contains 46-52% crystalline silica by weight. Since exposure to crystalline silica causes silicosis, lung cancer, and other diseases, Dal-Tile's assertion that its product is "one of the most environmentally friendly building materials you can buy today" is false and misleading.

1151. Section 2 of the Safety Data Sheet, regarding Hazards Identification, provides three hazard statements: "(H35) May cause CANCER," "(H335) may cause respiratory irritation;" and "Causes damage to organs (lung/respiratory) through prolonged or repeated exposure (inhalation)." The first statement is misleading because it suggests the product is not known to cause cancer, although it contains at approximately 50% crystalline silica, which is a known human carcinogen and was recognized as such by the International Agency for Research on Cancer in 1997. The second statement is misleading, because, the statement that the product "may cause respiratory irritation," suggests that respiratory exposure to the product is not very harmful, i.e., that one "may" experience irritant effects like one might experience cutting an onion. The third statement is also misleading, because it does not specify the duration of the "prolonged" exposure or the number of exposures that constitute "repeated" exposure that causes damage to organs. Workers therefore cannot know whether they must be exposed to the product for weeks, months, years or decades, or must be exposed hundreds, thousands, or tens of thousands of times to suffer organ damage. The statement is also misleading, because prolonged exposure suggests exposure of many years resulting in chronic disease, although artificial stone workers typically develop acute silicosis in less than 5 years or accelerated silicosis after 5 to 10 years of exposure. The hazard statements are also deficient because they do not mention silicosis as a health hazard of the product, although it is the major health hazard of the product. Indeed, the word "silicosis" does not appear in the entire Safety Data Sheet, even though the product contains approximately 50% crystalline silica. This constitutes a failure to warn of the health hazards of the product that violates the Hazard Communication

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Standard.

1152. After providing the three inadequate hazard statements in the "Hazards Identification" section of the Safety Data Sheet, Dal-Tile provides 5 "Precautionary Statements": (1) "Do not handle until all safety precautions have been read and understood," (although most artificial stone fabricators are immigrants who cannot read English), (2) "Do not breathe dust/spray" (as though workers should hold their breath throughout the work day), (3) "Wash hands thoroughly after handling/installing" (although the products do not present appreciable health hazards by skin absorption); (4) "Do not eat, drink or smoke when handling/installing this product" (although the product does not present any appreciable health hazard by ingestion and is not a fire hazard); and (5) "Wear protective gloves, protective clothing, eye protection, face protection when handling/installing this product" (rather than the critical information that it is essential to wear an air supplied respirator when fabricating or installing the product). Most noteworthy is the absence of any precautionary statement that respiratory protection is necessary, in particular that workers fabricating the product must wear a NIOSH-approved air supplied respirator to prevent silicosis.

1153. After the precautionary statements, the Safety Data Sheet states the following regarding "Potential Health Effects": "Inhalation: Do not breathe dust." This is an inadequate and harmful instruction for four reasons. First, the health effects of inhaling crystalline silica dust are known and very serious; they are not merely "potential." Second, no adverse health effects of inhaling crystalline silica are identified; silicosis and lung cancer are not mentioned as known health effects. Third, the instruction not to breathe dust is impossible to follow, because dust is always generated during the fabrication of artificial stone products and workers must breathe to work and to live. Lastly, the instruction doesn't inform workers how to do their work without inhaling dust from the product.

1154. Section 3 of the Safety Data Sheet (Composition/Information on Ingredients) begins with the following statements: "Slab products are made of silica, other naturally-occurring minerals, and resin that have been mixed and cured at low temperatures. Slabs are manufactured in various shapes, sizes, and colors. These products do not contain asbestos. Under normal conditions these products do not release hazardous materials after installation and are not considered hazardous waste

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should disposal be necessary." These statements are misleading, because they indicate that the product is made from "naturally-occurring minerals," which suggests that the product confers health benefits like mineral water and that the product is safe because it does not contain asbestos. The statement that "under normal conditions these products do not release hazardous materials after installation" is misleading because the product does release respirable crystalline silica when used as intended to fabricate countertops, and silica causes silicosis, lung cancer, and other diseases.

1155. In Section 8 ("Exposure Controls/Personal Protection")," the Safety Data Sheet provides recommended exposure limits for the "respirable fraction" of crystalline silica and for "total dust" without explaining these terms. The Safety Data Sheet then directs workers to "use adequate ventilation during installation and/or removal to keep exposure to dust below recommended exposure levels," without explaining how workers can know whether they are exposed above or below the recommended exposure levels. Regarding "Respiratory Protection," the Safety Data Sheet states: "Use of a properly fitted NIOSH/MSHA approved particulate respirator is recommended when cutting tiles for installation or during the removal of installed tile." This instruction is confusing, inadequate, and harmful. The instruction is confusing and inadequate, because it directs workers to use a respirator when cutting tile, which suggests that a respirator need not be used when cutting the product, but need only be used when cutting tile. The instruction is harmful, because it instructs workers to use a NIOSH-approved particulate respirator - a type of air-purifying respirator that is inadequate to prevent silicosis – rather than using a NIOSH-approved air-supply respirator – the only type of respirator that is adequate to prevent silicosis from fabricating artificial stone.

1156. Section 11 ("Toxicological Information") of the Safety Data Sheet provides the following "Potential Health Effects" information regarding "Primary Routes of Exposure": "None for intact tile. Inhalation and potential exposure to eyes, hands, or other body parts if contact is made with broken tile, and/or during procedures involving the cutting of products, and/or for operations involving the removal of installed products." This statement is confusing, because it concerns health effects of tile rather than the product. The statement is also inadequate, because it does not state that the primary route of exposure for the product is inhalation. The statement is harmful, because it falsely indicates that there is no primary route of exposure for the product, although respirable

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crystalline silica from the product causes multiple adverse health effects by inhalation.

1157. The Safety Data Sheet then states: "No acute effects from exposure to intact tile are known." This statement is confusing and misleading, because the product is not tile. The statement is also incorrect, because acute silicosis is a known health effect of acute exposure to the product, and is usually fatal, and is primarily caused by inhalation of artificial stone dust rather than by tile.

5. Dal-Tile's Letter to the Los Angeles County Board of Supervisors

1158. On July 28, 2023, Matthew Kahny, President of Dal-Tile, signed a letter to the Los Angeles County Board of Supervisors, urging the Board of Supervisors not to ban the importation and use of artificial stone in Los Angeles County. This letter stated: "Stone products are safely handled and worked on every day, including in Los Angeles County . . . ." This statement is false, because artificial stone products are not "safely handled and worked on every day, including in Los Angeles County," as is shown by the epidemic of accelerated silicosis among stone countertop fabricators which has its epicenter in Los Angeles County.

1159. The letter by CEOs of artificial stone manufacturers seeks to foist blame on the owners of the small fabrication shops that fabricate artificial stone, rather than accepting personal responsibility for the deadly effects of their defectively designed artificial stone products. Thus, the letter states that "fabrication employers must provide necessary training, air monitoring and adherence to air quality requirements, engineering air handling controls, personal protective equipment (PPE), and medical surveillance in compliance with OSHA regulations." While multi-billion dollar manufacturers and importers like Cambria, M S International, Dal-Tile, and of course, Caesarstone and Cosentino, have the financial resources to spend millions of dollars to make their manufacturing facilities safe for their workers, fabrication shops (most of which are small mom-and-pop businesses that have 2 to 10 workers and generate annual revenues of a few hundred thousand dollars) lack the financial resources to implement the necessary protective measures, which cost a few million dollars in capital costs per shop, with annual maintenance costs of a few hundred thousand dollars. Thus, it is facetious for the multibillion dollar manufacturers and importers to attempt to blame the fabrication shop owners for their inability to protect workers from the deadly

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hazards of their artificial stone products.

1160. The letter also states: "Stone products, including engineered stone, have been manufactured and fabricated safely for decades . . . ." This statement is false. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the letter that "engineered stone ha[s] been manufactured and fabricated safely for decades is clearly and indisputably false.

6. Dal-Tile's Endorsement of Misrepresentations by The Stone Coalition

1161. In October 2023, a Paid Advertisement titled "Illegal Cutting Processes, Not Stone Products, can Cause Silicosis," was published in the Los Angeles Times. The advertisement states that it was "Paid For By The Stone Coalition," info@stonecoalition.org, which is described as "a collaborative effort between the quarts surface and natural stone industries."

1162. The Stone Coalition is an industry trade association that was apparently formed in 2023 to defend the Stone Countertop Fabricator Silicosis Cases by mounting a public relations campaign to deflect liability from stone slab manufacturers, distributors and suppliers, by attempting to foist blame for the new stone fabricator silicosis epidemic on the victims, their employers, and regulatory and enforcement agencies – all to avoid accepting personal responsibility for the massive (ultimately fatal) harm that they have inflicted on thousands of young immigrant workers.

1163. The home page of the new website of The Stone Coalition bears the name and logo of the Natural Stone Institute, implicating that industry trade association with the new trade association. The home page states: "The Stone Coalition is dedicated to promoting safe, wet processing technology in stone-cutting facilities while prioritizing compliance with OSHA air

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monitoring standards and other silica rules. Safety is our unwavering commitment." That is quite a statement by stone companies that for years opposed OSHA's adoption of the Silica Standard.

1164. A webpage titled "About" describes "Our Organization" as follows: "The Silica Safety Coalition is a collective of dedicated stone fabricators, manufacturers, stone distributors, and industry professionals united by a shared commitment to promoting workplace safety within the stone cutting and fabrication sector. Our mission is to promote and maintain the highest standards of safety, supporting the well-being of workers throughout every stage of stone processing." These statements are at best mere industry propaganda and at worst blatant falsehoods. The Coalition is actually a collective of multibillion dollar stone manufacturers and distributors that have been sued for causing the new stone fabricator silicosis epidemic – companies that for years failed to prepare any Safety Data Sheets or labels for their stone products or prepared Safety Data Sheets and/or labels that were so deficient that they caused, rather than prevented, the new fabricator silicosis epidemic.

1165. The website of The Stone Coalition does not identify its members, but the "About" webpage contains a section titled "Workplace Safety" that informs readers to "Click the button to read our letter to the Los Angeles County Board of Supervisors." Clicking on the button reveals a letter dated July 28, 2023, to the Los Angeles County Board of Supervisors in which the authors of the letter attempt to persuade the Los Angeles County Board of Supervisors not to ban the importation and use of artificial stone products in Los Angeles County. The letter is signed by executive officers of four artificial stone companies: Marty Davis, CEO of Cambria; Rupesh Shah, Co-CEO of M S International, Inc.; Matthew Kahny, President of Dal-Tile; and Nate Kolenski, President of Block Tops, Inc.; and James A. Hieb, CEO of the Natural Stone Institute. The first three of these companies are among the most culpable defendants in the Stone Fabricator Silicosis Cases.

1166. The title of the Paid Advertisement is itself misleading and false, for two reasons. First, it states that stone products do not cause silicosis, although most silicosis cases over the millennia and at the present time have been and continue to be caused by crystalline silica dust from stone products. Second, it states that only "illegal cutting processes . . . can cause silicosis," although cutting stone slabs can cause silicosis whether the cutting process is performed "legally," i.e., in compliance with OSHA requirements, or "illegally," i.e. in violation of OSHA requirements. The

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Paid Advertisement begins with the following statement: "Silicosis, a rare lung disease resulting from the inhalation of crystalline silica dust from dry-cutting or grinding concrete, brick or stone, has been found in illegal and unregulated stone fabrication across California, with a significant concentration in the San Fernando Valley." This statement is at best misleading and at worst false, for a few reasons. First, silicosis is not a rare lung disease. It is the oldest lung disease known to humankind and has killed more workers over the millennia than any other lung disease, including all lung diseases caused by exposure to asbestos. Additionally, recent epidemiological studies have reported a prevalence of silicosis among stone fabricators in the range of 30% to 40%, making it an especially common occupational lung disease that is of great public health concern. Second, the statement falsely suggests that silicosis is only caused by dry-cutting or grinding, although many workers who regularly used water-dispensing powered tools to reduce the amount of dust in fabricating stone countertops now suffer from silicosis and the National Institute for Occupational Safety and Health (NIOSH) has done studies which show that wet processing methods are inadequate to prevent silicosis among workers who fabricate artificial stone countertops. Third, silicosis among countertop fabricators and other workers exposed to crystalline silica has been shown to occur even at exposure levels below limits adopted by the Occupational Safety and Health Administration (OSHA), i.e., "legal" stone fabrication.

1167. The Paid Advertisement then states: "Yet, this disease is preventable through wet processing techniques and strict adherence to existing OSHA regulations." This statement is also false, because studies by NIOSH show that even fabrication workers who regularly use water-dispensing tools and wear particulate filter respirators at all times they are in the fabrication shop still develop silicosis from exposure to artificial stone dust.

1168. The Paid Advertisement then states: Despite Federal and State regulations to prevent the use of 'drycutting,' or cutting of stone or tile without water, and requiring personal protective equipment (PPE), many noncompliant facilities continue to put their employees at risk by failing to implement these basic safety precautions." This statement is also misleading and false, because most stone countertop fabrication shops have followed the recommendations of artificial stone manufacturers to use powered tools that dispense water to suppress dust generated by the fabrication

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of artificial stone, as well as the manufacturers' recommendations to have their employees wear particulate filter masks. However, both of these precautionary measures recommended by stone slab manufacturers are inadequate to prevent silicosis among stone countertop fabricators, which recommendations misled both employers and fabrication workers to believe that following the manufacturers' recommendations would prevent fabrication workers from developing silicosis. The use of water-dispensing tools is inadequate to prevent silicosis in artificial stone fabricators because at most it merely reduces the amount of lethal crystalline dust to which fabrication workers are exposed, and particulate filter masks do not prevent the extremely small particles of crystalline silica from cutting artificial stone from being inhaled and causing silicosis. In fact, the recommendation of the artificial stone manufacturers to wear a "NIOSH-approved" mask has caused many workers to develop silicosis, because NIOSH-approved particulate filter masks do not prevent harmful silica exposure, the only type of respirator that is effective in doing so is an air-supplied respirator, which the manufacturers of artificial stone have not recommended as necessary protection for workers.

1169. The Paid Advertisement then states that Jim Hieb, CEO of the Natural Stone Institute, knows this doesn't have to happen and quotes him saying: "Silicosis is preventable. Any contractor that follows Cal/OSHA's guidelines ensures that any cutting of any stone product is done safely." This statement is also misleading and false for a few reasons. First, while silicosis from exposure to natural stone dust may be preventable, silicosis from exposure to artificial stone is not preventable, because unlike natural stone, the fabrication of artificial stone generates massive amounts of ultrafine and nanosized crystalline silica particles that penetrate through particular cartridge respirators and are inhaled by fabricators and cause progressive massive fibrosis, because they are extremely toxic to the lungs - much more so than larger silica particles from natural stone. Second, while it may theoretically be possible to prevent silicosis in artificial stone fabricators, in the real world it is not possible to prevent silicosis in artificial stone fabricators, because the cost of installing state-of-art ventilation systems, respiratory protection programs, exposure monitoring programs, administrative industrial hygiene programs, and medical monitoring programs necessary to prevent silicosis, the capital cost of implementing these programs is a few million dollars per shop with annual costs of several hundred thousand dollars, which small fabrication shops that generate annual revenues of

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a few hundred thousand dollars cannot afford. Third, OSHA's guidelines were developed to protect against respirable crystalline silica particles in the micron size range - not ultrafine and nanosized crystalline silica particles that are uniquely generated from the fabrication of artificial stone and present extraordinary fibrotic hazards to the human lung and while compliance with OSHA's exposure limits for respirable crystalline silica may reduce fibrotic lung disease or delay its occurrence among stone fabricators, multiple studies have shown that compliance with OSHA's exposure limits is inadequate to prevent all silicosis. It is therefore extremely irresponsible for the CEO of the Natural Stone Institute to state that compliance with OSHA guidelines "ensures that any cutting of any stone product is done safely." This is especially so, because exposure to respirable crystalline silica not only causes silicosis which may be dose-dependent, but also causes lung cancer and there is no level of exposure to crystalline silica that does not increase stone fabrication workers' risk of developing lung cancer later in life.

1170. The Paid Advertisement also states: "Almost all experts agree that what is being cut matters less than how the stone is cut and fabricated for placement within homes and offices." While this statement may generally be true for natural stone products, it is not true for artificial stone products which present unique respiratory hazards to stone countertop fabricators because artificial stone is manufactured by crushing and pulverizing quartz (crystalline silica) and then adding a polymeric resin, pigments and other additives and curing the mixture, so that when the finished slab is cut, the ultrafine and nanosized particles that are in the plastic matrix are released and are inhaled by fabricators even though they wear particulate filter respirators. Indeed, the extreme hazard of artificial stone is due not only to the extremely high crystalline silica content of the product (much higher than marble and granite), but is also due to the extremely small size of the crystalline silica particles that are released into the air when fabricators use powered tools to cut artificial stone.

