

Compilation

Recently Published Studies on Chrysotile Fibers – 2025

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1 Habit of elongate amphibole particles as a predictor of mesothelial carcinogenicity. *Toxicol Rep* 2025

Korchevskiy AA, Wylie AG. Habit of elongate amphibole particles as a predictor of mesothelial carcinogenicity. *Toxicol Rep.* 2025 Jan 14;14:101908. doi: 10.1016/j.toxrep.2025.101908. PMID: 39911320; PMCID: PMC11795147.

Korchevskiy and Wylie investigate the relationship between the physical characteristics ("habit") of amphibole particles and their potential to cause mesothelioma. The core argument is that the habit (asbestiform vs. non-asbestiform) of amphibole particles is a significant predictor of their biological activity and carcinogenicity. The authors propose a new metric, the Dimensional Coefficient of Carcinogenicity (DCC), based on particle dimensions, to classify amphiboles and predict their mesothelioma potency. They demonstrate that DCC, along with biosolubility, can accurately predict mesothelioma potency factors. The habit (shape and form) of elongate amphibole particles is a significant predictor of their carcinogenic potential. Specifically, the research suggests that acicular (needle-like) amphibole fibers are more likely to cause mesothelioma compared to other forms of amphibole particles. The authors discovered that amphibole particles with higher aspect ratios (length-to-width ratio) were associated with an increased risk of mesothelioma. The study emphasizes that non-asbestiform amphiboles pose a negligible mesothelioma risk compared to their asbestiform counterparts. This finding supports the idea that longer, thinner fibers are more hazardous than shorter, wider particles and underscore the importance of considering not just the presence of asbestos, but also the specific morphology of the fibers when evaluating potential health risks.

2 A risk assessment of mechanics who changed chrysotile asbestos containing brakes and other vehicle components in the 1950s-early 2000s era: an update on the 2004 evaluation. Crit Rev Toxicol 2025

Brew DW, Stevens ME, Langer AM, Paustenbach DJ. A risk assessment of mechanics who changed chrysotile asbestos containing brakes and other vehicle components in the 1950s-early 2000s era: an update on the 2004 evaluation. Crit Rev Toxicol. 2025 Feb 26:1-50. doi: 10.1080/10408444.2024.2427222. Epub ahead of print. PMID: 40009063.

Brew and co-authors provide a risk assessment update focusing on chrysotile asbestos exposure for mechanics who worked on vehicle brakes and components from the 1950s to the early 2000s. It reviews the toxicology, historical use in automotive products, and exposure studies related to asbestos. The study examines mechanic exposures from gaskets, clutches, and brakes, considering factors like fiber morphology, biopersistence, and thermal degradation. Airborne concentrations of chrysotile fibers during vehicle mechanic work were, on average, less than 0.04 f/cm³ (8-h TWA). The average lifetime cumulative dose was in the vicinity of 0.5–3 f/cm³-year for mechanics of that era. A significant point is the thermal and mechanical degradation of chrysotile asbestos during both the manufacturing process of brake linings and pads, and during the actual braking process. Epidemiological data on mechanics, background mesothelioma rates, bystander exposures, and take-home exposures were also evaluated. The review examines 31 epidemiology studies of vehicle mechanics from this era. "All but one indicate that there was no increased incidence of this disease in these workers." The authors acknowledge possible shortcomings in these studies, but overall, they support the conclusion of de minimis risk. The review addresses the EPA's 2024 risk assessment of chrysotile and their views on asbestos-containing brakes, stating that the EPA's analyses did not change the authors' view that exposures to mechanics posed no increased risk of asbestos-related disease. The authors conclude that the weight of evidence continues to suggest that asbestos-related health risks to vehicle mechanics from asbestos-containing components were de minimis. They also find take-home and bystander exposure posed de minimis or zero health risks.

3 Serpentine and Amphibole Asbestos [A Subset of Elongated Mineral Particles (EMPs)] 2024

Serpentine and Amphibole Asbestos [A Subset of Elongated Mineral Particles (EMPs)] Andrew A. "Tony" Havics and David M. Bernstein, Ph.D. Patty's Toxicology, Seventh Edition. Edited by Dennis Paustenbach, William Farland, Helmut Greim, James Klaunig and Len Levy. Copyright © 2024

This comprehensive chapter by Havics and Bernstein in Patty's Toxicology thoroughly explores the characteristics, uses, and health implications of serpentine and amphibole asbestos. It details the mineralogical forms, chemical properties, and historical uses of asbestos, while also addressing regulatory actions and exposure assessment methodologies. The chapter contrasts the toxicity of chrysotile versus amphibole asbestos, emphasizing the significance of crystal structure, fiber dimensions, biopersistence and acid solubility in the differential ability to develop disease. Industrial applications and regulatory history are reviewed where 90 % of commercial use was chrysotile with amphiboles limited to more niche applications. The toxicological mechanisms of fiber toxicology are based upon fiber biopersistence and dimensions including respirability and fiber length (fibers longer than 20 µm which, if not biosoluble can evade macrophage clearance, inducing chronic inflammation). The epidemiology studies show that chrysotile has limited mesothelioma risk in cohorts with low amphibole contamination (e.g., brake mechanics), while the amphiboles crocidolite exhibits the highest mesothelioma potency, followed by amosite. The high tremolite contamination in vermiculite (Libby, MT) caused significant morbidity. Chrysotile and amphibole asbestos exhibit distinct mineralogical and toxicological profiles, necessitating fiber-specific risk management. While chrysotile's rapid clearance mitigates long-term risks, amphiboles' durability underpins their high pathogenicity. Regulatory frameworks must integrate advanced fiber characterization (TEM) and biopersistence data to refine exposure limits and protect public health. Furthermore, the chapter provides an overview of historical and contemporary exposure levels in occupational and community settings. Quantitative risk models and management strategies are examined, alongside a call for a shift from hazard management to comprehensive risk management in asbestos policy. The chapter also highlights the importance of accurate sampling and analytical methods for assessing asbestos levels in various media (air, bulk materials, soil, water). This distinction between serpentine and amphibole asbestos is crucial for understanding the potential health risks associated with different types of asbestos exposure and for developing appropriate risk management strategies.