1171. The Paid Advertisement also states: "Despite studies and regulations that show that the type of product matters significantly less than the method of cutting, plaintiffs' attorneys have been trying to blame engineered stone for recent cases of Silicosis among stone workers." It is true that attorneys who represent the ever-increasing number of young male Hispanic immigrants who have developed silicosis with progressive massive fibrosis and are terminally ill unless they receive

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lung transplants, primarily blame artificial stone for causing the workers' fatal lung disease, so too do knowledgeable pulmonologists, occupational medicine specialists, epidemiologists, and public health experts. Indeed, the new occupational disease epidemic of accelerated silicosis among artificial stone fabricators is largely attributable to artificial stone, because it is an inherently dangerous and defective product whose purported benefits which are merely aesthetic in nature, are outweighed by the severe lung and other diseases that this product causes at with such a high disease prevalence.

1172. The Paid Advertisement then states: "Engineered stone products including Quartz, have been manufactured and fabricated safely for decades." This statement is a blatant lie. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the Paid Advertisement that "[e]ngineered stone products, including Quartz, have been manufactured and fabricated safely for decades" is absolutely false.

1173. The Paid Advertisement quotes Mr. Hieb as stating: "The biggest problem our industry faces is enforcement. Without efforts to stop those who are unaware of or unwilling to comply with current regulations, cases of Silicosis are going to keep increasing." This statement is also false and misleading. The biggest problem the stone industry faces is that artificial stone is the cause of a worldwide epidemic of accelerated silicosis among stone countertop fabricators. Stating that the biggest problem the industry faces is enforcement is merely an attempt by manufacturers of deadly artificial stone products to foist blame on OSHA due to its inability to prevent the disease and death that are primarily due to artificial stone products. OSHA is extremely underfunded and lacks the resources to initiate enforcement actions against the thousands of small fabrication shops

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nationwide and enforcement actions do nothing to prevent silicosis among the tens of thousands of countertop fabrication workers who have already been exposed to crystalline silica from stone products and who already have silicosis even though many of them have not yet exhibited symptoms of this disease. Moreover, many fabrication shops are unaware of the silicosis hazard because the manufacturers of artificial stone for many years did not prepare or provide their customers with Safety Data Sheets or product labels informing them of the silicosis hazard and none of the manufacturers ever provided their customers with use instructions that were adequate to prevent silicosis among fabricators.

1174. The Paid Advertisement also states: "Industry leaders provide resources to support smaller businesses in the industry." This statement is at best misleading and at worse false. For years the manufacturers of artificial stone concealed the nature and severity of the toxic hazards of their products from their customers and only provided them training on how to improve profitability. Only after the new silicosis epidemic was well under way did the manufacturers of artificial stone initiate any programs to "support smaller businesses in the industry," and those programs were public relations programs to deflect responsibility from the manufacturers of deadly artificial stone products to blame the epidemic on the victims, the owners of small fabrication shops that employed them, on regulators and governmental enforcement agencies – anyone except themselves for causing the harm.

7. Knowledge of the Silicosis Hazard by Dal-Tile Officers and Directors

1175. Throughout the time that Dal-Tile manufactured and sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, Dal-Tile's officers and directors were aware that Dal-Tile's artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that Dal-Tile provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by Dal-Tile's defective artificial stone products. Among Dal-Tile's officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers were the following officers and directors of the company:

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Officers

Jacques R. Sardas, President, Chief Executive Officer and Chairman of the Board;

W. Christopher Wellborn, Exec. Vice President, Chief Financial Officer, Assistant Secretary;

Scot B. Bernstein, Vice President, Supply Chain Planning;

D. Curtis Cook, Vice President, American Olean Distribution;

Dan L. Cooke, Vice President, Information Technology;

Silvano Cornia, Vice President, Research and Development;

David F. Finnigan, Vice President, Home Center Sales and Business Development;

William R. Hanks, Vice President, Manufacturing;

Matthew J. Kahny, who was Vice President of Marketing and is now President;

H. Clay Orme, Vice President, Operations;

Javier Eugenio Martinez Serna, Vice President, Mexico Operations;

Mark A. Solls, Vice President, General Counsel and Secretary;

Directors

Douglas D. Danforth, Director;

John F. Fiedler, Director;

Vincent A. Mai, Director;

Martin C. Murrer, Director;

Charles J. Pilliod, Jr., Director;

Norman E. Wells, Jr., Director.

G. Hanwha L&C USA LLC and HYUNDAI L&C USA LLC

1176. The Hanwha Group is a large business conglomerate in Souther Korea. Founded in 1952 as Korea Explosives company, the Hanwha Group has grown into a large multi-profile business conglomerate, with diversified holdings ranging from explosives to energy, materials, aerospace, mechatronics, finance, retail, and lifestyle services. In 1992, the company adopted its abbreviation as its new name: "Hanwha."

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1. Hanwha 2005 Material Safety Data Sheet for HanStone Quartz

1177. Hanwha has been manufacturing HanStone Quartz since at least 2005, in which year the Hanwha Living and Creative Corporation issued a Material Safety Data Sheet for HanStone Quartz by HanWha Surfaces dated June 30, 2005. This Material Safety Data Sheet identified the chemical composition of the product as containing more than 40% to approximately 90% Quartz (crystalline silica) by weight, with less than 10% of the product being Synthetic Resin, with a Colorant and Additives, each of which is less than 1% by weight and claimed to be a "trade secret."

1178. Section 3 (Hazards Identification) of the Material Safety Data Sheet, regarding "Potential Health Effects" begins by stating: "This product is not classified as dangerous." That is a false and misleading statement for this product that contains about 90% crystalline silica and causes silicosis. The Material Safety Data Sheet then states that "sawing, routing, drilling, and/or sanding can generate dust" and that "[d]ust generated during handling of this product can irritate eyes, nose and respiratory passages and cause sneezing and coughing." This statement downplays the respiratory hazard of the product which is much more severe than mere "irritation." The Material Safety Data Sheet then says: "Dust generated during handling of quartz surfaces products can contain particles of crystalline silica." This is also a misleading statement, because dust generated during handling of quartz surfaces products invariably does contain particles of crystalline silica. Only then does the Material Safety Data Sheet acknowledge that "overexposure to airborne crystalline silica can cause silicosis," although the Material Safety Data Sheet does not in any way quantify by amount or duration of exposure what constitutes "overexposure to airborne crystalline silica."

1179. Section 7 (Storage and Handline) of the Material Safety Data Sheet states: "Avoid breathing dust [and fumes] generated during sawing, sanding, routing or drilling." However, this instruction is meaningless because stone countertop fabrication workers have to breathe and they cannot hold their breath throughout an 8-hour workshift to "avoid breathing dust" and "fumes."

1180. Section 8 (Exposure Controls and Personal Protection) of the Material Safety Data Sheet provides information regarding Engineering Controls (Ventilation) and Personal Protection. Regarding the latter, the Material Safety Data Sheet says: Protective equipment: EYE/FACE/HAND

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PROTECTION Wear safety protector during operations such as sawing, sanding, drilling or routing." This is a grossly inadequate use instruction, because the Material Safety Data Sheet does not state what protective gear should be used to protect the eyes, face, or hands. Critically, the Material Safety Data Sheet does not inform workers that they need to wear respiratory protection whenever they fabricate the product or are present in the same room when other workers fabricate the product, and does not inform workers that the only type of respiratory protection that can prevent silicosis from inhaling dust of the product is an air-supplied respirator. By concealing from workers that they must always use respiratory protection, specifically an air-supplied respirator when fabricating the product, Hanwha concealed this critical safety information that is essential to prevent silicosis.

1181. Section 11 (Toxicological Information) of the Material Safety Data Sheet states that "epidemiology studies show limited evidence of lung cancer in occupations involving exposure to crystalline silica (quartz), such as stone cutters and granite industry workers." This statement is false and misleading because as early as 1997 - 8 years before issuance of the Material Safety Data Sheet - the International Agency for Research on Cancer issued its 1997 monograph regarding crystalline silica, concluding: "there is *sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources." International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Vol. 68: Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils," (IARC 1997).

1182. The most significant aspects of the June 30, 2005 Material Safety Data Sheet are that Hanwha was aware as early as 2005 that exposure to its product can cause silicosis and the company concealed from workers that they needed to wear respiratory protection so as not to get silicosis.

2. Hanwha L&C USA LLC and Hyundai L&C USA LLC

1183. On September 4, 2007, Maxforma LLC, a Delaware limited liability company, filed an Application for Registration with the California Secretary of State to conduct business in the State of California, designating its principal executive office in the State of California as 11165 Knott Ave., Suite C, Cypress, California.

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1184. On May 8, 2008, Maxforma LLC filed a Certificate of Amendment with the California Secretary of State whereby it changed its name to Hanwha L&C USA LLC.

1185. On July 1, 2009, Hanwha L&C USA published an advertisement in *Stone World* describing the company as "a leading surface manufacturer" of HanStone, Hanex and Miraton products.

1186. On October 1, 2009, Hanwha L&C USA published an advertisement in *Stone World* describing the company as "a leading manufacturer of innovative surfacing products," and announcing the grand opening of its 200,000 square foot Canadian manufacturing facility. The advertisement stated: "The facility's first phase of production will be the manufacturing of HanStone™ Fine Quartz surfaces for kitchen countertops, vanities and other surfaces for U.S. residential and commercial markets. The manufacturing facility will also be equipped with the most advanced Breton™ Technology, resulting in the production of the most sophisticated looks or designs of natural quartz, in an array of colors." The Advertisement reported an "initial investment of $70 plus million for the construction of the facility," stating that "[t]he new manufacturing plant will enable Hanwha to meet the growing demand for its premium product lines with greater production capabilities coupled with a premier distribution network." The Advertisement quoted Daniel Yu, President and CEO of Hanwha L&C USA stating: "Our new facility being built in London, Ontario, will be the most advanced, nature-friendly manufacturing plant in the Fine Quartz Surface business, and will produce top-quality HanStone products for our customers." The Advertisement also quoted him as saying: "We are confident that our HanStone™ Fine Quartz Surface and Hanwha L&C USA sustainable business will continue to grow and be successful in North America with continual strong support from the architectural and design industry segments." The Advertisement concluded: "In order to continuously supply the U.S. market with superior, green surface solutions, Hanwha L&C USA has begun preparing for future expansions, with plans to increase the Canadian facility by 180,000 square fee, investing an additional $40 million."

1187. On July 4, 2011, Hanwha L&C published an Advertisement in *Stone World* titled "Hanwha Surfaces Convenes Distributors to Address Market Needs." The Advertisement stated: "Hanwha L&C Surfaces, a leading global manufacturer of quartz and solid surfaces, met with select

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distributors this past week for its bi-annual meeting to review current marketplace initiatives, share ideas and discuss opportunities for continuing to build brand awareness for Hanwha Surfaces and its products: HanStone Quartz and Hanex Solid Surfaces."

1188. On December 3, 2014, Hanwha L&C published an Advertisement in *Stone World* announcing that the company had appointed Dan Boyd as its new Director of Direct Sales for both of its product lines, Hanstone quartz and Hanex solid surface, claiming that "Boyd's 30+ years within the hard surface industry will help the company establish a more aggressive identity as a supplier of quality surfaces for the residential and commercial markets."

1189. On March 15, 2018, Hanwha L&C published an Advertisement in *Stone World* stating: "Hanwha Surfaces, the American subsidiary of the international conglomerate Hanwha L&C, announced today the release of five new colors as part of the Boutique Collection," "the first to be created on HanStone Quartz's second production line featuring the world's most advanced Breton Technology," which "[u]sing robotic arms . . . Is able to create soft, deep veining and movement that closely mimics the appearance of natural stone."

1190. On January 24, 2019, Hanwha L&C USA LLC, filed a Name Change Amendment with the California Secretary of State whereby it changed its name to Hyundai L&C USA LLC.

1191. On March 29, 2019, the company published an Advertisement in *Stone World* stating: "Hyundai Department Store Group, a major South Korean conglomerate that operates a range of retail and service-based businesses, announced recently that it has completed the acquisition of Hanwha L&C, a leading manufacturer of premium building materials. As part of the acquisition, the company has also changed its name to Hyundai L&C to further position itself as a global leader in the interior products industry. Under this new ownership, Hyundai L&C remains firmly committed to maintaining and growing its premium surfacing, including HanStone Quartz and Hanex Solid Surfaces." The Advertisement also announced that the company had expanded its operations, "including a second HanStone Quartz production line in London, Ontario, the building of a new Hanex Solid Surfaces production facility in Temple, Texas (to be operational in the coming months), and the establishment of several service centers, warehouses and showrooms across the country." The Advertisement also claimed: "This new ownership by Hyundai Department Store

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Group, a $7 billion company, offers unparalleled financial stability and the ability to expand like never before to meet customers' growing requirements for premium surfacing."

1192. On June 27, 2019, Hyundai L&C USA LLC filed a Statement of Information with the California Secretary of State, listing its business address in California as 16031 Carmenita Rd., Cerritos, California 90703 and describing its business as "Countertop Wholesale."

1193. As recently as August 28, 2023, Hyundai L&C USA LLC filed a Statement of Information with the California Secretary of State, confirming that its business address in California is 16031 Carmenita Rd., Cerritos, California 90703 and that its business is "Countertop Wholesale."

3. March 23, 2023 Safety Data Sheet

1194. As noted above, the company's 2005 Material Safety Data Sheet concealed from workers that they need to wear respiratory protection to prevent getting silicosis from the product. It was not mere happenstance that the company concealed this critical information from stone countertop fabricators, because the company's most recent Safety Data Sheet for the product, dated March 23, 2023 also conceals from workers that they always must wear respiratory protection when fabricating the product so as not to get silicosis. That recent Safety Data Sheet merely prescribes: "If it not possible to reduce the exposure limits to below the permissible limits . . . , use NIOSH approved respiratory equipment for protection against crystalline silica/quartz dust." This most recent instruction still does not inform workers that they must always use an air-supplied respirator whenever they fabricate the product in order not to inhale crystalline silica dust and get silicosis.

4. Knowledge of Silicosis Hazard and Concealment by Hyundai L&C Managers

1195. The company's concealment of the true nature and severity of the silicosis hazard and the means of preventing silicosis was approved and ratified by the company's managers, Hyung Suk Kim, Sung Kim, and Jae Kak Lee.

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H. LX Hausys America, Inc.

1196. LX Hausys America, Inc. is a subsidiary of LX Hausys Ltd., a company headquartered in Seoul, Korea, that operates 7 overseas sales corporations, 4 overseas manufacturing corporations, and 5 overseas representative offices, mainly in the United States. In 1995 the company began producing acrylic solid surface products under the tradename "HIMACS." In 2005, it completed construction of a HIMACS plant in Adairsville, Georgia. Expanding its manufacturing operations in the United States, in 2011 the company completed construction of an engineered stone plant in Adairsville, Georgia and in 2021 it completed expansion of its third production line for engineered stone at the plant. LX Hausys America's artificial stone product is sold under the tradename Viatera.

1197. LX Hausys America, Inc. is headquartered in Atlanta, Georgia, and registered to do business in California in 1988 as Lucky America, Inc., a New Jersey corporation, and had its principal office in California at 13013 East 166th Street, Cerritos, California 90701. The company changed its name several times, to LG Chemical America, Inc. in 1995; to LG Chem America, Inc. in 2003, to LG Hausys America, Inc. in 2009, and to LX Hausys America, Inc. in 2021.

1. 2015 Safety Data Sheet for Viatera

1198. On June 20, 2015, LG Hausys America, Inc. issued a Safety Data Sheet for Viatera® (Engineered Stone), which it described as an agglomerate of natural quartz and polyester resin. In Section 3 of this Safety Data Sheet the company identified two hazardous ingredients: Quartz (≥90%) and Pigmented cured polyester (<10%).

1199. Section 2 of the Safety Data Sheet, regarding Hazards identification, provided two hazard statements: "May cause cancer" and "Causes damage to organs through prolonged or repeated exposure." The first statement is misleading because it suggests the product is not known to cause cancer, although it contains at least 90% crystalline silica, which is a known human carcinogen and was recognized as such by the International Agency for Research on Cancer in 1997. The second statement is also misleading, because it does not specify the duration of the "prolonged" exposure or the number of exposures that constitute "repeated" exposure that causes damage to organs.

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Workers therefore cannot know whether they must be exposed to the product for weeks, months, years or decades, or must be exposed hundreds, thousands, or tens of thousands of times to suffer organ damage. The statement is also misleading, because prolonged exposure suggests exposure of many years resulting in chronic disease, although artificial stone workers typically develop acute silicosis in less than 5 years or accelerated silicosis after 5 to 10 years of exposure. The hazard statements are also deficient because they do not mention silicosis as a health hazard of the product, although it is the major health hazard of the product. Indeed, the word "silicosis" does not appear in the entire Safety Data Sheet, even though the product contains more than 90% crystalline silica. This constitutes a gross failure to warn of the health hazards of the product that violates the Hazard Communication Standard.

1200. After providing the two inadequate hazard statements in the "Hazards identification" section of its 2015 Safety Data Sheet, LX Hausys America, Inc., provided 10 "Precautionary Statements": (1) "Obtain special instructions before use" (without stating what "special instructions" were to be obtained and from whom such special instructions could be obtained); (2) "Do not handle until all safety precautions have been read and understood," (although most artificial stone fabricators are immigrants who cannot read English), (3) "Do not breathe dust/fumes/gas/mist/vapors/spray" (as though workers should hold their breath throughout the work day), (4) "Wash hands thoroughly after handling" (although the products do not present appreciable health hazards by skin absorption); (5) "Do not eat, drink or smoke when using this product" (although the product does not present any appreciable health hazard by ingestion and is not a fire hazard); (6) "Wear protective gloves/protective clothing/eye protection/face protection," (rather than the critical information that it is essential to wear an air supplied respirator when fabricating the product); (7) "If exposed or concerned: Get medical advice/attention," (although fabricators are constantly exposed to the product when they cut, saw, grind, drill, edge, and polish the product); (8) "Get medical advice/attention if you feel unwell," (a useful instruction although it is generally not related to use of the product), (9) "Store locked up," (a pointless instruction, because slabs of the product are too large to lock up and are so heavy they can only be stolen with great difficulty), and (10) "Dispose of contents/container to hazardous or special waste collection point, in accordance with local,

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regional, national and/or international regulation." Most noteworthy is the absence of any precautionary statement that respiratory protection is necessary, in particular that workers fabricating the product must wear a NIOSH-approved air supplied respirator to prevent silicosis.

1201. In Section 3 of the Safety Data Sheet, LX Hausys America, Inc., also concealed the identities of the ingredients of the product other than quartz, by stating that the product contains "pigmented cured polyester," without identifying the ingredients of this component of the product, and without identifying any inorganic and/or metallic constituents of the product other than quartz.

1202. In Section 7 of the Safety Data Sheet, LX Hausys America, Inc., provided the following "precautions for safe handling": "Avoid breathing dust. Avoid cotact [sic] with slin [sic] and eyes. Provide good ventilation in process area to prevent formation of vapour. Obtain special instructions before use. Do not handle until all safety precautions have been read and understood. Avoid spilling the product, as this might cause danger of slippage and falls." The instruction to "avoid breathing dust," is meaningless without explaining how fabricators and installers could avoid breathing dust from the product without wearing air supply respirators (which LX Hausys does not advise is necessary to protect workers from silicosis). The misspelled instruction to avoid contact with skin and eyes is only minimally useful because crystalline silica is not dermally absorbed and no specific dermal or ocular protection is specified. The instruction to "provide good ventilation in process area to prevent formation of vapour," fails to specify the type or degree of ventilation that is necessary to prevent silicosis and fails to explain why vapor would be forming from the fabrication of artificial stone and if vapor formation is a hazard of the product, why it is a hazard, what vapors form, and how workers should protect themselves from such unspecified vapors. The instruction to "obtain special instructions before use" is meaningless without specifying what "special instructions" are to be obtained and from whom such special instructions can be obtained. The instruction "do not handle until all safety precautions have been read and understood" is pointless, because most artificial stone fabricators are Hispanic immigrants who can neither speak nor read English, and could not understand safety precautions in English, even if LX Hausys provided intelligible safe use instructions. The instruction to "[a]void spilling the product" makes no sense, because the product is extremely hard stone, rather than a liquid. Thus, LX Hausys's use instructions

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are meaningless and are not protective of worker health and safety.

1203. In Section 8 of the Safety Data Sheet, regarding"Exposure controls," LX Hausys America, Inc. recommended the following "respiratory protection": "Avoid inhalation of powder generated. Wear a respirator." The first of these instructions is nonsensical, because fabricators cannot avoid inhaling respirable crystalline silica dust when fabricating artificial stone; the second instruction concealed critical information necessary to prevent silicosis, i.e., the specific type of respirator that is necessary to prevent silicosis (an air-supplied respirator), and instead provided misleading information – that any respirator would protect workers from harm, although air-purifying respirators do not protect artificial stone fabricators from silicosis and actually contribute to the development of silicosis, because they do not adequately filter out respirable crystalline silica.

1204. In Section 11 of the Safety Data Sheet, regarding "Toxicological information," LX Hausys section of the Safety Data Sheet, Defendant provided misleading information regarding carcinogenicity by stating that the product "may cause cancer," although respirable crystalline silica is a known human carcinogen, i.e., it does cause cancer and has been classified as a known human carcinogen by the International Agency for Research on Cancer since 1997.

2. 2020 Safety Data Sheet for Viatera

1205. On January 17, 2020, LX Hausys America, Inc. issued a new Safety Data Sheet for Viatera (Engineered Stone). In Section 3 of this Safety Data Sheet, LX Hausys identified three ingredients of the product: Crystalline Silica (Quartz) (≤ 93%), Pigmented cured polyester (< 10%), and Polymethylmethacrylate (Polyester Resin Solution) (< 10%). Like its 2015 Safety Data Sheet, this revised Safety Data Sheet does not mention the hazard of silicosis, but conceals this hazard in violation of the Hazard Communication Standard. While the 2020 Safety Data Sheet corrects the spelling of some misspelled words in the 2015 Safety Data Sheet and provides a Proposition 65 cancer hazard warning, it does not correct the inadequate health hazard warnings regarding silicosis and the inadequate and harmful use instructions of the 2015 Material Safety Data Sheet.

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I. M S International, Inc.

1206. M S International, Inc. is commonly known as "MSI" and is often called "International" by stone fabricators.

1207. MSI's corporate headquarters is located at 2095 N. Batavia Street, in Orange, California; the company has distribution centers in Southern California at 9111 Sunland Blvd., Sun Valley, California, and in Northern California at 22300-B Hathaway Avenue in Hayward, California. MSI claims to have been founded in 1975, but was incorporated in Indiana in 1983 and registered with the California Secretary of State on September 7, 1984.

1208. MSI's website states that MSI was founded by Manu and Rika Shah and that in 1984 "Manu and Rika decided to move the company to Southern California, driven by their vision that, to ultimately succeed in distribution, a company must be located in focal distribution points."

1209. MSI's website states that "[i]n 1987, the Shahs realized that natural stone for residential and commercial usage had even higher market potential [than monuments and tombstones], and directed their efforts towards developing this sector of the industry.

1210. MSI's website states that "[i]n 1997, MSI embarked on its vision of becoming the first nationwide distributor of natural stone in the U.S. by opening a second location in Edison, New Jersey."

1211. MSI's website states that "[i]n 2003, with the company approaching nearly $50 million in annual revenues, Manu and Rika's sons, Raj and Rup, left their careers in investment banking to join the family business for the next stage of growth. Over the next five years, MSI focused on opening 1-3 new distribution centers each year, as well as dramatically broadening their product offering beyond just natural stone from India."

1212. On August 4, 2004, an article by Michael Reis was published in Stone World regarding M S International. This article reported: "As one of the first suppliers of Indian granite to the U.S., M S International (MSI) has been a contributor to the growth of the industry. Although MSI began as an importer and distributor of Indian granite, today it is one of the largest distributors of natural stone in the country. MSI currently has one of the largest stocks of natural stone with over

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20 million square feet of granite, marble, slate, travertine and limestone from over 25 countries. The inventory of tiles, slabs, landscaping products and monuments is stocked in five distribution centers located strategically across the country." The article also reported that the founder of M S International, Manu Shah, "moved his base of operations to Southern California in 1984, and MSI opened its own 6,000-square foot warehouse in 1987. That same year, the company introduced Black Galaxy granite -- which was quarried and processed in India by Enterprising Enterprises -- to the U.S. marketplace. The stone eventually became trademarked, and it became one of the most popular granites in the U.S." The article further reported: "The company's selection of materials steadily increased, as MSI began bringing in Italian stone as well as multi-colored Indian slate in 1987. The company started importing Norwegian granite in 1989, and it also expanded into crosscut travertine from Mexico in the early '90s. Another introduction was classifying products under the general term, "natural stone," according to Shah. That was a significant change, and by 1995 and 1996 this name was in vogue. Marble and granite became known as 'natural stone.'" The article further stated: "Shah reports that MSI will sell close to 6,000 containers of stone in 2004. This follows 11 straight years of growth, over which the company's volume increased by a factor of 10. Today, the majority of MSI's product comes from countries including India, Turkey, Brazil, China, Mexico and Spain."

1213. MSI's website states that "[b]y 2008, MSI was among the top importers of natural stone in the world, calling upon virtually every major source country across the globe, including India, Brazil, China, Turkey, Italy, Spain, and Mexico."

1214. On October 27, 2010, *Stone World* published a news report titled "MS International, Inc. announces the Grand Opening of its new Stone and tile Design Center in Orange, CA." This article announced the opening of MSI's new 15,000 square foot design gallery at its corporate headquarters in Orange, California. This article reported: "The new stone and tile design gallery incorporates the full line of MSI's product line of granite, marble, slate, travertine, limestone, quartz, porcelain, ceramic, sinks and glass mosaics -- serving the flooring, countertop and landscaping industries. In addition to a refreshed look for MSI's existing products, the new design center includes MSI's newest product offerings, including approximately 20 lines of porcelain, 25 new colors of

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natural stone slabs, 200 new varieties of wall tile and mosaics, Q Premium Natural Quartz and MSI's new line of prefabricated countertops and stainless steel sinks. With products imported from 36 different countries, MSI's corporate headquarters maintains over 1,500 containers of inventory, offering customers a selection of natural stone and related products among the largest in the country"

1215. MSI's website states that "[i]n 2012, with MSI approaching $500 million in annual revenues, Raj and Rup Shah were appointed Co-Presidents of MSI, to lead the next phase of growth. Since 2012, not only has the Company maintained its leadership in natural stone, but it also has become the leader in the distribution of many manufactured hard-surfacing products, including porcelain and ceramic tile, quartz countertops, and decorative mosaics. Additionally, since that time, the Company has doubled the number [of] distribution centers across the country to over 25 . . . ."

1216. On May 1, 2015, an article by Jason Kamery was published in *Stone World* titled "MIA/Stone World Dallas Stone Summit talks about metrics and the new silica regulations." This article reported: "Inviting fabricators from all over the area, MS International, Inc. (MSI) hosted the Stone Industry Education presented by the Marble Institute of America (MAI) and *Stone World* magazine. The event included a main presentation in the morning, networking opportunities, a warehouse tour and a Fabricator Forum, which provided an opportunity for attendees to discuss a number of industry topics. The event included 45 fabricators from 27 companies and 83 total participants." The article reported that "GK Naquin of Stone Interiors North America started off the day with a presentation about analyzing shop performances from sales to production and measuring metrics" and that "[a]s the event continued it covered topics such as evaluating the cost of installing countertops, the cost of overhead, how the market has changed in 20 years, servicing the customer base and understanding what they want, sales techniques and, finally, setting expectations for your sales representatives." The article stated: "In between discussing the major topics of the program, Naquin discussed the changes in the new silica regulations coming out. "It's very straining to our industry," said Naquin. "They are cutting it in half from 100 measures to 50. Some wet shop operations may not meet the silica requirements in the new proposed legislation. This is designed – and it says it right here, and it's from OSHA – 'Workers exposure to silica during countertop manufacturing, finishing and installation.' Now would you consider that to be a targeted publication? Is

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everyone seeing the big red dot on their back? How many people think OSHA isn't going to visit their shop in the next few years? If you raised your hand, guess what, get your $10,000 ready right now." This news report shows that at least as early as 2015 MSI was aware of the hazard that silica presented to stone countertop fabricators and installers. The news report also shows that although MSI hosted this event about "metrics and the new silica regulations," the new silica regulations were not one of the "Major topics of the program," but was only briefly discussed "[i]n between discussing the major topics of the program" and did not address the health hazards of fabrication workers, but merely lamented that countertop fabrication companies would have a "big red dot on their back" and would incur $10,000 in expense regarding OSHA inspections of stone countertop fabrication shops. The article also shows that even though MSI had claimed for years that it was an importer and distributor of stone slabs rather than a retail seller, that MSI could identify local stone countertop fabrication shops and invite them to an educational seminar where MSI could inform them of the toxic hazards that silica presented to their employees and how to protect their employees from those hazards, although MSI did not communicate such information to the stone countertop fabrication companies that it invited to its educational seminar in Dallas, Texas.

1217. On October 8, 2015, MSI hosted an education seminar at its facility in Southern California on how to better market your business. This seminar featured Marty Gould, a marketing consultant to the stone industry, and was directed to stone countertop fabrication businesses in Southern California. This seminar was part of MSI's plan to market its products to stone countertop fabrication businesses in Southern California. Although many owners of stone countertop fabrication businesses in Southern California attended this seminar at MSI's facility in Southern California at which MSI informed them how to better market their business, MSI did not inform any of the stone countertop fabrication companies that attended the MSI seminar of the toxic hazards that crystalline silica in its products presented to their employees and did not provide them any information how to protect their employees from the toxic respiratory hazards of its products at this seminar.

1218. MSI's website states that "[i]n 2017, MSI crossed $1 billion in annual revenues and over 1,750 employees worldwide."

1219. On September 29, 2017, *Stone World* published a news report titled "MS International

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Updates Video Library" which stated: "Consumers often turn to video as an educational tool as they go through the tile and flooring materials buying process. MS International (MSI) recently added 10 new videos to the company's video library for retailers and designers to embed on their company websites, post on social media, or use for internal training." Although these videos extolled the benefits of the stone slabs marketed by MSI, none of them mentioned the silicosis hazard to the workers who fabricated and installed MSI's stone products as countertops in consumers' kitchens and bathrooms, although this hazard was well known to MSI and its officers and directors at the time.

1220. MSI's website states that"MSI announced the establishment of a 360,000 square foot Domestic Quartz Manufacturing facility, based in Latta, South Carolina in 2019. MSI's domestic manufacturing plant provides the most advanced state-of-the-art machinery combined with patent production processes to produce the most natural-looking quartz countertops in the market." MSI's website states that "[i]n 2021, MSI crossed $2 billion in annual revenues and over 2,500 employees worldwide.

1221. On June 2, 2022, *Stone World* reported that the Association for Corporate Growth awarded M S International Top Company for Sustainable Growth at the organization's 27th annual awards event in Orange, California.

1222. MSI's website states that today, "[w]ith over $2.8 billion in annual revenue, 3,000+ U.S. employees, and helping create over 400,000 jobs around the world across their supplier base, MSI has very ambitious expansion plans for the future. This includes opening additional branches across the U.S. and Canada, as well as continuing to introduce new and innovative products across all major product lines."

1223. According to its website, "MSI imports materials from 36 countries while maintaining purchasing offices in India, Turkey, Brazil, China, and Italy. Headquartered in Orange, California, MSI's nationwide system of 18 state-of-the-art distribution centers and 2 additional sales office is focused on efficiency, making sure the over 30,000 containers we import arrive as expected."

1224. On its website, M S International, Inc. provides Installation Guidelines for its Premium Natural Quartz. However, these guidelines do not mention any protective measures that workers need to follow to prevent exposure to respirable crystalline silica and silicosis.

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1. M S International's 2021 Safety Data Sheet

1225. On March 11, 2021, MSI issued a Safety Data Sheet for "Quartz" which stated that "encompasses all types of Quartz products manufactured/sourced by M S International, Inc." The Safety Data Sheet states that the "Recommended Use" of the product is a "Building Material."