4 Cancer mortality in chrysotile miners and millers, Russian Federation: main results (Asbest Chrysotile Cohort-Study). J Natl Cancer Inst 2024

Schüz J, Kovalevskiy E, Olsson A, Moissonnier M, Ostroumova E, Ferro G, Feletto E, Schonfeld SJ, Byrnes G, Tskhomariia I, Straif K, Morozova T, Kromhout H, Bukhtiyarov I. Cancer mortality in chrysotile miners and millers, Russian Federation: main results (Asbest Chrysotile Cohort-Study). J Natl Cancer Inst. 2024 Jun 7;116(6):866-875. doi: 10.1093/jnci/djad262. PMID: 38247448; PMCID: PMC11160488.

The publication by Schuz and co-authors is one of the most important recent studies in that it investigated mortality in workers of the world's largest chrysotile mine and enrichment factories located in the town of Asbest, Russian Federation. The study's main objective was to investigate cancer mortality in workers occupationally exposed to chrysotile asbestos, particularly to obtain more precise quantification of site-specific cancer risks in a large workforce that had not been systematically studied before. This "Asbest Chrysotile Cohort Study," is large-scale epidemiological investigation into the mortality experience of workers at the world's largest chrysotile mine and enrichment factories in Asbest, Russian Federation. The study, conducted by the International Agency for Research on Cancer (IARC) and Russian collaborators, aimed to quantify site-specific cancer risks associated with occupational exposure to chrysotile asbestos. The study included 30,445 workers (32% women) employed for at least one year between 1975 and 2010 at the Uralasbest mining and milling operations. Follow-up extended to the end of 2015, accumulating 721,312 person-years at risk. The authors reported that for lung cancer in men, there was a statistically significant exposure-response relationship between cumulative dust exposure and lung cancer mortality ($P_{\text{trend}} = .02$). No association was found for women. *However, interestingly enough, the authors do not specifically discuss that there was no statistically significant association with lung cancer when based upon chrysotile fiber exposure. These were relegated to the Supplementary material tables.* Based on 13 deaths from mesothelioma out of 30,445 workers, for both sexes combined (there were too few cases of mesothelioma to analyse by sex. In addition, there was no discussion of the age or length of employment of the cases and when in time they worked.) Based on these 13 cases a statistically significant increased risk of mesothelioma mortality was observed with high fiber exposure (at least 80 fibers per cm^3 years) and high dust exposure (at least 150 mg/m^3 years).

5 Evaluation of airborne asbestos concentrations associated with the maintenance of brakes on an industrial overhead crane. *Inhalation Toxicology* 2024

Ferracini T, Brown S, Simmons B, Avens H, Gaffney S, Dotson S, Sahmel J. Evaluation of airborne asbestos concentrations associated with the maintenance of brakes on an industrial overhead crane. *Inhal Toxicol.* 2024 Jul;36(6):391-405. doi: 10.1080/08958378.2024.2367422. Epub 2024 Jul 2. PMID: 38952303.

Ferracini and co-authors evaluated potential airborne asbestos exposures during brake maintenance and repair activities on an industrial overhead crane, specifically a P&H CB-16 Clapper Type Brake. Personal and area airborne fiber concentrations were monitored during various tasks including brake tests, removal, hand sanding, compressed air use, and reattachment of chrysotile-containing brake linings. Potential exposure during the handling of the mechanic's clothing was also assessed. The study found that all brake linings contained chrysotile asbestos (19.9% to 52.4%), but no amphibole fibers were detected. Importantly, the study concluded that all personal and area time-weighted average (TWA) fiber concentrations measured during crane brake maintenance and clothes handling tasks were below the current OSHA 8-hour TWA Permissible Exposure Limit (PEL) for asbestos of 0.1 f/cc and the 30-minute Excursion Limit (EL) of 1 f/cc. Following manufacturer's procedures resulted in no measurable airborne chrysotile fibers. While the exposures were below regulatory limits, minimizing exposure is still a prudent approach when dealing with asbestos-containing materials. The study adds to the existing body of knowledge on asbestos exposure in brake maintenance, with a specific focus on industrial overhead cranes.

6 Occupational exposures to asbestos in the steel industry: An analysis of the AISI sampling campaign (1989-1997). *J Occup Environ Hyg* 2024

Stevens ME, Brew DW, Paustenbach DJ. Occupational exposures to asbestos in the steel industry: An analysis of the AISI sampling campaign (1989-1997). *J Occup Environ Hyg*. 2024 May-Jun;21(6):439-449. doi: 10.1080/15459624.2024.2328804. Epub 2024 Apr 12. PMID: 38608274.

Stevens and co-authors analyzed a previously unorganized dataset of asbestos exposure measurements taken in American steel mills from 1989-1997. The data, collected by the American Iron and Steel Institute (AISI), includes 520 samples from five companies and evaluates airborne asbestos concentrations related to various tasks and asbestos-containing materials (ACMs). This analysis found that the airborne asbestos concentrations generated due to interactions with asbestos-containing materials (ACMs) in steel mills from 1989 to 1997, and likely well before these dates, were far below regulatory guidance values. The mean concentration for all the representative workday samples (sampling duration of 180 min or greater) collected was 0.02 f/cc (which is 1/5th the prevailing PEL), and the mean of samples with sampling times less than 180 min was 0.06 f/cc (which is less than 1/16th the prevailing EL). The airborne asbestos concentrations in steel mills during this period were generally low and frequently below regulatory limits, indicating effective control measures and a phasing out of asbestos-containing materials (ACMs). The study also highlights the limitations of using Phase Contrast Microscopy (PCM), which may overestimate asbestos concentrations due to counting non-asbestos fibers and the likely presence of respiratory protection used by workers.

7 Asbestos exposures associated with the use and handling of drilling mud additives. *Toxicol Ind Health* 2024

Anderson E, Holton M, Ellis J, Meyler S, Adams R, Daniel G. Asbestos exposures associated with the use and handling of drilling mud additives. *Toxicol Ind Health*. 2024 Jul;40(7):366-375. doi: 10.1177/07482337241249548. Epub 2024 May 5. PMID: 38706164.

Anderson and co-authors analyzed historical asbestos exposure data from 1972-1985 related to drilling mud additives (DMAs) on oil and gas rigs. The research examines 1,171 air samples to assess airborne fiber concentrations during the handling of short-fiber chrysotile asbestos collected from over 20 drilling rigs. The average airborne fiber concentrations measured during asbestos handling activities ranged from 0.62 f/cc to 3.39 f/cc using phase-contrast microscopy (PCM). Eight-hour time-weighted average (8-h TWA) results, calculated using short-term samples, along with long-term samples greater than 240 min, did not exceed contemporaneous Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs). Asbestos-containing DMAs were rarely used on drilling rigs and for only short periods of time (e.g., an average of nine bags were dumped per sampling event, and dumping activities occurred for about 30 min). When the use of asbestos-containing DMA was indicated, additions would typically be made manually once per day in small amounts, rarely exceeding 500 pounds at a time. The analysis concludes that exposures related to asbestos-containing DMAs were of short duration and limited quantity. The study found that both short-term and full-shift (calculated 8-hour time-weighted average or TWA) exposures were below the contemporaneous OSHA permissible exposure limits (PELs). The authors suggest that these exposures would not reasonably be expected to confer a significant risk of asbestos-related disease.

8 Quantitative assessment of mesothelioma and lung cancer risk based on Phase Contrast Microscopy (PCM) estimates of fibre exposure: an update of 2000 asbestos cohort data. *Environmental Research* 2023

Darnton L. Quantitative assessment of mesothelioma and lung cancer risk based on Phase Contrast Microscopy (PCM) estimates of fibre exposure: an update of 2000 asbestos cohort data. *Environ Res.* 2023 Aug 1;230:114753. doi: 10.1016/j.envres.2022.114753. Epub 2023 Mar 23. PMID: 36965802.

Darnton presents an updated meta-analysis of asbestos-related mesothelioma and lung cancer risks based on exposure estimates using Phase Contrast Microscopy (PCM). It builds upon previous work by Hodgson and Darnton (2000), incorporating new studies and refining the quantitative relationship between cumulative asbestos exposure (by fibre type) and cancer incidence. The study aims to provide a more precise assessment of the risk associated with different asbestos fibre types (particularly chrysotile, amphibole, and mixed exposures) and to evaluate the linearity of the exposure-response relationship. The findings suggest variations in risk depending on fibre type and the cohort examined, emphasizing the complexities of asbestos-related cancer risk assessment. The updated analysis attempts to address some of the limitations in previous meta-analyses, particularly concerning the non-linearity of exposure-response curves and the heterogeneity of exposure scenarios. A key focus is on differentiating the risks associated with different asbestos fibre types: chrysotile, amphiboles (crocidolite and amosite), and mixed exposures. The results point to variations in the risk per unit exposure for different fibre types: "The cumulative mesothelioma risks (per cent of total expected mortality) per unit cumulative exposure (f/cc.yr), R_m , were 0.51 for crocidolite; 0.14 for amosite; and amphiboles and chrysotiles with significant heterogeneity was present for cohorts classed as chrysotile, with R_m values of 0.01 for chrysotile textiles cohorts and 0.0014 for chrysotile mining cohorts."

9 Toxicological and epidemiological approaches to carcinogenic potency modeling for mixed mineral fiber exposure: the case of fibrous balangeroite and chrysotile. *Inhalation Toxicology* 2023

Korchevskiy AA, Wylie AG. Toxicological and epidemiological approaches to carcinogenic potency modeling for mixed mineral fiber exposure: the case of fibrous balangeroite and chrysotile. *Inhal Toxicol.* 2023 Jan-Dec;35(7-8):185-200. doi: 10.1080/08958378.2023.2213720. Epub 2023 May 23. PMID: 37220304.

Korchevskiy and Wylie examine the carcinogenic potential of fibrous balangeroite, a mineral found alongside chrysotile in the Balangero mine in Italy, and its possible role in elevated mesothelioma cases among mine workers. The study combines toxicological and epidemiological approaches to model the carcinogenic potency of balangeroite by analyzing its fiber dimensions using transmission electron microscopy. The authors compare balangeroite's characteristics to other mineral fibers, estimate its contribution to observed mesothelioma cases, and reconstruct its biopersistence in human lungs. By considering mixed fiber exposures, they aim to better understand cancer risks associated with complex mineral environments. The findings suggest that even small proportions of minerals like balangeroite can significantly influence overall cancer risk, with a potential carcinogenic potency that is substantial.

10 The health effects of short fiber chrysotile and amphibole asbestos. Crit Rev Toxicol 2022

Bernstein DM. The health effects of short fiber chrysotile and amphibole asbestos. Crit Rev Toxicol. 2022 Feb;52(2):89-112. doi: 10.1080/10408444.2022.2056430. Epub 2022 Jun 15. PMID: 35703172.

Bernstein examined the toxicity of short asbestos fibers, particularly chrysotile, and amphibole, analyzing their impact on human health. It examines epidemiology, toxicology, and in-vitro studies to understand the effects of short fibers compared to longer ones. This review highlights that short fibers are generally considered less harmful due to their clearance mechanisms in the respiratory system. The epidemiology studies used for determining cancer potency estimates were based upon relatively high exposure concentrations and provide a conservative assessment that shorter fibers would have little, if any, effect, especially under controlled exposure or environmental conditions that may occur today. QSAR models have shown that fiber aspect ratio and Mg content are excellent predictors of cancer potency and that short fibers/particles of amphibole would have no effect. The studies of motor vehicle mechanics and, in particular, workers who serviced chrysotile containing brakes with the majority of the fibers being short provides further evidence that motor vehicle mechanics, including workers who were engaged in brake repair, are not at an increased risk of mesothelioma. Several inhalation toxicology studies clearly differentiated that short chrysotile and amphibole asbestos fibers did not produce a significant carcinogenic effect in the lung or pleural cavity. It also addresses the limitations of past studies and the importance of accurate fiber characterization. The review concludes with a summary of findings, emphasizing the negligible health risks associated with short asbestos fibers in controlled exposures.