1226. Section 2 ("Hazards Identification") of the Safety Data Sheet states: "Quartz products are mixtures [of] natural occurring minerals that have been mined. The finished products are odorless, stable, non-flammable, and pose no immediate hazard to health. Respiratory, hand, and eye protection may be needed to prevent excess exposure to airborne particulates if dust is produced by cutting product during installation or by any other operations, including demolition/removal projects." The statement that the "finished products . . . pose no immediate hazard to health" is false and misleading for two reasons. First, the product is not a "finished product" sold to consumers, but is a "building material," i.e., a slab of artificial stone, that must be fabricated as a countertop and installed in a consumer's kitchen or bathroom before it becomes a "finished product." Second, the ordinary, intended and expected use of the product is for workers to cut, grind, polish and otherwise fabricate the product, which generates dangerous levels of respirable crystalline silica dust that causes silicosis and other occupational diseases, including acute silicosis, such that the product does "pose an immediate hazard to health." The statement that "respiratory, hand, and eye protection may be needed to prevent excess exposure to airborne particulates if dust is produced by cutting [the] product . . . or by any other operations" is also false and misleading for two reasons. First, dust is *always* produced by cutting the product and by other fabrication processes such as grinding, drilling, routing, edging, and polishing the product. Second, an air supplied respirator must always be worn when the product is being fabricated, because fabricating artificial stone slabs generate high levels of crystalline that a NIOSH-approved air supplied respirator must always be worn to prevent all exposure to respirable crystalline silica dust and the consequent development of silicosis. The statements in the Hazards Identification section of the Safety Data Sheet are also noteworthy for what they do not state: They do not mention the greatest health hazard of the product: silicosis. Indeed, the only two hazards to the lungs are mentioned. The first is "respiratory tract irritation," a

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transitory, common effect of exposure that results from many activities, such as cutting an onion. The second respiratory hazard mentioned is "damage to organs (lungs/respiratory) through prolonged or repeated exposure (inhalation)." This statement is misleading, because it does not specify the duration of the "prolonged" exposure or the number of exposures that constitute "repeated" exposure that causes damage to the lungs or the respiratory tract. Workers therefore cannot know whether they must be exposed to the product for weeks, months, years or decades, or must be exposed hundreds, thousands, or tens of thousands of times to suffer lung damage. The statement is also misleading, because prolonged exposure suggests exposure of many years resulting in chronic disease, although artificial stone workers typically develop acute silicosis in less than 5 years or accelerated silicosis after 5 to 10 years of exposure. The misleading statements therefore endanger the health of workers.

2. M S International's Letter to the Los Angeles County Board of Supervisors

1227. On July 28, 2023, Rupesh Shah, Co-CEO of M S International, Inc., signed a letter to the Los Angeles County Board of Supervisors, urging the Board of Supervisors not to ban the importation and use of artificial stone in Los Angeles County. This letter stated: "Stone products are safely handled and worked on every day, including in Los Angeles County . . . ." This statement is false, because artificial stone products are not "safely handled and worked on every day, including in Los Angeles County," as is shown by the epidemic of accelerated silicosis among stone countertop fabricators which has its epicenter in Los Angeles County.

1228. The letter by CEOs of artificial stone manufacturers seeks to foist blame on the owners of the small fabrication shops that fabricate artificial stone, rather than accepting personal responsibility for the deadly effects of their defectively designed artificial stone products. Thus, the letter states that "fabrication employers must provide necessary training, air monitoring and adherence to air quality requirements, engineering air handling controls, personal protective equipment (PPE), and medical surveillance in compliance with OSHA regulations." While multi-billion dollar manufacturers and importers like Cambria, M S International, Dal-Tile, and of course, Caesarstone and Cosentino, have the financial resources to spend millions of dollars to make their

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manufacturing facilities safe for their workers, fabrication shops (most of which are small mom-and-pop businesses that have 2 to 10 workers and generate annual revenues of a few hundred thousand dollars) lack the financial resources to implement the necessary protective measures, which cost a few million dollars in capital costs per shop, with annual maintenance costs of a few hundred thousand dollars. Thus, it is facetious for the multibillion dollar manufacturers and importers to seek to blame fabrication shop owners for their inability to protect workers from the deadly hazards of their artificial stone products.

1229. The letter also states: "Stone products, including engineered stone, have been manufactured and fabricated safely for decades . . . ." This statement is false. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the letter that "engineered stone ha[s] been manufactured and fabricated safely for decades is clearly and indisputably false.

3. M S International's Endorsement of Misrepresentations by The Stone Coalition

1230. In October 2023, a Paid Advertisement titled "Illegal Cutting Processes, Not Stone Products, can Cause Silicosis," was published in the Los Angeles Times. The advertisement states that it was "Paid For By The Stone Coalition," info@stonecoalition.org, which is described as "a collaborative effort between the quarts surface and natural stone industries."

1231. The Stone Coalition is an industry trade association that was apparently formed in 2023 to defend the Stone Countertop Fabricator Silicosis Cases by mounting a public relations

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campaign to deflect liability from stone slab manufacturers, distributors and suppliers, by attempting to foist blame for the new stone fabricator silicosis epidemic on the victims, their employers, and regulatory and enforcement agencies – all to avoid accepting personal responsibility for the massive (ultimately fatal) harm that they have inflicted on thousands of young immigrant workers.

1232. The home page of the new website of The Stone Coalition bears the name and logo of the Natural Stone Institute, implicating that industry trade association with the new trade association. The home page states: "The Stone Coalition is dedicated to promoting safe, wet processing technology in stone-cutting facilities while prioritizing compliance with OSHA air monitoring standards and other silica rules. Safety is our unwavering commitment." That is quite a statement by stone companies that for years opposed OSHA's adoption of the Silica Standard.

1233. A webpage titled "About" describes "Our Organization" as follows: "The Silica Safety Coalition is a collective of dedicated stone fabricators, manufacturers, stone distributors, and industry professionals united by a shared commitment to promoting workplace safety within the stone cutting and fabrication sector. Our mission is to promote and maintain the highest standards of safety, supporting the well-being of workers throughout every stage of stone processing." These statements are at best mere industry propaganda and at worst blatant falsehoods. The Coalition is actually a collective of multibillion dollar stone manufacturers and distributors that have been sued for causing the new stone fabricator silicosis epidemic – companies that for years failed to prepare any Safety Data Sheets or labels for their stone products or prepared Safety Data Sheets and/or labels that were so deficient that they caused, rather than prevented, the new fabricator silicosis epidemic.

1234. The website of The Stone Coalition does not identify its members, but the "About" webpage contains a section titled "Workplace Safety" that informs readers to "Click the button to read our letter to the Los Angeles County Board of Supervisors." Clicking on the button reveals a letter dated July 28, 2023, to the Los Angeles County Board of Supervisors in which the authors of the letter attempt to persuade the Los Angeles County Board of Supervisors not to ban the importation and use of artificial stone products in Los Angeles County. The letter is signed by executive officers of four artificial stone companies: Marty Davis, CEO of Cambria; Rupesh Shah, Co-CEO of M S International, Inc.; Matthew Kahny, President of Dal-Tile; and Nate Kolenski,

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President of Block Tops, Inc.; and James A. Hieb, CEO of the Natural Stone Institute. The first three of these companies are among the most culpable defendants in the Stone Fabricator Silicosis Cases.

1235. The title of the Paid Advertisement is itself misleading and false, for two reasons. First, it states that stone products do not cause silicosis, although most silicosis cases over the millennia and at the present time have been and continue to be caused by crystalline silica dust from stone products. Second, it states that only "illegal cutting processes . . . can cause silicosis," although cutting stone slabs can cause silicosis whether the cutting process is performed "legally," i.e., in compliance with OSHA requirements, or "illegally," i.e., in violation of OSHA requirements.

1236. The Paid Advertisement begins with the following statement: "Silicosis, a rare lung disease resulting from the inhalation of crystalline silica dust from dry-cutting or grinding concrete, brick or stone, has been found in illegal and unregulated stone fabrication across California, with a significant concentration in the San Fernando Valley." This statement is at best misleading and at worst false, for a few reasons. First, silicosis is not a rare lung disease. It is the oldest lung disease known to humankind and has killed more workers over the millennia than any other lung disease, including all lung diseases caused by exposure to asbestos. Additionally, recent epidemiological studies have reported a prevalence of silicosis among stone fabricators in the range of 30% to 40%, making it an especially common occupational lung disease that is of great public health concern. Second, the statement falsely suggests that silicosis is only caused by dry-cutting or grinding, although many workers who regularly used water-dispensing powered tools to reduce the amount of dust in fabricating stone countertops now suffer from silicosis and the National Institute for Occupational Safety and Health (NIOSH) has done studies which show that wet processing methods are inadequate to prevent silicosis among workers who fabricate artificial stone countertops. Third, silicosis among countertop fabricators and other workers exposed to crystalline silica has been shown to occur even at exposure levels below limits adopted by the Occupational Safety and Health Administration (OSHA), i.e., "legal" stone fabrication.

1237. The Paid Advertisement then states: "Yet, this disease is preventable through wet processing techniques and strict adherence to existing OSHA regulations." This statement is also false, because studies by NIOSH show that even fabrication workers who regularly use water-

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dispensing tools and wear particulate filter respirators at all times they are in the fabrication shop still develop silicosis from exposure to artificial stone dust.

1238. The Paid Advertisement then states: "Despite Federal and State regulations to prevent the use of 'drycutting,' or cutting of stone or tile without water, and requiring personal protective equipment (PPE), many noncompliant facilities continue to put their employees at risk by failing to implement these basic safety precautions." This statement is also misleading and false, because most stone countertop fabrication shops have followed the recommendations of artificial stone manufacturers to use powered tools that dispense water to suppress dust generated by the fabrication of artificial stone, as well as the manufacturers' recommendations to have their employees wear particulate filter masks. However, both of these precautionary measures recommended by stone slab manufacturers are inadequate to prevent silicosis among stone countertop fabricators, which recommendations misled both employers and fabrication workers to believe that following the manufacturers' recommendations would prevent fabrication workers from developing silicosis. The use of water-dispensing tools is inadequate to prevent silicosis in artificial stone fabricators because at most it merely reduces the amount of lethal crystalline dust to which fabrication workers are exposed, and particulate filter masks do not prevent the extremely small particles of crystalline silica from cutting artificial stone from being inhaled and causing silicosis. In fact, the recommendation of the artificial stone manufacturers to wear a "NIOSH-approved" mask has caused many workers to develop silicosis, because NIOSH-approved particulate filter masks do not prevent harmful silica exposure, the only type of respirator that is effective in doing so is an air-supplied respirator, which the manufacturers of artificial stone have not recommended as necessary protection for workers.

1239. The Paid Advertisement then states that Jim Hieb, CEO of the Natural Stone Institute, knows this doesn't have to happen and quotes him saying: "Silicosis is preventable. Any contractor that follows Cal/OSHA's guidelines ensures that any cutting of any stone product is done safely." This statement is also misleading and false for a few reasons. First, while silicosis from exposure to natural stone dust may be preventable, silicosis from exposure to artificial stone is not preventable, because unlike natural stone, the fabrication of artificial stone generates massive amounts of ultrafine and nanosized crystalline silica particles that penetrate through particular cartridge respirators and

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are inhaled by fabricators and cause progressive massive fibrosis, because they are extremely toxic to the lungs - much more so than larger silica particles from natural stone. Second, while it may theoretically be possible to prevent silicosis in artificial stone fabricators, in the real world it is not possible to prevent silicosis in artificial stone fabricators, because the cost of installing state-of-art ventilation systems, respiratory protection programs, exposure monitoring programs, administrative industrial hygiene programs, and medical monitoring programs necessary to prevent silicosis, the capital cost of implementing these programs is a few million dollars per shop with annual costs of several hundred thousand dollars, which small fabrication shops that generate annual revenues of a few hundred thousand dollars cannot afford. Third, OSHA's guidelines were developed to protect against respirable crystalline silica particles in the micron size range - not ultrafine and nanosized crystalline silica particles that are uniquely generated from the fabrication of artificial stone and present extraordinary fibrotic hazards to the human lung and while compliance with OSHA's exposure limits for respirable crystalline silica may reduce fibrotic lung disease or delay its occurrence among stone fabricators, multiple studies have shown that compliance with OSHA's exposure limits is inadequate to prevent all silicosis. It is therefore extremely irresponsible for the CEO of the Natural Stone Institute to state that compliance with OSHA guidelines "ensures that any cutting of any stone product is done safely." This is especially so, because exposure to crystalline silica not only causes silicosis which may be dose-dependent, but also causes lung cancer and there is no level of exposure to crystalline silica that does not increase fabrication workers' risk of getting lung cancer later in life.

1240. The Paid Advertisement also states: "Almost all experts agree that what is being cut matters less than how the stone is cut and fabricated for placement within homes and offices." While this statement may generally be true for natural stone products, it is not true for artificial stone products which present unique respiratory hazards to stone countertop fabricators because artificial stone is manufactured by crushing and pulverizing quartz (crystalline silica) and then adding a polymeric resin, pigments and other additives and curing the mixture, so that when the finished slab is cut, the ultrafine and nanosized particles that are in the plastic matrix are released and are inhaled by fabricators even though they wear particulate filter respirators. Indeed, the extreme hazard of

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artificial stone is due not only to the extremely high crystalline silica content of the product (much higher than marble and granite), but is also due to the extremely small size of the crystalline silica particles that are released into the air when fabricators use powered tools to cut artificial stone.

1241. The Paid Advertisement also states: "Despite studies and regulations that show that the type of product matters significantly less than the method of cutting, plaintiffs' attorneys have been trying to blame engineered stone for recent cases of Silicosis among stone workers." It is true that attorneys who represent the ever-increasing number of young male Hispanic immigrants who have developed silicosis with progressive massive fibrosis and are terminally ill unless they receive lung transplants, primarily blame artificial stone for causing the workers' fatal lung disease, so too do knowledgeable pulmonologists, occupational medicine specialists, epidemiologists, and public health experts. Indeed, the new occupational disease epidemic of accelerated silicosis among artificial stone fabricators is largely attributable to artificial stone, because it is an inherently dangerous and defective product whose purported benefits which are merely aesthetic in nature, are outweighed by the severe lung and other diseases that this product causes at with such a high disease prevalence.

1242. The Paid Advertisement then states: "Engineered stone products including Quartz, have been manufactured and fabricated safely for decades." This statement is a blatant lie. Artificial stone is a relatively new product in commerce that first began being manufactured by Caesarstone in 1987 and was first imported into the United States in the 1990s. The first case of artificial stone-induced silicosis was seen in 1997 by physicians at the National Lung Transplantation Center in Israel. This worker was exposed to Caesarstone, developed silicosis, and underwent lung transplantation. Over the next 14 years, researchers at the National Lung Transplant Center in Israel diagnosed silicosis in 25 patients exposed to Caesarstone, of whom 15 (60%) were determined to be lung transplant candidates. Kramer MR, et al., "Artificial Stone Silicosis: Disease Resurgence Among Artificial Stone Workers," *Chest* 2012; 142(2):419-424. Thus, the statement in the Paid Advertisement that "[e]ngineered stone products, including Quartz, have been manufactured and fabricated safely for decades" is absolutely false.

1243. The Paid Advertisement quotes Mr. Hieb as stating: "The biggest problem our

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industry faces is enforcement. Without efforts to stop those who are unaware of or unwilling to comply with current regulations, cases of Silicosis are going to keep increasing." This statement is also false and misleading. The biggest problem the stone industry faces is that artificial stone is the cause of a worldwide epidemic of accelerated silicosis among stone countertop fabricators. Stating that the biggest problem the industry faces is enforcement is merely an attempt by manufacturers of deadly artificial stone products to foist blame on OSHA due to its inability to prevent the disease and death that are primarily due to artificial stone products. OSHA is extremely underfunded and lacks the resources to initiate enforcement actions against the thousands of small fabrication shops nationwide and enforcement actions do nothing to prevent silicosis among the tens of thousands of countertop fabrication workers who have already been exposed to crystalline silica from stone products and who already have silicosis even though many of them have not yet exhibited symptoms of this disease. Moreover, many fabrication shops are unaware of the silicosis hazard because the manufacturers of artificial stone for many years did not prepare or provide their customers with Safety Data Sheets or product labels informing them of the silicosis hazard and none of the manufacturers provided their customers with instructions that were adequate to prevent silicosis among fabricators.

1244. The Paid Advertisement also states: "Industry leaders provide resources to support smaller businesses in the industry." This statement is at best misleading and at worse false. For years the manufacturers of artificial stone concealed the nature and severity of the toxic hazards of their products from their customers and only provided them training on how to improve profitability. Only after the new silicosis epidemic was well under way did the manufacturers of artificial stone initiate any programs to "support smaller businesses in the industry," and those programs were public relations programs to deflect responsibility from the manufacturers of deadly artificial stone products to blame the epidemic on the victims, the owners of small fabrication shops that employed them, on regulators and governmental enforcement agencies – anyone except themselves for causing the harm.

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4. Knowledge of the Silicosis Hazard by M S International's Officers

1245. Throughout the time that M S International sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, M S International's officers and directors were aware that the company's artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that M S International provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by M S International's defective artificial stone products. Among M S International's officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers are: Manu Shah, Chief Executive Officer; Rajesh Shah, Co-President; Rupesh Shah, Co-President; Phillip Caudillo, Vice President of Operations; Judy Hatti Botchlet, Vice President; Steve Dickeson, Chief Financial Officer.

J. Paragon Industries, Inc. (dba Bedrosians Tile & Stone)

1. Corporate History

1246. Paragon Industries was incorporated in the State of California on September 18, 1974. The company has long done business under the fictitious business name Bedrosians Tile and Stone.

1247. On July 18, 2019, Paragon industries filed a Statement of Information with the California Secretary of State stating that its principal executive office is 4285 N. Golden State Blvd., Fresno, California 93722 and identifying its corporate officers as Larry E. Bedrosian, Chief Executive Officer and Janice A. Bedrosian, Secretary and Chief Financial Officer. The Statement of Information described by company's type of business as "Wholesale/Retail Sales."