11 Asbestos exposure, lung fiber burden, and mesothelioma rates: Mechanistic modelling for risk assessment. Computational Toxicology 2022

Korchevskiy A.A., Wylie A.G. (2022). Asbestos exposure, lung fiber burden, and mesothelioma rates: Mechanistic modelling for risk assessment. Computational Toxicology, 24, 100249.

Korchevskiy and Wylie investigated the link between the shape of amphibole particles and their potential to cause mesothelioma. The authors focused on tremolite, analyzing asbestiform (fibrous) and non-asbestiform (massive) varieties. By using mathematical modeling, they developed a new metric, the Dimensional Coefficient of Carcinogenicity (DCC), to distinguish between these forms based on their dimensions and predict mesothelioma potency. The model utilizes first-order kinetics to describe the uptake and removal of asbestos fibers from human lungs. The model was tested using data from a British case-control study. The study estimates elimination coefficients for different asbestos fiber types and demonstrates how lung burden changes with exposure intensity and duration, and how recent exposure events influence lung burden more significantly than earlier ones. For several mineral types (crocidolite, amosite, Libby amphiboles, anthophyllite, chrysotile, and erionite), it was demonstrated that mesothelioma potency factors can be predicted based on DCC and biosolubility with a high level of accuracy ($R=0.98$, $R^2=0.96$, $p < 0.006$). It was demonstrated that modeled mesothelioma potency correlates with relative potency for pleural instillation in Wistar rats and correlates inversely with membranolytic toxicity index HC50. Mesothelioma potency was demonstrated to be negligible in all non-asbestiform sets. The model determined the following estimated fiber elimination coefficients: Crocidolite: 0.099 years⁻¹; Amosite: 0.169 years⁻¹; and Chrysotile: 6.45 years⁻¹. These values generally align with previously published estimations. The authors also examined the dimensional distribution of fiber width and aerodynamic diameters of fiber in the lungs. They found that the width of fibers in human lungs in seemed to be lower than is typical of the minerals in exposed populations, and correspondingly the aerodynamic diameter decreases from exposure to lung burden. The authors suggested that for each mineral type, the wider particles are cleared more efficiently than, the thinner varieties, or otherwise they do not reach the alveolar space being filtered in the upper respiratory tract, and or that wider fiber bundles disaggregate to form thin single fibrils. *However, they also stated that this would not hold if chrysotile were compared to amphibole because chrysotile is the quickest to dissolve in human lungs and has the lowest median width among the observed mineral types. Also, the retained particles of slowly clearing asbestiform tremolite apparently are wider than chrysotile, amosite, or crocidolite.*

12 Final results from a 90-day quantitative inhalation toxicology study evaluating the dose-response and fate in the lung and pleura of chrysotile-containing brake dust compared to TiO₂, chrysotile, crocidolite or amosite asbestos: Histopathological examination, confocal microscopy and collagen quantification of the lung and pleural cavity. *Toxicol Appl Pharmacol* 2021

Bernstein DM, Toth B, Rogers RA, Kunzendorf P, Phillips JI, Schaudien D. Final results from a 90-day quantitative inhalation toxicology study evaluating the dose-response and fate in the lung and pleura of chrysotile-containing brake dust compared to TiO₂, chrysotile, crocidolite or amosite asbestos: Histopathological examination, confocal microscopy and collagen quantification of the lung and pleural cavity. *Toxicol Appl Pharmacol*. 2021 Aug 1;424:115598. doi: 10.1016/j.taap.2021.115598. Epub 2021 May 30. PMID: 34077769. This publication was preceded by two interim publications on the same study providing more detail¹.

Bernstein and co-authors report on a comprehensive inhalation toxicology study of inhaled brake dust containing chrysotile asbestos in rats, comparing it to the effects of TiO₂ (a low-toxicity particle), chrysotile alone, and two amphibole asbestos types (crocidolite and amosite). The exposure groups were as follows:

- Air Control
- Low (0.2 mg/m³ with 2 WHO f/cm³), Mid (0.34 mg/m³ with 5 WHO f/cm³), and High (0.7 mg/m³ with 7 WHO f/cm³) doses of brake dust containing chrysotile
- Titanium Dioxide (TiO₂) (0.7 mg/m³) as a low-toxicity particle control
- Low (119 WHO f/cm³ with 28 f/cm³ > 20 μm) and High (233 WHO f/cm³ with 72 f/cm³ > 20 μm) doses of Chrysotile alone
- High (181 WHO f/cm³ with 23 f/cm³ > 20 μm) dose of Crocidolite Asbestos
- High (281 WHO f/cm³ with 48 f/cm³ > 20 μm) dose of Amosite Asbestos

The study assessed pathological responses and tumorigenicity after 90 days of exposure, followed by a lifetime observation period. The key finding is that brake dust with chrysotile did not produce significant pathological or tumorigenic responses in the respiratory tract, even at exposure levels exceeding those experienced by humans. In addition, chrysotile was not biopersistent, exhibiting in the lung a deterioration of its matrix, which resulted in breakage into particles and short fibers, which could then be cleared by alveolar macrophages and which could continue to dissolve. This contrasts sharply with the amphibole asbestos groups, which exhibited significant inflammation, fibrosis, and tumor development following the 90 day exposure with life time observation. Approximately 10,500,000 fibers L > 20 μm per lung were observed at 12 months. The tumors in the crocidolite and amosite exposure groups were considered to be exposure-related. Numerous amphibole fibers, both long and short, including fibers longer than 40 μm, with alveolar macrophages and granulomas, were present in the lung. This is accompanied by an extensive collagen matrix that persists through 24 months. Increased collagen and mesothelial thickness were also observed in both the

¹ Interim publications on the same study providing more detail: Bernstein DM, Toth B, Rogers RA, Kling DE, Kunzendorf P, Phillips JI, Ernst H. Evaluation of the exposure, dose-response and fate in the lung and pleura of chrysotile-containing brake dust compared to TiO₂, chrysotile, crocidolite or amosite asbestos in a 90-day quantitative inhalation toxicology study - Interim results Part 1: Experimental design, aerosol exposure, lung burdens and BAL. *Toxicol Appl Pharmacol*. 2020 Jan 15;387