1248. The most recent Statement of Information that was filed with the Secretary of State on September 18, 2023, provides the same business address, lists the same corporate officers, and also lists Gary A. Bedrosian, Larry E. Bedrosian, Janice A. Bedrosian, and Linda R. Hovannisian as

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Directors of the company. This most recent Statement of Information describes the company's type of business as "Wholesale and retail sale of building supplies."

2. Company Website

1249. Paragon Industries, Inc. has a website"Bedrosians" that is accessed at bedrosians.com. The website has an "About Us" webpage that states the company's Vision as follows: "Our vision is to be the most customer-centric tile company in the United States."

1250. The "About Us" webpage states the company's Mission as follows: "Our mission is to offer clients a place to buy the most trend-setting tile and stone products available in the market through a seamless purchasing experience."

1251. The "About Us" webpage also states: "We value and practice social responsibility; encourage employee development; care about employee and customer relationship; and love to acknowledge good work."

1252. Under a heading "Our Story," the "About Us" webpage tells the company's story:

> In 1948, Bedrosians began providing tile and setting materials to contractors and builders in Central California. Today, 70 years later, we have over 40 branches located throughout California, Arizona, Colorado, Georgia, Idaho, Nevada, Oregon, Texas, Utah, Washington, North Carolina, and Florida with a national and international customer base.
>
> Our growth has made Bedrosians one of the largest independent porcelain tile and stone importers and distributors in the United States. However, our philosophy is the same today as it was in 1948 when our founder, Ed Bedrosian, opened the doors. We believe in and strive to provide the highest possible level of service, the best technical and design assistance available, excellent product quality, and competitive pricing.
>
> The quantity, variance, and quality of our lines allows us to meet the needs and performance requirements of any project whether commercial, institutional, industrial, or residential in nature, in the United States or around the world. This strong buying power enables us to provide products falling well within a project's budgetary constraints.
>
> If you are located near one of our showrooms or service centers, we invite you to come in and explore the wide product selection. Our purchasing department is committed to buying and stocking the newest design trends in porcelain tile and stone products. Come meet with our trained customer service and showroom personnel, as well as our architectural representatives, who are ready to assist you with your next project.

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3. Stone Slabs Purchased and Sold

1253. On April 18, 2024, a deposition on behalf of Paragon Industries, Inc. was given by Jeramy Janz, Southern California Regional Manager of the company, in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs, et al.,* LASC Case No. 22STCV31907. He testified that Bedrosians is a supplier of a number of surfaces, including tile, stone, engineered wood, SBC, flooring and countertop surface material. He testified that Bedrosians sells natural stone, including granite, marble, limestone, travertine, and quartzite, and that the company also sells quartz (engineered stone), ceramic and porcelain.

1254. On April 30, 2024, a deposition on behalf of Paragon Industries, Inc. was given by Max Aschoff, National Director of Slab Sales of the company, in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs, et al.,* LASC Case No. 22STCV31907. He testified that the factories that manufactured artificial stone slabs purchased by Bedrosians included Diresco, US Surfaces, Pure Surfaces, got Badan, Grant Quartz, Opalus, MXM Surfaces, Sonte Konnection, Aruelia, and Empire.

4. 2021 Safety Data Sheet for SequelEncore

1255. On March 12, 2021, Paragon Industries issued a Safety Data Sheet for its product Sequel Encore™, identifying the manufacturer/supplier of the product as Bedrosians. Section 3 of this Safety Data Sheet identified one "Dangerous Component" in the product: Quartz (SiO2) at a concentration > 90%. This section of the Safety Data Sheet also identified as "Non-hazardous components" "Resins and trace minerals including: Fe_2O_3, Fe_3O_4, TiO_2, Al_2O_3, CaO, MgO, Na_2O, K_2O . . ."

1256. Section 2 of the Safety Data Sheet, regarding "Hazard(s) Identification" identified two health hazards: "H350 May cause cancer" and "STOT RE 1 H372 Causes damage to the lung through prolonged or repeated exposure. Route of exposure: Inhalation." The first statement, that exposure to the product "may cause cancer," is misleading, because it suggests that crystalline silica is not a known cause of cancer although crystalline silica is, in fact, a known human carcinogen, i.e., it does cause cancer and has been classified as a known human carcinogen by the International Agency for

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Research on Cancer since 1997. The second statement is also misleading, because it does not specify the duration of the "prolonged" exposure or the number of exposures that constitute "repeated" exposure that "causes damage to the lung." Workers therefore cannot know whether they must be exposed to the product for weeks, months, years or decades, or must be exposed hundreds, thousands, or tens of thousands of times to suffer lung damage. The statement is also misleading, because prolonged exposure suggests exposure of many years resulting in chronic disease, although artificial stone workers typically develop acute silicosis in less than 3 to 5 years or accelerated silicosis after 5 to 10 years of exposure. The hazard statements are also deficient because they do not mention silicosis as a health hazard of the product, although it is the major health hazard of the product. Lastly, the statement conceals from workers the true nature and severity of "damage to the lung," i.e., that exposure to the product causes silicosis, a progressive, irreversible and fatal lung disease.

1257. After providing inadequate hazard statements in the "Hazards identification" section of the Safety Data Sheet, Bedrosians provided 15 "Precautionary Statements": (1) "Obtain special instructions before use" (without stating what "special instructions" were to be obtained and from whom such special instructions could be obtained); (2) "Do not handle until all safety precautions have been read and understood," (although most artificial stone fabricators are immigrants who cannot read English), (3) "Do not breathe dust/fumes/gas/mist/ vapors/spray" (as though workers should hold their breath throughout the work day), (4) "Avoid breathing dust/fume/gas/mist/vapors/ spray" (same); (5) "Wash hands thoroughly after handling" (although the products do not present appreciable health hazards by skin absorption); (6) "Do not eat, drink or smoke when using this product" (although the product does not present any appreciable health hazard by ingestion and is not a fire hazard); (7) Use only outdoors or in a well-ventilated area (without defining quantitatively or by ventilation type what constitutes a "well ventilated area"), (8) "Wear protective gloves/protective clothing/eye protection/face protection," (rather than the critical information that it is essential to wear an air supplied respirator when fabricating the product); (9) "IF INHALED: Remove person to fresh air and keep comfortable for breathing" (although fabricators always inhale respirable crystalline silica dust from the product in doing their work); (10) IF exposed or concerned:

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Get medical advice/attention" (although fabricators are constantly exposed to the product when they cut, saw, grind, drill, edge, and polish the product); (11) "Call a poison center/doctor if you feel unwell" (although poison control centers do not treat silicosis, a chronic disease); (12) "Get medical advice/attention if you feel unwell," (a useful instruction although it is generally not related to use of the product), (13) "Store in a well-ventilated place. Keep container tightly closed" (an inapplicable instruction because artificial stone slabs need not be stored in a well-ventilated place and need not be stored in containers whether tightly closed or not); (14) "Store locked up," (a pointless instruction, because slabs of the product are too large to lock up and are so heavy they can only be stolen with great difficulty), and (15) "Dispose of contents/container to hazardous or special waste collection point, in accordance with local, regional, national and/or international regulation." Absent is any precautionary statement that respiratory protection is necessary, i.e., that workers fabricating the product must wear a NIOSH-approved air supplied respirator to prevent silicosis.

1258. In Section 7 of the Safety Data Sheet, Bedrosians provided the following "precautions for safe handling": "When cutting, grinding or removing, use equipment with integral dust collection and/or use local exhaust ventilation. Use wet cutting methods to reduce generation of dust. Use respiratory protection in the absence of effective engineering controls." These statements are inadequate because individually and collectively, they are insufficient to prevent silicosis, and therefore mislead workers to believe that following these instructions will keep them safe. In particular, the instruction to "use respiratory protection in the absence of effective engineering controls" is misleading and inadequate, because the instruction does not inform workers that the only type of respirator that can prevent silicosis is a NIOSH-approved air supplied respirator and that air-purifying respirators are inadequate to prevent silicosis, and because engineering controls alone are never effective in preventing silicosis when performing artificial stone fabrication tasks.

1259. In Section 8 of the Safety Data Sheet, Bedrosians recommended the following "Exposure controls": "Ventilation must be adequate to maintain the ambient workplace atmosphere below the exposure limit(s) outlined in the SDS. Where acceptable concentrations cannot be maintained by general mechanical ventilation, local exhaust ventilation is recommended." This is an inadequate and harmful instruction, because general mechanical ventilation is never adequate to

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prevent workplace exposure to respirable crystalline silica dust among artificial stone fabricators below exposure limits due to the extremely high crystalline silica content of the product, and is therefore inadequate to prevent silicosis, and it is impossible for a worker to know whether exposure limits are being exceeded, absent constant exposure monitoring which is industrially infeasible.

1260. In Section 8 of the Safety Data Sheet, Bedrosians states the following regarding "Breathing equipment": "Use of a properly fitted NIOSH-MSHA approved particulate respirator is recommended when cutting natural stone products for installation or during the removal of installed product." This instruction conceals critical information necessary to prevent silicosis, i.e., the specific type of respirator that is necessary to prevent silicosis (an air-supplied respirator), and instead provides misleading information – that a particulate respirator would protect workers from harm, although air-purifying respirators do not protect artificial stone fabricators from silicosis and contribute to the development of silicosis, because they do not filter out respirable crystalline silica. The instruction is also inadequate because wearing a particulate filter respirator provides no protection for toxic vapors generated from other fabricating artificial stone products.

1261. In Section 11 of the Safety Data Sheet, regarding the carcinogenicity of crystalline silica Bedrosians states: "According to the current state of the art, worker protection against silicosis can be consistently assured by respecting the existing regulatory occupational exposure limits." This is a false statement, because silicosis has been reported among workers in various industries despite compliance with regulatory occupational exposure limits and published studies have long concluded that regulatory exposure limits have been set at levels that cause silicosis, such that compliance with regulatory exposure limits causes silicosis rather than preventing silicosis.

1262. Section 15 of the Safety Data Sheet, regarding "Regulatory Information" provides a warning regarding California Proposition 65 that states: "WARNING: This product can expose you to chemicals including crystalline silica (airborne particles of respirable size) in dust created during fabrication/installation only if the product is dry cut/ground or pulverized, which are known to the State of California to cause cancer." This is a false statement, because artificial stone fabricators are always exposed to respirable crystalline silica when they cut, grind, drill, polish, or otherwise fabricate artificial stone when using power tools, even when they use wet processing methods. The

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warning statement fails to comply with California's Safety Drinking Water and Toxic Enforcement Act (Proposition 65) and is false and misleading, because it falsely suggests to workers that they cannot be and are not exposed to respirable crystalline silica unless they dry-cut the product, which multiple published studies have shown is not true.

1263. Lastly, Section 16 of the Safety Data Sheet states: "It is the responsibility of the user to determine applicability of this information and the suitability of the material or product for any particular purpose." Although the Hazard Communication Standard imposes duties on manufacturers and importers of hazardous chemical products to evaluate their hazards and to provide safe use instructions, by this statement Bedrosians appears to disclaim those duties, fails to take responsibility for its defective product and defective warnings and use instructions, and wrongfully attempts to shift its responsibility for causing silicosis among fabricators to "the user," i.e., to the fabricators themselves who are the victims of the artificial stone silicosis epidemic.

1264. Apparently, Paragon Industries, Inc. never prepared a Safety Data Sheet for any of the products the company imported, distributed or sold at any time prior to March of 2021.

5. Knowledge of the Silicosis Hazard by Paragon Industries' Officers

1265. Throughout the time that Paragon Industries sold artificial stone products, exposing stone countertop fabricators and installers to crystalline silica from the products, Paragon Industries' officers and directors were aware that its artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that the company provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators from the lethal silicosis hazard presented by Paragon Industries' defective artificial stone products. Among Paragon Industries' officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators are: Larry E. Bedrosian, CEO; Gardnar O'Brien, CFO; Janice A. Bedrosian, Secretary; Nirbhay Gupta, CTO; Matteo Polvara, VP Italia Operations; Bob Papazian, Director Medical & Science Operations; Eddie Bedrosian, Marketing Director.

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K. Surface Warehouse LP

1. Corporate History

1266. In 2006, Lee P. Wood, a Texas attorney, and Robert Butts, a Texas businessman, founded Surface Warehouse L.P. in Austin Texas.

1267. On May 8, 2006, Surface Warehouse, L.P. filed its Certificate of Formation as a Limited Partnership with the Texas Secretary of State, providing 8868 Research Blvd., Ste. 309, Austin, Texas 78758 as its business address and identifying Surface Enterprises, LLC as its general partner. The Certificate was dated April 13, 2006, and signed by Lee P. Wood, as Vice-President.

1268. On May 7, 2024, Lee Wood gave a deposition in the case of *Gustavo Reyes-Gonzalez v. Aaroha Radiant Marble & Granite Slabs, et al.,* LASC Case No. 22STCV 31907, on behalf of Surface Warehouse, L.P. at which he testified: "The purpose of the business was to supply countertop material known as solid surface, which is an acrylic-based material," Dupont's Corian being the major brand of that surface material.

1269. At the company's deposition in the *Reyes-Gonzalez* case, Mr. Wood testified that when Surface Warehouse was formed, it began distributing acrylic solid surface materials that were branded Livingstone and contained no silica, but that as quartz became more popular, the company realized that if it was going to stay in business and continue to grow the business, the company needed to enter into the quartz business.

1270. On May 13, 2009, Surface Warehouse, L.P. filed an Application for Registration as a Foreign Limited Partnership with the California Secretary of State.

1271. At the company's deposition in the *Reyes-Gonzalez* case, Lee Wood testified that in 2016 Surface Warehouse launched the quartz line that was called Vadara. Mr. Wood testified that Vadara is an engineered stone product that contains approximately 85% to 90% quartz, i.e., silica.

1272. At the company's deposition in the *Reyes-Gonzalez* case, Mr. Wood also testified that Surface Warehouse, L.P. has done business under the name U.S. Surface Warehouse and the name US Surfaces.

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2. Company Website

1273. According to a press release that was on Vadara's website, "Vadara Quartz Surfaces was founded in 2016 in Los Angeles, California, under the parent company US Surface Warehouse." According to the press release, "Vadara represents the collaboration of Arik Tendler, former CEO of Caesarstone Quartz, and solid surface pioneer Robert Butts, who currently owns US Surface Warehouse. Together, they have catapulted Vadara to success with a savvy combination of leadership experience, innovative products, and state-of-the-art technology integration." "Vadara Quartz Surfaces has become the fastest growing quartz brand in 2016 with rapid openings of distribution centers across the United States. In 2016, the company opened their first distribution center in Los Angeles and by year's end added three more locations in San Francisco, Chicago, and Atlanta." https://www.vadaraquartz.com/news-press/press-release/year-in-review-vadara-quartz-surfaces-opens-four-distribution-centers-in-2016/#:~:text=Vadara%20represents%20the%20collaboration%20of,currently%20owns%20US%20Surface%20Warehouse.

1274. The company now a has a website under the name "us surfaces" at ussurfaces.com. This website has an "About Us" webpage that states: "Since 2007, US Surfaces has been in the business of marketing and distributing premium quality, cost-effective building products to both residential and commercial customers. We are the creators of premier brands Vadara Quartz Surfaces and LivingStone Solid Surfaces. Our products are extremely competitive and we are exceptionally easy to do business with. Join us."

1275. The "About Us" webpage has a section that bears a heading "Formation" that states: "US Surfaces is a vertically integrated company that creates, markets and distributes solid-surface sheets and quartz slabs. It was formed in 2007 by industry veterans to disrupt the outmoded ways surfacing materials were produced and brought to market. We are now the 3rd largest solid surface company in the U.S. and Vadara® is the fastest growing quartz brand."

1276. A "No Middlemen" section of the webpage states: "Conventional, multi-step distribution involves products being bought and sold many times before reaching the ultimate user. US Surfaces is a vertically integrated company, meaning that no agents or middlemen tack on their costs.

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3. Arik Tendler Joins the Company to Launch Vadara

1277. At a deposition that he gave in the case of *Victor Gonzalez v. ADB Global Trade LLC,* LASC Case No. 21STCV06984 on July 21, 2023, Arik Tendler, formerly the Chief Executive Officer of Caesarstone USA, Inc., testified that towards the end of 2015 he joined Surface Warehouse, L.P. to market Vadara as a "private label quartz company" under the Vadara brand name. At that time Surface Warehouse began to lease a facility at 8969 Bradley Avenue in Sun Valley, California, and later leased facilities in Hayward, California and Costa Mesa, California.

1278. When Surface Warehouse began marketing artificial stone slabs under the Vadara brand name, the company imported artificial stone slabs from China as well as some other countries. At the company's deposition in the *Reyes-Gonzalez* case, Lee Wood recalled that Surface Warehouse L.P. imported artificial stone from Foshan, Monica, Teltos, Basix, and Loyalty Enterprise Stone Company in China, as well as Lion Chemtech Company and LE Korea in South Korea.