Bernstein DM, Toth B, Rogers RA, Kling DE, Kunzendorf P, Phillips JI, Ernst H. Evaluation of the dose-response and fate in the lung and pleura of chrysotile-containing brake dust compared to TiO₂, chrysotile, crocidolite or amosite asbestos in a 90-day quantitative inhalation toxicology study - Interim results Part 2: Histopathological examination, Confocal microscopy and collagen quantification of the lung and pleural cavity. *Toxicol Appl Pharmacol*. 2020 Jan 15;387

visceral and parietal pleural. Confocal microscopy further confirmed these findings, showing increased collagen and mesothelial thickness in amphibole-exposed groups only. Amphibole fibers $L > 20 \mu\text{m}$ in the crocidolite and amosite exposure groups cleared with $T_{1/2}$ of 518 and 13,446 days, respectively. The study demonstrates a clear difference in the pathological response and tumorigenicity between brake dust with chrysotile, chrysotile alone, and amphibole asbestos. The study demonstrates a clear difference in the pathological response and tumorigenicity between brake dust with chrysotile, chrysotile alone, and amphibole asbestos. The lack of significant response to brake dust is attributed to the low biopersistence of chrysotile. Its structure allows it to break down into smaller particles that can be cleared by macrophages or dissolved. The study highlights the role of chronic inflammation in the development of cancer, as observed with the amphibole asbestos exposure, where long, durable fibers cause persistent inflammation and tissue injury. The exposure concentrations in this study were significantly higher than those historically reported for human exposure to brake dust, suggesting a wide margin of safety.

13 A critical review of the 2020 EPA risk assessment for chrysotile and its many shortcomings. Crit Rev Toxicol 2021

Paustenbach D, Brew D, Ligas S, Heywood J. A critical review of the 2020 EPA risk assessment for chrysotile and its many shortcomings. *Crit Rev Toxicol*. 2021 Jul;51(6):509-539. doi: 10.1080/10408444.2021.1968337. Epub 2021 Oct 15. PMID: 34651555.

Paustenbach and co-authors critically review the EPA's 2020 risk assessment of chrysotile asbestos, questioning its scientific rigor and methodology. The authors highlight shortcomings such as the EPA's reliance on a Science Advisory Committee lacking sufficient expertise and the use of flawed systematic review processes. In addition, they challenge the EPA's assumptions about current exposures to asbestos, particularly in brake and gasket work, citing evidence of low or nonexistent exposures. The review also addresses concerns regarding the EPA's cancer potency factor for chrysotile and the use of the linear no-threshold model. Ultimately, the authors argue that the EPA's assessment could lead to unwarranted litigation and propose recommendations for a more scientifically sound evaluation. They stress the need for expert panels to evaluate the EPA's process and the scientific basis for their actions. The document asserts that a proper risk evaluation is needed to avoid misrepresenting potential dangers from working with products that contained asbestos.

14 Modeling mesothelioma risk factors from amphibole fiber dimensionality: mineralogical and epidemiological perspective. Journal of Applied Toxicology, 2020

Wylie, A.G., Korchevskiy, A., Segrave, A.M., & Duane, A. (2020). Modeling mesothelioma risk factors from amphibole fiber dimensionality: mineralogical and epidemiological perspective. *Journal of Applied Toxicology*, 1-10. <https://doi.org/10.1002/jat.3923>

Wylie and co-authors explore the correlation between amphibole fiber dimensions and mesothelioma risk. The authors modeled mesothelioma potency (RM) using data from mining and milling cohorts, focusing on the proportion of elongated mineral particles with specific width and length parameters. The models aim to quantify RM for amphibole occurrences, even where epidemiological data is lacking. Results indicate that narrower fibers are more potent, and the models can predict RM for different amphibole types. Asbestosis and lung cancer may be related to longer or wider fibers that may be preferentially retained by the lung. The findings have implications for risk assessment, public policy, and regulations regarding exposure to elongated mineral particles. The study emphasizes that fiber dimensionality and mineralogical composition are crucial factors in determining mesothelioma risk.

15 The toxicology of chrysotile-containing brake debris: implications for mesothelioma. Crit Rev Toxicol 2019

Poland CA, Duffin R. The toxicology of chrysotile-containing brake debris: implications for mesothelioma. *Crit Rev Toxicol*. 2019 Jan;49(1):11-35. doi: 10.1080/10408444.2019.1568385. Epub 2019 Mar 15. PMID: 30873891.

Poland and Duffin examine the toxicity of chrysotile asbestos found in brake debris and its relationship to mesothelioma. They explore how the physicochemical properties of chrysotile, released during brake maintenance, might be modified, potentially altering its toxicity profile. The authors investigate factors like fiber length, biopersistence, heat modification, and interactions with the resin matrix in brake pads. They review epidemiological studies, analyzing the incidence of asbestos-associated diseases in mechanics, and considers the significance of the biological effective dose. Epidemiological and meta-analysis studies, in terms of weight of evidence, show no significant risk of malignant mesothelioma in mechanics working with such chrysotile-containing friction products. Ultimately, the article suggests that modifications to chrysotile in brake debris could explain the apparent disconnect between exposure and the risk of developing mesothelioma. The study calls for further research on the characteristics of released particles to better understand their potential health impacts.

16 Empirical model of mesothelioma potency factors for different mineral fibers based on their chemical composition and dimensionality. *Inhalation Toxicology* 2019

Korchevskiy A, Rasmuson JO, Rasmuson EJ. Empirical model of mesothelioma potency factors for different mineral fibers based on their chemical composition and dimensionality. *Inhal Toxicol.* 2019 Apr;31(5):180-191. doi: 10.1080/08958378.2019.1640320. Epub 2019 Jul 22. PMID: 31328588.