4. Knowledge of Health Hazards

1279. At his deposition in the *Victor Gonzalez* case, Arik Tendler testified that he learned of the disease called silicosis before he left Caesarstone towards the end of 2011, by which time a lawsuit had been filed in Texas against Caesarstone USA for causing silicosis. At that time his understanding was the lawsuit was of people fabricating countertops unsafely who got sick.

1280. At the deposition of Surface Warehouse L.P. in the *Reyes-Gonzalez* case, Lee Wood testified that he was aware as early as 2015 or 2016 that "overexposure to silica can lead to health hazards, including silicosis." He explained that by "overexposure" he meant "that exposure over the period of time that is not conducted in a safe workplace with a safe work environment may lead to silicosis." At that time he understood that silicosis is a lung disease that is caused by inhaling silica dust.

1281. At his deposition that he gave in the *Victor Gonzalez* case, Mr. Tendler testified that "in this industry is always dust. . . . So it's part of the business. It has always been."

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5. Vadara's 2017 Safety Data Sheet

1282. On May 1, 2017, Vadara issued a Safety Data Sheet for Vadara Quartz Surfaces, identifying the manufacturer/supplier of the product as Vadara Quartz Surfaces, 8969 Bradley Avenue, Sun Valley, California 91352."

1283. Section 3 of the Safety Data Sheet states that the ingredients of the product as Quartz (>85%) and "Non-Regulated Ingredients" (<15%)."

1284. Section 2 of the Safety Data Sheet, titled "Hazards Identification," provides the following statement regarding "Classification" of the product: "As shipped, non-hazardous quartz surfacing product." This is a misleading statement, because the product is not a finished consumer product, but is rather an industrial product that must be fabricated into a countertop before being installed in kitchens and bathrooms as a consumer product, and in the process of fabricating the product, respirable crystalline silica dust is generated at air concentrations that cause silicosis.

1285. Section 2 of the Safety Data Sheet then provides the following information as Hazard Warnings: "Exposure limits may be applicable when cutting or grinding product creating dust, which can contain particles of crystalline silica (quartz). Overexposure to airborne quartz particles can cause silicosis." The first statement is false and downplays the hazard of silicosis, because exposure limits ***are always*** applicable when cutting or grinding artificial stone that contains crystalline silica. The second statement is misleading, because it does not explain what constitutes an "overexposure" to airborne quartz particles, and because exposures to silica below the permissible exposure limit have been shown to cause silicosis among workers exposed to artificial stone dust.

1286. Section 2 of the Safety Data Sheet then provides the following information as "Signal Word": "Danger: Do not breathe dust (522). Wear suitable respiratory equipment when ventilation insufficient (538)." The first statement an inadequate and harmful instruction, because dust is always generated when artificial stone is fabricated, workers must breathe to work and live, workers cannot hold their breath an entire workshift, and the statement does not inform workers how they can do their work without breathing dust from the product. The second statement is also inadequate, because it does not explain to workers how they can tell whether ventilation is insufficient and it

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does not specify the type of respiratory equipment that workers must wear to prevent silicosis (i.e., a NIOSH-approved air supplied respirator), thereby misleading workers to believe that air-purifying respirators will protect them, although air-purifying respirators are inadequate to protect workers fabricating artificial stone from silicosis due to the extremely high crystalline silica content of the product and the very fine respirable crystalline silica dust that is generated using power tools.

1287. Section 2 of the Safety Data Sheet then provides the following statement as a "Risk Phrase": "Danger of serious health damage by prolonged exposure through inhalation. ® 20/48)." This statement is also inadequate, because it does not explain whether the "prolonged" exposure that can cause serious health damage is one that lasts days, weeks, months, years, or decades, and because acute silicosis has typically been reported among artificial stone fabrication workers after about 3 years of exposure, but has even been detected in artificial stone workers after as little as 1 or 2 years of exposure, which is not a "prolonged" exposure. The statement is therefore inadequate and would mislead workers to believe they are safe because they have been exposed for just a few years.

1288. Section 8 of the Safety Data Sheet, titled Exposure Control/ Personal Protection, provides the following information regarding Exposure Limit Values: "Not appropriate for material as shipped from manufacturer. When cutting or grinding for example, workers should seek from their employer appropriate personnel protective equipment as required by the work environment conditions and equipment." This first statement is incorrect, because the product is an industrial material that must be fabricated into countertops which necessarily involves cutting, grinding and polishing the product, generating respirable crystalline silica dust and other airborne particulates and fumes for which regulatory exposure limits apply. The second statement is inadequate and constitutes a refusal on the part of the company to provide critical safe use and handling information. Since Vadara knows that its high silica content product will be cut, ground and polished, it is incumbent on Vadara to inform workers that they must wear a NIOSH-approved air supplied respirator when performing any and all fabrication tasks to prevent exposure and silicosis.

1289. Section 8 of the Safety Data Sheet, titled Exposure Control/ Personal Protection, also provides the following information regarding Respiratory Protection: "In case of insufficient ventilation, wear suitable respiratory equipment. Dust masks do not provide suitable respiratory

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protection." This use instruction is inadequate and constitutes a dangerous, harmful use instruction for several reasons. First, to prevent silicosis, adequate respiratory protection is necessary whenever workers fabricate artificial stone or are present where it is being fabricated. However, the instruction suggests that respiratory protection may not be needed when workers are fabricating artificial stone, thereby subjecting them to harmful exposure to respirable crystalline silica and putting them at substantial risk of silicosis and other occupational diseases. Second, the instruction does not provide workers with any quantitative information or explain to them how they can determine whether the ventilation where they are working is "insufficient," although ventilation of respirable crystalline silica from the fabrication of artificial stone is always insufficient to prevent silicosis. Third, although the statement that "dust masks do not provide suitable respiratory protection" is true, it is misleading, because it suggests to workers they should wear a particulate filter respirator or an organic vapor respirator, although all air-purifying respirators are inadequate to protect artificial stone fabricators from silicosis, because only a NIOSH-approved air supply respiratory can do so.

6. Knowledge of the Silicosis Hazard by Vadara's Officers

1290. Throughout the time that Vadara manufactured and sold its artificial stone products, exposing stone countertop fabricators and installers to respirable crystalline silica from the company's products, Vadara's officers were aware that the company's artificial stone products were defective because they contained extremely high concentrations of crystalline silica, were aware that the use instructions that Vadara provided were inadequate to prevent silicosis and would actually cause silicosis in exposed workers, and were aware that fabrication companies could not protect fabricators and installers from the lethal silicosis hazard presented by Vadara's defective artificial stone products. Among Vadara's officers and directors who had this knowledge but who nevertheless consciously disregarded the health and safety of fabricators and installers are: Stephen A. Schwarzman, Chairman and Chief Executive Officer; Jonathan D. Gray, President & Chief Operating Officer; Hamilton E. James, Executive Vice Chairman; David S. Blitzer, Global Head of Tactical Opportunities; Arik Tendler, Chief Executive Officer; Lee Wood; Robert Butts; Ed Rogers.

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X. CAUSES OF ACTION

A. First Cause of Action - Negligence

1291. Plaintiffs incorporate herein by reference, as though fully set forth herein, the allegations and facts contained in all of the foregoing paragraphs.

1. General Duty of Due Care

1292. A basic tenet of California law is that everyone is required to use ordinary care in their activities so as to regard the safety of others and prevent injury to others from their conduct or omissions. (Civil Code, § 1714, subd. (a); *Williams v. J-M Manufacturing Co., Inc.* (2024) 102 Cal. App.5th 250, 259; *Pedeferri v. Seidner Enterprises* (2013) 216 Cal.App.4th 359, 365; *Cabral v. Ralphs* (2011) 51 Cal.4th 764; *Merrill v. Navegar, Inc.* (2002) 26 Cal.4th 465; *Hilyar v. Union Ice Co.* (1955) 45 Cal.2d 30, 36.) Civil Code § 1714 does not limit responsibility for negligence to a certain class of defendants; rather, it provides that "[e]very one is responsible for an injury occasioned to another by [one's] want of ordinary care or skill." (*Safeco Insurance Co. v. Robert S.* (2001) 26 Cal.4th 758, 764.)

> Negligence may be active or passive in character. It may consist in heedlessly doing an improper thing or in heedlessly refraining from doing the proper thing. Whether the circumstances call for activity or passivity, one who does not do what he should is equally chargeable with negligence with him who does what he should not.

(*Basler v. Sacramento Gas & Electric Co.* (1910) 158 Cal. 514, 518.) Under general negligence principles, everyone is "obligated to exercise due care in his or her own actions so as not to create an unreasonable risk of injury to others, and this legal duty generally is owed to the class of persons

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who it is reasonably foreseeable may be injured as the result of the actor's conduct." (*Lugtu v. California Highway Patrol* (2001) 26 Cal.4th 703, 716 (emphasis added); Cal. Civ. Code, § 1714; see generally Rest.2d Torts, § 281; Prosser & Keeton on Torts (5th ed. 1984) § 31, p. 169; 3 Harper, et al., *The Law of Torts* (2d ed. 1986) § 18.2, 654-655.)

1293. As manufacturers, importers, distributors, suppliers, brokers, designers, testers, and/or contractors of stone slab, block and tile products, Defendants owed Plaintiff a legal duty to exercise due care in manufacturing, designing, testing, importing, producing, supplying, brokering, contracting, and/or distributing stone products to which Plaintiff was exposed in his work as a countertop fabricator and installer.

2. Breach of the General Duty of Due Care

1294. At all times herein mentioned, Defendants, singularly and jointly, failed to use ordinary care to prevent harm to others, negligently acted or failed to act, negligently did things that a reasonably careful person would not do in the same situation, negligently failed to do things that a reasonably careful person would do in the same situation, negligently and carelessly researched or failed to research, manufactured, designed or failed to design, modified or failed to modify, tested or failed to test, warned or failed to warn of the health hazards, failed to provide safe use instructions or provided use instructions that were inadequate and thereby caused harm, labeled or failed to label, assembled, distributed, purchased, offered for sale, supplied, sold, inspected or failed to inspect, marketed, warranted, rebranded, manufactured for others, packaged and advertised, and/or failed to recall the stone products, so that said products proximately caused personal injuries to users, bystanders, family members, and others, including the plaintiff herein (hereinafter collectively called "exposed persons"), while being used in a manner that was reasonably foreseeable, thereby rendering said products and substances unsafe and dangerous for use by exposed persons.

1295. Defendants negligently and carelessly manufactured, designed, imported, produced, sold, tested, failed to test, supplied, contracted, brokered and/or distributed the stone slab and block products to which Plaintiffs were exposed in their work as a countertop fabricators.

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1296. Defendants failed to adequately warn Plaintiffs of the toxic hazards of their stone products and failed to provide adequate instructions to Plaintiffs, how to safely use their products so as to prevent him from developing and suffering from silicosis and other disease.

1297. Defendants, knew, or should have known, that the aforementioned stone products when used as intended, and/or foreseeably misused, would result in the indiscriminate release of toxic and carcinogenic dust, and exposure to "exposed persons," including plaintiff herein.

1298. Plaintiffs used and were otherwise exposed to artificial stone products referred to herein in a manner that was reasonably foreseeable and from the intended use of the stone products.

3. Duties Imposed on Defendants by Statutes and Regulations

1299. Labor Code § 6390.5 is a health and safety statute enacted to protect, among others, workers in the position of Plaintiffs, and imposing on manufacturers and distributors of any hazardous substance the duty to label each container of a hazardous substance consistent with the Hazard Communication Standard. (8 C.C.R. § 5194).

1300. The Hazard Communication Standard (8 C.C.R. § 5194) is a health and safety regulation promulgated to protect, among others, workers in the position of Plaintiffs, and imposing on manufacturers, importers and distributors of chemical products the duty to, among other things:

(a) evaluate their products to determine if they are hazardous [8 C.C.R. § 5194(d)(1)];

(b) identify and consider the available scientific evidence concerning such hazards [8 C.C.R. § 5194(d)(2) et seq.];

(c) consider a product containing at least one percent of a component as presenting the same health hazard as that component [8 C.C.R. § 5194(d)(5)(B)];

(d) consider as carcinogenic a product containing at least 0.1% of a component which has been determined under 8 C.C.R. § 5194(d)(4) to be a carcinogen [8 C.C.R. § 5194(d)(5)(B)];

(e) consider as hazardous a product which contains a component in a concentration of less than one percent which could be released in concentrations which would exceed the established OSHA permissible exposure limit or ACGIH Threshold Limit Value, or could present

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a health hazard to workers in those concentrations [8 C.C.R. § 5194(d)(5)(D)];

(f) consider as carcinogenic a product which contains a component which has been determined under 8 C.C.R. § 5194(d)(4) to be carcinogenic in a concentration of less than .1% which could be released in concentrations which would exceed the established OSHA permissible exposure limit or ACGIH Threshold Limit Value, or could present a health hazard to workers in those concentrations [8 C.C.R. § 5194(d)(5)(D)];

(g) ensure that each container of hazardous chemicals leaving their facilities is labeled, tagged or marked with the (i) identity of the hazardous chemical(s); (ii) appropriate hazard warnings; and (iii) the name and address of the chemical manufacturer or other responsible party [8 C.C.R. § 5194(f)(1)];

(h) obtain or develop a material safety data sheet for each hazardous substance they produced [8 C.C.R. § 5194(g)(1)];

(i) include on the material safety data sheet the chemical and common names of each hazardous substance [8 C.C.R. §5194(g)(2)(A)];

(j) include on the material safety data sheet the health hazards of the hazardous substance, including signs and symptoms of exposure, and any medical conditions which are generally recognized as being aggravated by exposure to the substance [8 C.C.R. § 5194(g)(2)(D)];

(k) include on the material safety data sheet the primary routes of entry [8 C.C.R. § 5194(g)(2)(E)];

(l) include on the material safety data sheet the OSHA permissible exposure limit, ACGIH Threshold Limit Value, and any other exposure limit used or recommended by defendants [8 C.C.R. § 5194(g)(2)(F)];

(m) include on the material safety data sheet whether the hazardous chemical is listed in the National Toxicology Program (NTP) Annual Report on Carcinogens (latest edition) or has been found to be a potential carcinogen in the International Agency for Research on Cancer (IARC) Monographs (latest editions), or by OSHA [8 C.C.R. § 5194(g)(2)(G)];

(n) include on the material safety data sheet generally applicable precautions for safe handling and use known to defendants, including appropriate hygienic practices, protective measures

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during repair and maintenance of contaminated equipment, and procedures for clean-up of spills and leaks [8 C.C.R. § 5194(g)(2)(H)];

(o) include on the material safety data sheet generally applicable control measures known to defendants, such as appropriate engineering controls, work practices, or personal protective equipment [8 C.C.R. § 5194(g)(2)(I)];

(p) include on the material safety data sheet a description in lay terms, if not otherwise provided, of the specific potential health risks posed by the hazardous substance intended to alert the person reading the information [8 C.C.R. § 5194(g)(2)(M)];

(q) ensure that the information contained on material safety data sheets accurately reflects the scientific evidence used in making the hazard determination [8 C.C.R. § 5194(g)(5)];

(r) update material safety data sheets with newly-discovered significant information regarding the hazards of products and/or their components within three months [8 C.C.R. § 5194(g)(5)]; and,

(s) ensure that material safety data sheets complying with the Hazard Communication Standard are provided to employers, directly or via a distributor [8 C.C.R. § 5194(g)(6) & (7)].

1301. Defendants are manufacturers, suppliers, importers, producers, brokers, contractors, and/or distributors of artificial stone products to which Plaintiffs were exposed in the course of their work, and were obligated to comply with California Labor Code § 6390.5 and the Hazard Communication Standard (8 C.C.R. § 5194).

4. Breach of Duties Imposed on Defendants by Statutes and Regulations

1302. Defendants violated California Labor Code § 6390.5 and the Hazard Communication Standard (8 C.C.R. §5194) in the manufacture, importation, supply, brokering, contracting, production, and distribution of their toxic stone products to which Plaintiffs were exposed by:

(a) failing and refusing to evaluate their products to determine if toxic chemicals contained in their products presented a health hazard of causing silicosis and lung disease to workers using or exposed to their products [8 C.C.R. § 5194(d)(1)];

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(b) failing and refusing to identify and consider the available scientific evidence to determine if the toxic chemicals contained in their products presented a health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(d)(2) et seq.];

(c) failing and refusing to identify their products as presenting a health hazard of causing silicosis even though the toxic chemicals contained in their products presented a health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(d)(5)];

(d) failing and refusing to ensure that each container of their products was labeled, tagged or marked to (i) identity the toxic chemicals contained in their products and (ii) appropriately warn that the toxic chemicals contained in their products presented a health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(f)(1)];

(e) failing and refusing to obtain or develop a material safety data sheet for the toxic chemicals contained in their products [8 C.C.R. § 5194(g)(1)];

(f) failing and refusing to include on the material safety data sheet the chemical and common names for the toxic chemicals contained in their products [8 C.C.R. § 5194(g)(2)(A)];

(g) failing and refusing to include on the material safety data sheet that the toxic chemicals contained in their products presented a health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(D)];

(h) failing and refusing to include on the material safety data sheet the primary routes of entry for the toxic chemicals contained in their products in respect of the health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(E)];

(i) failing and refusing to include on the material safety data sheet the OSHA permissible exposure limit, ACGIH Threshold Limit Value, and any other exposure limit used or recommended by defendants for the toxic chemicals contained in their products in respect of the health hazard of causing interstitial lung disease to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(F)];

(j) failing and refusing to include on the material safety data sheet whether the toxic chemicals contained in their products is listed in the National Toxicology Program (NTP) Annual Report on Carcinogens (latest edition) or has been found to be a potential carcinogen in the

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International Agency for Research on Cancer (IARC) Monographs (latest editions), or by OSHA [8 C.C.R. § 5194(g)(2)(G)];

(k) failing and refusing to include on the material safety data sheet generally applicable precautions for safe handling and use known to Defendants for the toxic chemicals contained in their products in respect of preventing the health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(H)];

(l) failing and refusing to include on the material safety data sheet generally applicable control measures known to Defendants for the toxic chemicals contained in their products in respect of preventing the health hazard of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(I)];

(m) failing and refusing to include on the material safety data sheet or otherwise the specific potential health risks posed by the toxic chemicals contained in their products in respect of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(2)(M)];

(n) failing and refusing to ensure that the information contained on material safety data sheets accurately reflects the scientific evidence of the health risks posed by the toxic chemicals contained in their products in respect of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(5)];

(o) failing and refusing to update material safety data sheets with newly-discovered significant information regarding the hazards of the toxic chemicals contained in their products in respect of causing silicosis to workers using or exposed to their products [8 C.C.R. § 5194(g)(5)];

(p) failing and refusing to ensure that material safety data sheets complying with the Hazard Communication Standard (including specifying the potential health risks posed by the toxic chemicals contained in their products in respect of causing silicosis to workers using or exposed to their products) were provided to Plaintiffs' employers, directly or via a distributor. [8 C.C.R. § 5194(g)(6) & (7)]

1303. Plaintiffs, are members of the class of persons designed to be protected by Labor Code § 6390.5 and the Hazard Communication Standard (8 C.C.R. § 5194).

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5. Standard of Care of Manufacturers of Highly Toxic Chemical Products

1304. In addition to the foregoing common law duties of due care and the statutory and regulatory duties that Defendants owed to Plaintiff as manufacturers, importers, and distributors of hazardous chemical products, Defendants, as manufacturers and suppliers of highly toxic chemical products owed special duties of care to Plaintiffs, and other persons who would be exposed to the toxic, fibrogenic, and carcinogenic dust from Defendants' stone products.

1305. Thus, in *Warner v. Santa Catalina Island Co.* (1955) 44 Cal.2d 310, 317, the California Supreme Court wrote: "The risk incident to dealing with fire, firearms, explosive or highly inflammable matters, corrosive or otherwise dangerous or noxious fluids requires a great deal of care to be exercised. In other words, the standard of care required of the reasonable person when dealing with such dangerous articles is so great that a slight deviation therefrom will constitute negligence."

1306. Consistent with the duty of due care that those who manufacture and supply highly toxic chemical products must exercise, Defendants owed Plaintiff and others duties of due care consistent with industrial standards of care of responsible chemical manufacturers and suppliers.

In 1976, Dow Chemical Company published a"Product Stewardship" brochure saying:

> **Responsible Care Commitment.** We are committed to exercising responsible care for our products both in manufacturing and distribution and later in their handling by distributors and use by our customers. This means assessing the environmental impact of the products and then taking appropriate steps to protect employee and public health, and the environment as a whole.
>
> **Responsibilities of Research and Development.** We expect Research and Development to:
>
> Determine that product testing is conducted at each stage of product development so that safety hazards and both short and long range environmental effects can be assessed . . . ."
>
> Give primary consideration to human safety . . . in selecting products for development and sale. . . .
>
> Dow employees, customers, plant communities and the public at large must be considered, as well as both short and long range environmental hazards in the distribution [and] use of our products.
>
> Provide information ... so ... distributors of our products, and customers may be instructed in the safe . . . use . . . of our products.

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> **Responsibilities of Marketing.** We expect Marketing to:
>
> Furnish customers and distributors of Dow products appropriate information to foster the safe handling [and] use of Dow products.
>
> Alert Dow personnel immediately to problems of use involving human or environmental safety and assist in modifications of either products or use patterns, as required, to correct these problems.

1307. In 1991, Dow Chemical Company issued a brochure titled "*Product Stewardship*: Guidelines for Visits to Customer Facilities." This brochure stated:

> **Customer Outreach.** Depending on the hazard potential of the product and the knowledge of the customer, it may be appropriate to visit the customer's facilities to help them understand the safe and proper handling, use, and disposal of our products. Customer visits should be considered whenever: a product is being used for the first time at a location; there is a product health or environmental concern; or, there is a need to better understand how a product is used by the customer.
>
> **Customer Plant Visits.** Most visits at customers' plants will be very positive and require little follow-up beyond the customary letter and any reports. However, occasionally a hazardous situation may be observed in a customer's plant or a product's misuse may be uncovered that demands immediate attention and follow-up.
>
> **Concern for Health and Safety of Customer's Employees.**
>
> If there is serious concern on the use of the product or for the health and safety of the customer's employees, or for the environment, the following steps should be taken:
>
> Inform the customer of your concern and get assurance that the situation will get immediate attention and be corrected by a given date.
>
> Offer to work with the customer and provide information that may assist him to solve his problems.
>
> Review the situation with your product management group and with legal counsel.
>
> Confirm, either by a visit or by a letter from the customer, that the situation has been corrected on the agreed follow-up date.
>
> If insufficient or no corrective action is taken, stop sales to the customer until adequate corrective action is taken.

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1308. In 1998, Gregory G. Bond, Ph.D., Corporate Director of Product Responsibility of The Dow Chemical Company, wrote an article titled "Product Stewardship: A New Mindset," that was reprinted in the March 1998 edition of *Environmental Protection*. Dr. Bond wrote: "Product stewardship is a basic requirement for every business operating in today's atmosphere of concern for the environment. . . . The purpose of product stewardship is obvious: to protect employees, community neighbors, customers and the environment." He wrote: "Our goal is to eliminate all injuries, prevent adverse environmental and health impacts, reduce wastes and emissions and promote resource conservation at every sage of the life cycle of our products." Critically, Dr. Bond wrote: "It is not enough to develop a full EH&S program in your own company. Product stewardship must be transferred to distributors, customers, the customers of customers and other product receivers. This is particularly important for the more hazardous products." Product stewardship transfer involves communicating all relevant EH&S product information to the customer. "Depending on the hazard of the product, it may also involve visiting a customer's or distributor's plant to make sure safe handling and emergency equipment and processes are in place and functioning, and to determine the appropriateness of the customer's application. A responsible producer will not sell a product for inappropriate uses." . . . . Commensurate with risk, there may be a review of the customer's storage, unloading and safe-handling practices. This may also include a pre-delivery inspection of the customer's facilities, periodic reinspections, product safety training for employees, industrial hygiene surveys to determine the exposures of the employees, a dosimeter program to test average exposure over an employee's shift and analytical services if the product hazard necessitates them. In case of any discrepancies noticed during an audit, a remediation program is instituted." The article concluded with the following statement: **"It is our policy to cease sales of a product if the customer . . . is unable or unwilling to take appropriate steps to handle the product safely."** (Emphasis added.)

1309. These industrial standards of care have been implemented by responsible chemical product manufacturers and suppliers not only for toxic liquid chemicals, but also for solid chemical products that result in the formation of airborne toxic dust during fabrication processes.

1310. Brush Wellman has long been the largest producer of beryllium metal and alloys.

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1311. Beryllium and crystalline silica are similar because beryllium is a metal and silica is a metalloid; they are both toxic to the lungs; they both cause pulmonary fibrosis, i.e., they scar the lung; crystalline silica causes "silicosis;" beryllium causes "berylliosis;" they both cause lung cancer.

1312. In 1993, Brush Wellman adopted a policy titled "Promoting Customer Safe Handling Practices" which stated:

> **Purpose.** The following is designed to provide a uniform method for dealing with customers who are observed to be handling Brush [beryllium] products in such a way as to create a real or potential health hazard to their employees and/or customers. The steps outlined hereinafter are designed primarily to curtail such practices in a step-by-step manner in keeping with Brush Wellman's environmental, health and safety policies. BWI has a history of promoting a safe environment for its own employees and the general public. The purpose of the program outlined below is to reaffirm and formalize that policy as much as is reasonably possible for Brush's customers, their employees, and third parties with whom they may have contact. . . .
>
> **Stepwise Approach.** The following is a series of progressive steps aimed toward encouraging the safe handling of our products:
>
> Any new customers or existing customers who are observed to be involved in potentially unsafe practices should be notified and offered available educational, advisory and safe handling programs or materials to include, at a minimum, safe handling videotapes, applicable environmental health and safety sales literature, and where requested, individual training and attention at the customer site. The latter assistance may take the form of customer visit by Brush environmental, safety or medical personnel followed if appropriate by a written advisory report outlining what, if any, steps could be taken to improve the working environment.
>
> If, as a result of any later observation, the customer continues an unsafe practice, reinforcement of the need for proper handling procedures should be made immediately.
>
> If rigorous encouragement fails to correct the practice(s), a written advisory should be prepared and forwarded to the customer outlining our concerns and urging the customer to correct those practices immediately. A follow up to this written advisory should be made by Brush personnel.
>
> If all steps outlined above fail in their purpose and/or the customer affirmatively refuses to correct unsafe practices, consideration must be given to withholding further sale of our products to that customer.

1313. Thus, by the mid-1990s the industrial standard of care among manufacturers and suppliers of highly toxic chemical products, including solid chemical products that emitted toxic,

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fibrogenic, and carcinogenic dust when fabricated, required such companies to monitor the use of their toxic chemical products by their customers, to assure that their customers were using their products safely and in a manner that would not endanger the health and safety of their employees and other persons exposed to their toxic chemical products, to counsel customers who were observed not to be using their products safely, and to cease selling their products to customers who persisted in using their products unsafely, endangering the health and safety of their employees and others.

1314. The standard of care requiring manufacturers and suppliers of highly toxic chemical products to cease sales to customers who endanger the health and safety of their workers has been recognized by companies that sell natural and artificial stone slabs. Thus, Arik Tendler, the former Chief Executive Officer of Surface Warehouse L.P., which distributes Vadara artificial stone slabs, testified as follows: at a deposition in a stone countertop fabricator silicosis case on July 21, 2023:

> It is a basic rule in this industry. If you don't cut wet, you're not a fabricator so I won't even sell the slabs if I know. I am not going to sell you slabs. . . . When we know somebody is working unsafely, we don't sell him.... Usually market reps are the people -- our salespeople are the people that say, "Hey, I don't want to sell him. It is all dry over there." So it is a pretty well-known standard in the industry.

Deposition of Arik Tendler in the case of *Victor Gonzalez et al. v. ADB Global Trade LLC, et al.,* Los Angeles Superior Court Case No. 21STCV06984 at page 318, line 16 to page 319, line 6.

1315. Defendants breached these industrial standards of care by failing to monitor the use of their toxic stone products by customers, by failing to assure that customers were using their products safely, by failing to counsel customers who were not using their products safely, and by failing to cease selling their products to customers who persisted in using their products unsafely, thereby endangering the health and safety of their employees and others exposed to their products.

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6. Plaintiffs' Exposure to Defendants' Stone Products

1316. Plaintiffs all were exposed to Defendants' artificial stone products as alleged above, and to silica, metals and other toxins contained therein and released therefrom as alleged above.

7. Plaintiffs' Need for Medical Monitoring

1317. As a direct and proximate result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins entered Plaintiffs' bodies and remain in Plaintiffs' bodies, thereby causing inflammation and other bodily changes which necessitate lifetime medical monitoring to detect the onset of all silica-related diseases so that Plaintiffs may obtain prompt treatment for such diseases and thereby avoid terminal illness and death.

B. Second Cause of Action for Strict Liability - Defective Product Warnings

1318. Plaintiffs incorporate herein by reference, as though fully set forth herein, the allegations and facts contained in all of the foregoing paragraphs.

1319. At all times mentioned herein, defendants were the manufacturers, importers, and distributors of artificial stone slab, block, and tile products to which Plaintiffs were exposed in fabricating and installing artificial stone countertops.

1320. The artificial stone products which Defendants manufactured, imported, produced, contracted, supplied, brokered and distributed, and to which Plaintiffs were exposed, were defective, because they lacked warnings or contained warnings that were inadequate to apprise Plaintiffs of their toxic hazards and their serious effects upon the human body, and they either lacked instructions for handling and use or lacked instructions adequate to prevent exposure and disease to Plaintiffs, thereby causing serious injury and disease, to wit, silicosis, pulmonary fibrosis and other diseases and medical conditions.

1321. Plaintiffs were occupationally exposed to Defendants' toxic artificial stone products.

1322. Each of the toxic artificial stone products to which Plaintiffs were exposed, was manufactured, designed, imported, distributed, contracted, and/or supplied by Defendants.

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1323. From their use of Defendants' artificial stone products, Plaintiffs were exposed to Defendants' toxic artificial stone products.

1324. Each of the artificial stone products to which Plaintiffs were exposed, was manufactured, imported, distributed and/or supplied by Defendants.

1325. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins within said stone products entered Plaintiffs' bodies.

1326. Plaintiffs have not received medical testing to determine whether they have silicosis, silica-related diseases or any other diseases caused by Defendants' artificial stone products.

1327. As a direct and proximate result of the defective warnings and use instructions of Defendants' stone products, Plaintiffs are at significantly increased risk of developing silicosis and other silica-related diseases.

1328. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins entered Plaintiffs' bodies and remain in Plaintiffs' bodies, thereby causing inflammation and other bodily changes which necessitate lifetime medical monitoring to detect the onset of all silica-related diseases so that Plaintiffs may obtain prompt treatment for such diseases and thereby avoid terminal illness and death.

1329. Defendants' conduct in exposing Plaintiffs to their artificial stone products without adequate warnings of their toxic hazards and without adequate instructions for safe handling and use was despicable, malicious, oppressive, and perpetrated in conscious disregard of the rights and safety of Plaintiffs, entitling Plaintiffs to medical monitoring and, if allowed in this case, punitive damages.

C. Third Cause of Action - Products Liability - Defective Product Design

1330. Plaintiffs incorporate herein by reference, as though fully set forth herein, the allegations and facts contained in all of the foregoing paragraphs.

1331. At all times mentioned herein, Defendants were the manufacturers, importers, distributors and suppliers of artificial stone products to which Plaintiffs were exposed in the course

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of their work as countertop fabricators and installers. Defendants defectively designed their artificial stone products and failed to warn Plaintiffs that their products were defectively designed.

1332. Defendants' stone products were defective in their design because they failed to perform as safely as an ordinary user would expect when used in an intended or reasonably foreseeable manner and the risks inherent in said design outweighed the benefits thereof. Specifically, Defendants' artificial stone products were defective in their design because they contained extremely high concentrations (approximately 93-95%) of crystalline silica, Defendants' products also contained fibrogenic metals and resins which released toxic volatile organic compounds when fabricated using electric powered tools, and because Defendants' artificial stone products released ultrafine and nanosized crystalline silica particles which are extremely toxic to the human body because they are inhaled into the deep recesses of the lungs and are thereupon systemically distributed to bodily tissues where they cause organ toxicity and damage.

1333. Defendants' stone products were also defective in their design because they did not perform as safely as ordinary workers would expect when used or misused in an intended or reasonably foreseeable way.

1334. Defendants knew and intended that their products would be used without inspection and testing for defects therein and without knowledge of the hazards involved in such use. Defendants' products were defective and unsafe for their intended purpose because exposure to artificial stone dust causes accelerated silicosis, other silica-related chronic diseases and death.

1335. These design defects existed in Defendants' artificial stone products when their artificial stone products left defendants' possession.

1336. Each of the toxic artificial stone products to which Plaintiffs were exposed, was manufactured, designed, imported, distributed, and/or supplied by Defendants.

1337. As a direct and proximate result of said design defects, while using Defendants' stone products in a manner that was reasonably foreseeable and intended by Defendants, Plaintiffs were exposed to respirable crystalline silica and other toxins from Defendants' artificial stone products.

1338. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins within said stone products entered Plaintiffs' bodies.

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1339. Plaintiffs have not received medical testing to determine whether they have silicosis, silica-related diseases, or any other diseases caused by Defendants' artificial stone products.