Korchevskiy and co-authors have developed an empirical model to predict the mesothelioma potency of different mineral fibers. The model uses the chemical composition and dimensionality (aspect ratio) of fibers to reconstruct potency factors. It identifies key factors like silicon dioxide (SiO₂), iron oxides, magnesium oxide (MgO), and aspect ratio as influential in determining a fiber's ability to cause mesothelioma. The study uses a statistical approach to correlate these factors with mesothelioma potency based on data from various asbestos types and erionite. The derived models demonstrate that higher aspect ratios and increased SiO₂ and iron oxide content are associated with greater potency, while higher MgO content correlates with lower potency. The authors clarify that while iron is a stoichiometric component (about 27%, w/w) in amphiboles such as crocidolite and amosite, in chrysotile, it is a contaminant (about 1–6%, w/w), replacing isomorphous magnesium and silicon. *Chrysotile is composed of about 40 % MgO, while most crocidolite and amosite have less than 6 %, thus indicating that chrysotile correlates with lower potency.* The authors further state that it is remarkable that a combination of aspect ratio of fibers and Mg fraction by itself allows to model mesothelioma potency factor with good accuracy, though with a slightly lower correlation coefficient. The research suggests a starting point for further studies into the toxicological mechanisms of mesothelioma and seeks to ultimately develop quantitative structure-activity relationship approaches for understanding the dangers of mineral fibers.

17 Standardized methods for preparation and bi-variate length & diameter counting/sizing of aerosol and tissue digestion fiber samples. *Toxicology and Applied Pharmacology* 2018

Bernstein DM, Kunzendorf P. Standardized methods for preparation and bi-variate length & diameter counting/sizing of aerosol and tissue digestion fiber samples. *Toxicol Appl Pharmacol.* 2018 Dec 15;361:174-184. doi: 10.1016/j.taap.2018.04.026. Epub 2018 Apr 27. PMID: 29705294.

Bernstein and Kunzendorf's 2018 paper provides standardized methods for preparing and sizing fiber samples from aerosols and digested tissues. The study emphasizes the importance of accurately representing fiber length distributions, as longer fibers are considered more relevant in pathogenesis. The methods, refined over years of experience, focus on optimizing fiber counting and sizing rules for particles and fibers in specific size ranges. The described methods aim to provide a stable estimate of the number of particles and fibers present in specific size ranges. In order to do so, samples were counted and sized as follows: Particles; fibers < 5 μm ; Fibers 5–20 μm ; and Fibers > 20 μm .

- For fibers with a length $\leq 5 \mu\text{m}$ = 100 fibers (200 fiber ends)
- For fibers with a length between 5 and 20 μm = 200 fibers (400 fiber ends)
- For fibers with a length > 20 μm = 100 fibers (200 fiber ends)

The authors advocate for the use of high-resolution SEM over TEM due to its higher reproducibility and ability to analyze larger sample areas. These techniques are applicable to various fiber types, including synthetic vitreous fibers and asbestos, and are crucial for comparing fiber distributions in different sample types. The study also provides guidance on statistical analysis and addresses potential conflicts of interest.

18 Proceedings of The Monticello Conference on Elongate Mineral Particles (EMP). *Toxicol Appl Pharmacol* 2018

Weill D. Proceedings of The Monticello Conference on Elongate Mineral Particles (EMP). *Toxicol Appl Pharmacol*. 2018 Dec 15;361:1-2. doi: 10.1016/j.taap.2018.11.005. PMID: 30558741.

The Monticello Conference on Elongate Mineral Particles (EMP) convened experts to address the complexities of defining and assessing the health risks associated with EMPs. The conference aimed to clarify terminology, investigate disease mechanisms, and discuss human exposure risks. Key conclusions included the need to move beyond simple aspect ratio characterization and to focus on disease-specific research. Discussions highlighted the importance of fiber dimensions and biopersistence in determining toxicity, while also addressing the role of emerging materials like carbon nanotubes. The conference also explored the development of predictive models for fiber toxicity assessment. Funded by the National Stone, Sand, and Gravel Association, the proceedings reflect diverse opinions and insights into the multifaceted nature of EMP-related health concerns. Concerning mechanisms of toxicity, "There was broad consensus that what happens at the lung level is based on a population of fibers getting to the deep part of the lung and not based on one EMP interacting with one lung cell." "For EMPs that are long and durable, decreasing widths result in increasing carcinogenic potential." "EMPs with length less than 5 microns present insignificant risk for EMP-related cancer." Sufficiently high and prolonged inhalation exposures to some respirable EMPs can increase the risk of diseases like malignant mesothelioma and lung cancer, with chronic inflammation playing a crucial causal role. The physical characterization of retained EMPs from the lungs is extremely important in providing information regarding the etiology of the disease they may produce. In addition, they agreed that "Thresholds exist for excess disease risk from the inhalation of EMPs. Subthreshold exposures do not result in human disease development."

19 Past and current asbestos exposure and future mesothelioma risks in Britain: The Inhaled Particles Study (TIPS). *Int J Epidemiol* 2018

Gilham C, Rake C, Hodgson J, Darnton A, Burdett G, Peto Wild J, Newton M, Nicholson AG, Davidson L, Shires M, Treasure T, Peto J; TIPS Collaboration. Past and current asbestos exposure and future mesothelioma risks in Britain: The Inhaled Particles Study (TIPS). *Int J Epidemiol*. 2018 Dec 1;47(6):1745-1756. doi: 10.1093/ije/dyx276. PMID: 29534192; PMCID: PMC6280925.

Gilham and co-authors investigate the relationship between asbestos lung burden and mesothelioma risk in Britain. The study aimed to predict future mesothelioma rates based on the lung burdens of workers and the general population, particularly those born after asbestos use largely ceased in the UK (post-1980). The authors conclude that while environmental asbestos exposure presents a lower risk now (approximately 1 in 10,000 lifetime risk for those born since 1965), certain exposed workers and occupants of contaminated buildings still face significantly higher risks. The study focused on amphibole fibers (amosite and crocidolite) due to their longer half-life in the lungs and greater association with mesothelioma. Chrysotile (white asbestos) is largely ignored in the analysis, even though it constituted 88% of UK asbestos imports between 1955 and 1990 but only 2% of asbestos fibres in the lungs of men with mesothelioma or lung cancer, born 1940–64. The authors state that "Chrysotile (white asbestos) fibres are ignored in our analyses which are based on amphibole fibres, mainly amosite (brown asbestos) and crocidolite (blue asbestos). our data because its half-life in the lung is too short for lung burden to reflect lifetime exposure."