1340. As a direct and proximate result of the defective design of Defendants' artificial stone products, Plaintiffs are at a significantly increased risk of silicosis and other silica-related diseases.

1341. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins entered Plaintiffs' bodies and remain in Plaintiffs' bodies, thereby causing inflammation and other bodily changes which necessitate lifetime medical monitoring to detect the onset of all silica-related diseases so that Plaintiffs may obtain prompt treatment for such diseases and thereby avoid terminal illness and death.

1342. In the case of *Gustavo Reyes-Gonzalez v. ADB Global Trade et al.,* Los Angeles Superior Court Case No. 22STCV31907, a jury rendered a verdict against Defendants, Caesarstone USA, Inc., and Cambria Company, LLC, finding that their artificial stone products were defectively designed, and judgment on the verdict was entered on November 14, 2024, so those two defendants are collaterally estopped from denying their artificial stone products were defectively designed.

1343. The defective design and sale of Defendants' artificial stone products was despicable, malicious, oppressive, and perpetrated in conscious disregard of the rights and safety of Plaintiffs, entitling Plaintiffs to medical monitoring and, if allowed in this case, punitive damages.

D. Fourth Cause of Action - Fraudulent Concealment

1344. Plaintiffs incorporate the allegations and facts contained in the foregoing paragraphs.

1345. Per *Tenet Healthsystem Desert, Inc. v. Blue Cross of California* (2016) 245 Cal.App.4th 821, 838:

> Less specificity is required of a complaint when it appears from the nature of the allegations that the defendant must necessarily possess full information concerning the facts of the controversy; even under the strict rules of common law pleading, one of the canons was that less particularity is required when the facts lie more in the knowledge of the opposite party. Per *Jones v. ConocoPhillips* (2011) 198 Cal.App.4th 1187, the Second Appellate district held that allegations of fraudulent concealment far less than what are stated herein are sufficient to state a cause of action for fraudulent concealment.

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The question of which corporate officer was responsible for the alleged concealment, or ought to have been responsible for disclosure, is a fact which "lie[s] more in the knowledge" of Defendants, and thus need not be pleaded with specificity. *Id.* As the *Jones* court wrote, beginning on pages 1198-1200 of the court's decision (emphasis added):

> Not every fraud arises from an affirmative misstatement of material fact. 'The principle is fundamental that "[deceit] may be negative as well as affirmative; it may consist of suppression of that which it is one's duty to declare as well as of the declaration of that which is false." [Citations.] Thus section 1709 of the Civil Code provides: "One who wilfully deceives another with intent to induce him to alter his position to his injury or risk, is liable for any damage which he thereby suffers." Section 1710 of the Civil Code in relevant part provides: "A deceit, within the meaning of the last section, is either: ... 3. The suppression of a fact, by one who is bound to disclose it, or who gives information of other facts which are likely to mislead for want of communication of that fact...." ' " (*Lovejoy v. AT&T Corp.* (2001) 92 Cal.App.4th 85, 95, 111 Cal.Rptr.2d 711.) "**[T]he elements of a cause of action for fraud based on concealment are: ' "(1) the defendant must have concealed or suppressed a material fact, (2) the defendant must have been under a duty to disclose the fact to the plaintiff, (3) the defendant must have intentionally concealed or suppressed the fact with the intent to defraud the plaintiff, (4) the plaintiff must have been unaware of the fact and would not have acted as he did if he had known of the concealed or suppressed fact, and (5) as a result of the concealment or suppression of the fact, the plaintiff must have sustained damage."** ' " (*Kaldenbach v. Mutual of Omaha Life Ins. Co.* (2009) 178 Cal.App.4th 830, 850, 100 Cal.Rptr.3d 637.)...
>
> The Joneses respond that, "[g]enerally speaking, manufacturers have a duty to warn consumers about the hazards inherent in their products. [Citation.] The requirement's purpose is to inform consumers about a product's hazards and faults of which they are unaware, so that they can refrain from using the product altogether or evade the danger by careful use." (*Johnson v. American Standard, Inc.* (2008) 43 Cal.4th 56, 64–65, 74 Cal.Rptr.3d 108, 179 P.3d 905, citing *Anderson v. Owens–Corning Fiberglas Corp.* (1991) 53 Cal.3d 987, 1003, 281 Cal.Rptr. 528, 810 P.2d 549; accord, *Pannu v. Land Rover North America, Inc.* (2011) 191 Cal.App.4th 1298, 1316, 120 Cal.Rptr.3d 605.) Thus, the Joneses argue, defendants owed a duty to share information about the toxicity of their products with those who could be expected to use those products, namely employees like Carlos, and they as plaintiffs should be permitted to explore the extent of defendants' knowledge of these hazards in discovery without first identifying specific acts by defendants, precisely because defendants alone know when they became aware of the particular hazards associated with their products. Requiring specificity at this juncture, they assert, is neither realistic nor mandated by case law. As one court has aptly observed, "it is harder to apply [the requirement of specificity] to a case of simple nondisclosure. 'How does one show "how" and "by what means" something didn't happen, or "when" it

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never happened, or "where" it never happened?' " (*Alfaro v. Community Housing Improvement System & Planning Assn., Inc.* (2009) 171 Cal.App.4th 1356, 1384, 124 Cal.Rptr.3d 271 (*Alfaro*); see also *Committee on Children's Television, Inc. v. General Foods Corp.* (1983) 35 Cal.3d 197, 217, 197 Cal.Rptr. 783, 673 P.2d 660 [" '[e]ven under the strict rules of common law pleading, one of the canons was that less particularity is required when the facts lie more in the knowledge of the opposite party ...' "].)

These principles are equally pertinent to the scope of defendants' duty to disclose. Although, typically, a duty to disclose arises when a defendant owes a fiduciary duty to a plaintiff (see, e.g., *Goodman v. Kennedy* (1976) 18 Cal.3d 335, 346–347, 134 Cal.Rptr. 375, 556 P.2d 737), a duty to disclose may also arise when a defendant possesses or exerts control over material facts not readily available to the plaintiff. (See, e.g., *Magpali v. Farmers Group, Inc.* (1996) 48 Cal.App.4th 471, 482, 55 Cal.Rptr.2d 225 [" '[t]he duty to disclose may arise without any confidential relationship where the defendant alone has knowledge of material facts which are not accessible to the plaintiff' "].) In *LiMandri v. Judkins* (1997) 52 Cal.App.4th 326, 60 Cal.Rptr.2d 539, a decision relied upon by defendants, each of the circumstances cited by the court in which a duty to disclose may exist absent the presence of a fiduciary relationship concerns the defendant's exertion of control over material facts that were not disclosed to the plaintiff, that is, "when the defendant ha[s] exclusive knowledge of material facts not known to the plaintiff"; "when the defendant actively conceals a material fact from the plaintiff"; or "when the defendant makes partial representations but also suppresses some material facts." (Id. at p. 336, 60 Cal.Rptr.2d 539.)

Here, the amended complaint alleges defendants were "aware of the toxic nature of their products" and "owed a duty to disclose the toxic properties of their products to [Carlos] because [they] alone had knowledge of material facts, to wit the toxic properties of their products, which were not available to [Carlos]." It also alleges defendants owed a duty to disclose because they "made representations regarding their products, but failed to disclose additional facts which materially qualify the facts disclosed, and/or which rendered the disclosures made likely to mislead [Carlos]." These conclusory allegations are supplemented with respect to the single compound, DMF. The Joneses cite studies published as early as 1969 attesting to DMF's toxicity, several years before Carlos began working at Goodyear where he was exposed to the Dow product containing DMF.

At a minimum, the amended complaint states a viable claim for fraudulent concealment against Dow Chemical, the manufacturer of the product Polymide 2080–D/DHV, which allegedly contained DMF. The Joneses have alleged DMF was known to be hazardous as early as 1969, and Dow Chemical concealed the toxic properties of their product, which Carlos would not have used had he been fully advised of its toxicity....

On balance, we conclude the amended complaint does provide adequate notice to the remaining defendants of the material facts they

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> allegedly concealed from Carlos. Based upon the existing allegations, each defendant has received notice of the particular product it made that was used at the Goodyear and Upjohn plants at which Carlos worked. The pleading further alleges these products "contained significant concentrations of organic solvents ... and other toxic chemicals" and "[t]he toxicity of various organic solvents to the liver and kidney has long been recognized." Each defendant is therefore on notice that it allegedly concealed or failed to disclose the toxic properties of the product it sold to Goodyear and Upjohn during the course of Carlos's employment. Although sparse, nothing more is required at this early stage of the litigation.

1346. At all times mentioned herein, Defendants were the manufacturers, designers, importers, distributors and suppliers of artificial stone products which Plaintiffs used and to which they were exposed in the course of their work as countertop fabricators and/or installers.

1347. Defendants' stone products are toxic and fibrogenic to the human lungs.

1348. Prior to Plaintiffs' exposure to Defendants' stone products, Defendants were aware of the toxic and fibrogenic nature of their stone products and that exposure to them causes silicosis.

1349. Pursuant to the Hazard Communication Standard, Defendants were under a legal duty to disclose by labels to Plaintiffs and by Safety Data Sheets to Plaintiffs' employers or hirers both the toxic and fibrogenic properties and hazards of their products and use instructions that were adequate to prevent silicosis and other silica-related diseases.

1350. Pursuant to California common law, Defendants were also under a legal duty to fully disclose the toxic and fibrogenic properties of their artificial stone products directly to Plaintiffs.

1351. Defendants also owed a duty to disclose the toxic hazards of their stone products to Plaintiffs, because Defendants alone had knowledge of material facts, to wit the toxic properties and hazards of their artificial stone products, which were not accessible to Plaintiffs.

1352. Defendants also owed a duty to disclose the toxic hazards of their artificial stone products to Plaintiffs, because Defendants made representations regarding their artificial stone products, but failed to disclose additional facts that materially qualify the facts disclosed, and/or which rendered the disclosures made by Defendants likely to mislead Plaintiffs.

1353. Notwithstanding their knowledge of the extreme toxic and fibrogenic hazards of their artificial stone products, at all material times hereto, Defendants concealed said toxic hazards from Plaintiffs, so that Plaintiffs would use, fabricate, and install Defendants' artificial stone products.

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1354. Prior to Plaintiffs' exposure to Defendants' artificial stone products, Defendants were aware that their artificial stone products contained extremely high concentrations of crystalline silica (approximately 95%), which produced extremely high levels of respirable crystalline silica dust in their ordinary and expected use, when fabricators and/or installers cut, grind, drill, edge, otherwise fabricate and polish and install the artificial stone products as finished countertops, so Defendants' artificial stone products presented extreme hazards and risks to the health of exposed workers, in comparison with natural stone products such as granite (which contains about 35% crystalline silica) and marble (which only contains about 3-5% crystalline silica).

1355. Prior to Plaintiffs' exposure to Defendants' stone products, Defendants were aware that commonly used and recommended protective measures (e.g., use of wet processing methods and air purifying respirators) were inadequate to prevent fabricators and installers from getting silicosis.

1356. Prior to Plaintiffs' exposure to Defendants' stone products, Defendants were aware that Plaintiff's employers lacked knowledge of the extreme toxic hazards of Defendants' stone products and that Plaintiffs' hirers or employers were unaware of the extreme protective measures that are necessary to prevent fabricators and installers from getting silicosis from exposure to Defendants' artificial stone products.

1357. At all times prior to Plaintiffs' exposure to Defendants' artificial stone products, Defendants nevertheless concealed from Plaintiffs and from their employers or hirers the extreme protective measures that are necessary to prevent fabricators and installers from getting silicosis from exposure to Defendants' artificial stone products.

1358. At all times prior to Plaintiffs' exposure to Defendants' artificial stone products, Defendants failed to check and monitor the use of Defendants' stone products to determine whether Plaintiffs' employers or hirers were using the products in such a manner so as not to endanger the health and safety of Plaintiffs, or whether Plaintiffs' employers or hirers were endangering the health and safety of their workers by using Defendants' artificial stone products in such a manner as would cause silicosis, pulmonary fibrosis, other diseases, and death.

1359. At all times prior to Plaintiffs' exposure to Defendants' artificial stone products, Defendants failed to cease selling their toxic and lethal stone products to Plaintiffs' employers or

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hirers, who, even with best efforts and intentions, were incapable of using Defendants' stone products safely, were incapable of protecting fabricators and installers from the respiratory and lethal hazards of Defendants' artificial stone products, and, although they attempted to use Defendants' stone products as directed and intended, were nevertheless endangering the health and safety of their workers by exposing them to the toxic and lethal hazards of Defendants' artificial stone products.

1360. Notwithstanding their knowledge of the carcinogenic, toxic and fibrogenic hazards of their stone products, at all material times hereto, Defendants concealed said hazards from Plaintiffs, so they would use Defendants' artificial stone products in their work.

1361. At all material times hereto, Plaintiffs were unaware of the toxic and fibrogenic of Defendants' artificial stone products and were thereby exposed to respirable crystalline silica and other toxins from Defendants' artificial stone products when they fabricated and/or installed them.

1362. As a direct and proximate result of Defendants' fraudulent concealment of the toxic and fibrogenic hazards of their stone products, Plaintiffs were exposed to Defendants' artificial stone products in the course of their work as countertop fabricators and/or installers.

1363. Each of the toxic artificial stone products to which Plaintiffs were exposed, was manufactured, designed, imported, distributed, and/or supplied by Defendants.

1364. As a direct and proximate result of said design defects, while using Defendants' stone products in a manner that was reasonably foreseeable and intended by Defendants, Plaintiffs were exposed to respirable crystalline silica and other toxins from Defendants' artificial stone products.

1365. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins within said stone products entered Plaintiffs' bodies.

1366. Plaintiffs have not received medical testing to determine whether they have silicosis, silica-related diseases, or any other diseases caused by Defendants' artificial stone products.

1367. As a direct and proximate result of the defective design of Defendants' artificial stone products, Plaintiffs are at a significantly increased risk of silicosis and other silica-related diseases.

1368. As a result of Plaintiffs' exposure to Defendants' artificial stone products, silica, metals and other toxins entered Plaintiffs' bodies and remain in Plaintiffs' bodies, thereby causing inflammation and other bodily changes which necessitate lifetime medical monitoring to detect the

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onset of all silica-related diseases so that Plaintiffs may obtain prompt treatment for such diseases and thereby avoid terminal illness and death.

1369. In exposing Plaintiffs to said toxic and fibrogenic artificial stone products via their fraudulent concealment, Defendants consciously disregarded Plaintiffs' safety despite knowledge of the probable dangerous consequences of their products, and willfully and deliberately failed to avoid said dangerous consequences befalling Plaintiffs. Defendants were either aware of, or culpably indifferent to, unnecessary risks of injury to Plaintiffs and failed and refused to take steps to eliminate or adequately reduce the risk of said dangerous consequences to Plaintiffs. Defendants concealed known hazards of their stone products from Plaintiffs, specifically by failing to warn Plaintiffs of adverse toxic effects of their stone products, and such hazards were known by and such concealment was ratified by the corporate officers and managers of each of the defendants.

1370. Defendants consciously decided to market their artificial stone products with knowledge of their harmful effects and without remedying the toxic effects of their stone products, and such marketing despite knowledge of the foregoing toxic hazards of Defendants' products was ratified by the corporate officers and managers of each of the defendants. Defendants also misrepresented the nature of their artificial stone products, by withholding information from Plaintiff regarding toxic and fibrogenic substances, including silica and metals, released from their products during their anticipated or reasonably foreseeable uses, and such misrepresentation and withholding of information was ratified by the corporate officers and managers of each of the Defendants.

1371. Defendants' conduct in exposing Plaintiffs to their toxic and fibrogenic artificial stone products without adequate warnings of their toxic hazards and without adequate instructions for safe handling and use necessary to prevent disabling lung disease was despicable, malicious, oppressive, and perpetrated in conscious disregard of the rights and safety of Plaintiffs, entitling Plaintiffs to medical monitoring and, if allowed in this case, punitive damages.

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occupational & environmental lung
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XI. PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. Medical Monitoring

For Defendants to contribute sufficient money to a medical monitoring fund to provide Plaintiffs and/or to compensate Plaintiffs for periodic medical examinations, to facilitate the early detection and treatment of all silica-related diseases in accordance with the University of California's Ideal Medical Monitoring Program and such other medical surveillance techniques are in accord with the state of art at the time of class certification and/or trial.

B. Attorney's Fees

For Plaintiffs' reasonable attorney's fees, pursuant to Rule 23(h) of the Federal Rules of Civil Procedure.

C. Costs

For Plaintiffs' costs of suit.

D. Other Relief

For such other relief as the Court deems just and proper.

DATE: January 14, 2026

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DEMAND FOR JURY TRIAL

Pursuant to Rule 38 of the Federal Rules of Civil Procedure, Plaintiffs hereby demand trial by jury of all issues which may be tried to a jury.

DATE: January 14, 2025

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