20 History of knowledge and evolution of occupational health and regulatory aspects of asbestos exposure science: 1900-1975. Crit Rev Toxicol 2017

Barlow CA, Sahmel J, Paustenbach DJ, Henshaw JL. History of knowledge and evolution of occupational health and regulatory aspects of asbestos exposure science: 1900-1975. Crit Rev Toxicol. 2017 Apr;47(4):286-316. doi: 10.1080/10408444.2016.1258391. Epub 2017 Mar 22. PMID: 28328293

Barlow and co-authors provide a comprehensive overview of the historical development of asbestos-related occupational health knowledge and regulations during the 20th century. This paper traces the evolution of scientific understanding and regulatory approaches to asbestos exposure over a 75-year period from the early 1900s to the mid-1970s. Barlow's publication examines the evolution of regulatory measures implemented to address asbestos exposure in occupational settings. Initially, the dangers of high concentrations of asbestos dust were recognized, but the carcinogenic nature wasn't widely understood until the mid-1950s. Advancements in sampling methods (membrane filter) in the late 1960s and early 1970s allowed for a more precise characterization of exposure-response relationships, leading to the establishment of Occupational Exposure Levels (OELs). The introduction of various safety standards, exposure limits, and protective measures over time are reviewed. The paper also explores how the asbestos industry responded to emerging scientific evidence and regulatory pressures during this period. It is interesting to note that Merewether, in 1952, commented on the physical and chemical differences between chrysotile, amosite, crocidolite, and anthophyllite. The note as well that the PCM method, which is the most commonly used to assess asbestos exposures, cannot distinguish chrysotile fibers from amphibole fibers or even asbestos fibers from other airborne fibers, such as fiberglass or clothing fibers. The authors also show that historical occupation limits in the US were from the 1930s to the 1960s set at 30 f/cc (when applied), and only with the implementation of OSHA in 1969 were they reduced gradually to 0.1 f/cc in 1990. (as a side: It is interesting to note that all the major epidemiology studies were from exposures prior to 1969) This review examines in detail the evolution of industrial hygiene knowledge of asbestos and how the evaluation and control of workplace exposures evolved over time.

21 Pleural mesothelioma and lung cancer risks in relation to occupational history and asbestos lung burden. *Occup Environ Med* 2016

Gilham C, Rake C, Burdett G, Nicholson AG, Davison L, Franchini A, Carpenter J, Hodgson J, Darnton A, Peto J. Pleural mesothelioma and lung cancer risks in relation to occupational history and asbestos lung burden. *Occup Environ Med*. 2016 May;73(5):290-9. doi: 10.1136/oemed-2015-103074. Epub 2015 Dec 29. PMID: 26715106; PMCID: PMC4853597.

Gilham and co-authors present a UK based population-based study examining the relationship between asbestos exposure, lung burden, and the risks of developing pleural mesothelioma and lung cancer. The researchers interviewed and analyzed lung samples from 133 mesothelioma patients and 262 lung cancer patients. Asbestos fibers longer than 5 μm were counted using transmission electron microscopy. Britons born before the 1960s have the highest mesothelioma death-rate worldwide. Of the five million tonnes imported into the UK since 1954, over this period 89% was chrysotile, 9% amosite and 2% crocidolite. Crocidolite use had ended by 1970 and amosite by 1980. Chrysotile imports had fallen by 90% by 1990 and ended by 2000. Few of the asbestos fibres detected were chrysotile, which disappears from the lung with a half-life of a few months. The majority of counted asbestos fibres were amosite (75%) or crocidolite (18%), with much lower numbers for chrysotile (1.9%), tremolite (1%), anthophyllite (2%), actinolite (0.6%) and uncharacterised amphiboles (1.7%). The study found an approximately linear relationship between asbestos lung burden and lifetime mesothelioma risk. Specifically, the lifetime mesothelioma risk was estimated to be approximately 0.020% per 1000 asbestos fibers per gram of dry lung tissue. This relationship held over a wide range of exposures, from heavily exposed building workers to the general population. The most prevalent asbestos fibers found were amosite (75%) and crocidolite (18%). Chrysotile, despite being the most heavily imported type of asbestos in the UK, was rarely found due to its rapid clearance from the lungs. The study estimated that crocidolite might be slightly more potent than amosite in causing mesothelioma, with one crocidolite fiber having approximately 1.3 times the risk of one amosite fiber. The lung burdens of chrysotile and other amphiboles were too low for their effect on risk to be estimated. These results confirm the major contribution of amosite to UK mesothelioma incidence and the substantial contribution of non-occupational exposure, particularly in women.

22 An updated evaluation of reported no-observed adverse effect levels for chrysotile asbestos for lung cancer and mesothelioma. *Crit Rev Toxicol* 2016

Pierce JS, Ruestow PS, Finley BL. An updated evaluation of reported no-observed adverse effect levels for chrysotile asbestos for lung cancer and mesothelioma. *Crit Rev Toxicol*. 2016 Aug;46(7):561-86. doi: 10.3109/10408444.2016.1150960. Epub 2016 Mar 31. PMID: 27031024.

Pierce and co-authors reevaluate the no-observed adverse effect levels (NOAELs) for chrysotile asbestos concerning lung cancer and mesothelioma. It analyzes multiple studies to determine exposure levels at which no increased risk of these diseases is evident. The study considers factors like fiber length, amphibole contamination, and smoking that may influence cancer risk. The authors ultimately aim to refine risk assessments associated with chrysotile asbestos exposure by synthesizing updated data from various occupational cohorts. The primary objective was to determine NOAELs (No Observed Adverse Effect Levels) for lung cancer and mesothelioma based on a review of epidemiological studies. These NOAELs represent exposure levels below which no increased risk of these cancers is observed in the studied populations. The best estimate NOAELs were determined to be 89-168 f/cc-years for lung cancer and 208-415 f/cc-years for mesothelioma. The authors also stated the following limitations and Uncertainties: 1) Smoking as a Confounding Factor: Controlling for smoking was difficult due to variations in smoking habits and potential misclassification or incomplete data. Residual confounding due to smoking is a concern in some studies. 2) Exposure to Amphiboles: Exposure to amphibole asbestos (e.g., crocidolite, amosite, tremolite) in chrysotile cohorts is a significant confounding factor. Even small amounts of amphiboles can significantly increase cancer risk. 3) Statistical Significance: The statistical significance of risk estimates at the NOAEL is a source of uncertainty. Borderline statistically significant results can impact the best-estimate NOAEL calculations. This updated analysis provides a valuable assessment of NOAELs for chrysotile asbestos, considering recent studies and updated information. The findings highlight the importance of fiber length, industry-specific exposures, and potential confounding factors such as amphibole contamination and smoking. The information is critical for characterizing potential health risks and informing future risk assessments related to chrysotile asbestos exposure.

23 The So-called Short-Fiber Controversy: Literature Review and Critical Analysis. Archives of Pathology & Laboratory Medicine 2015

Roggli VL. The So-called Short-Fiber Controversy: Literature Review and Critical Analysis. Arch Pathol Lab Med. 2015 Aug;139(8):1052-7. doi: 10.5858/arpa.2014-0466-RA. PMID: 26230599.

Roggli critically analyzed the existing scientific literature concerning the pathogenicity of short asbestos fibers ($\leq 5 \mu\text{m}$ in length). The author concludes that there is no convincing evidence from experimental animal studies or human studies to support the claim that short asbestos fibers are pathogenic and contribute to asbestos-related diseases like asbestosis, lung cancer, or mesothelioma. The author refutes arguments made by those who believe short fibers play a significant role, citing flaws in their methodologies and interpretations. Inhalation studies in animals consistently show that longer amphibole fibers are associated with fibrosis and neoplasia, while short fibers are not. Human lung tissue analyses support the pathogenicity of long amphibole fibers. Several studies found a correlation between mesothelioma risk and the presence of amphibole fibers of specific lengths (e.g., $\geq 8.0 \mu\text{m}$, $> 5.0 \mu\text{m}$, $\geq 10 \mu\text{m}$). The review directly addresses as well concerns raised by researchers who argue that short fibers should not be ignored. It specifically critiques the work of Suzuki et al., Dodson et al., Lemen, and Aust et al. The author maintains that the scientific evidence overwhelmingly supports the conclusion that asbestos fibers greater than $5 \mu\text{m}$ in length are the primary drivers of asbestos-related diseases. The concerns raised about the potential pathogenicity of short fibers are not supported by robust scientific data.

24 Estimating the asbestos-related lung cancer burden from mesothelioma mortality. *Br J Cancer* 2012

McCormack V, Peto J, Byrnes G, Straif K, Boffetta P. Estimating the asbestos-related lung cancer burden from mesothelioma mortality. *Br J Cancer*. 2012 Jan 31;106(3):575-84. doi: 10.1038/bjc.2011.563. Epub 2012 Jan 10. Erratum in: *Br J Cancer*. 2014 Dec 9;111(12):2381. PMID: 22233924; PMCID: PMC3273352.

McCormack and co-authors found that quantifying the asbestos-related lung cancer burden is difficult in the presence of this disease's multiple causes. They explored two methods to estimate this burden using mesothelioma deaths as a proxy for asbestos exposure. They analysed 55 asbestos-exposed cohorts, the researchers established fiber-type-specific ratios linking ARLC to mesothelioma mortality, revealing that all asbestos types except crocidolite cause at least twice as many lung cancer deaths as mesothelioma fatalities. While the authors do not discuss this, as reviewed by Barlow et al 2017, historical occupation limits in the US were from the 1930's to the 1960's set at 30 f/cc (when applied), and only with the implementation of OSHA in 1969 were they reduced gradually to 0.1 f/cc in 1990. The epidemiology studies cited were from exposures prior to 1969 and included high exposures that occurred many years ago. The authors estimated fiber-specific ratios which characterize the overall lung asbestos related lung cancer to mesothelioma relationship across different exposure circumstances and over a long period of time. In these studies, there was a marked correlation between lung cancer SMR and mesothelioma cohorts exposed to the amosite asbestos (amphibole). For amphibole asbestos, estimates suggest there was between a 6% and 10% increase in lung cancer deaths for every mesothelioma death in 1000 deaths. Chrysotile cohorts had a wider range of estimates, resulting from little correlation between excess lung cancers and mesotheliomas. When present, the authors state that it appears that many of the mesotheliomas were actually due to amphibole exposure. Their analysis does not exclude a lung cancer effect from these older cohorts but does mention that smoking can be a major contributor. Of particular importance is their conclusion that *"for chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths, and the latter cannot be used to infer no excess risk of lung or other cancers"*.

25 Occupational, domestic and environmental mesothelioma risks in the British population: a case–control study. *British Journal of Cancer* 2009

Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, Peto J. Occupational, domestic and environmental mesothelioma risks in the British population: a case-control study. *Br J Cancer*. 2009 Apr 7;100(7):1175-83. doi: 10.1038/sj.bjc.6604879. Epub 2009 Mar 3. PMID: 19259084; PMCID: PMC2669989.

Rake and co-authors reported on a large, population-based case-control study in Britain investigating the relationship between mesothelioma risk and lifetime occupational/residential history of asbestos exposure. Researchers interviewed mesothelioma patients and a control group to gather lifetime occupational and residential histories. The study confirms strong links between specific occupations (especially carpentry, plumbing/electrical work, construction, and shipbuilding) and mesothelioma. It highlights the significant impact of asbestos exposure before age 30. The study provides a strong link between the UK's historically high use of amosite asbestos (brown asbestos) and its elevated mesothelioma rates. "The mesothelioma risk caused by amosite (brown asbestos) is two orders of magnitude greater than that by chrysotile (white asbestos)..." The UK used much more amosite per capita than the US. The study finds that "A comparison of current mesothelioma death rates and imports to the US (Virta, 2006) and UK (MRC Institute for Environment and Health, 1997) of white, brown and blue (crocidolite) asbestos also suggests that the much higher mesothelioma death-rate in the UK was caused by its much greater use of amosite." Researchers concluded that a significant portion of male mesothelioma cases were attributable to occupational asbestos exposure, while a substantial percentage of female cases remained unexplained. The study underscores the long-term impact of asbestos exposure and highlights the importance of understanding exposure routes to mitigate future risks.