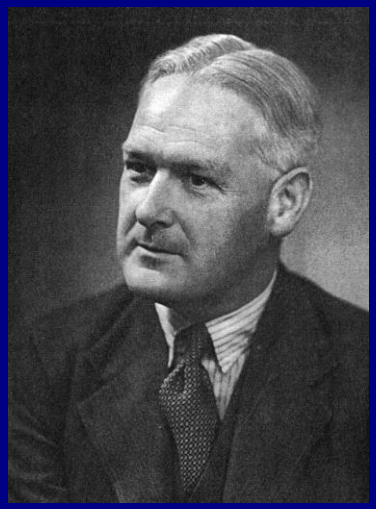
Chrysotile causes mesothelioma:

Hill's Considerations

Hill's Considerations for Determining Causality



Sir Austin Bradford Hill

Plausibility

Coherence

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As an overall model for determining causality, the considerations espoused by Sir Austin Bradford Hill are well accepted and have been widely used by epidemiologists.

While respected as a framework for determining causation, each of Hill's considerations has been subject to criticism.

Accordingly, as Hill noted, "None of my nine view points can bring indisputable evidence for or against the cause-and-effect hypothesis, and none can be required as a *sine qua non*."

Hill, A.B., The Environment and Disease: Association or Causation?

58(5) Proc. Royal Soc'y Med. 295, 299 (1965)

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"Biological plausibility" is an assessment of whether or not the theory that explains how an exposure causes a disease is consistent with other known mechanisms of disease causation.

Physicians do not usually require a specific understanding of the underlying mechanism of an injury or disease before assessing causation.

The contemplation of biological plausibly is the most onerous of Hill's considerations to satisfy in that it demands a level of detail of a disease's etiology that is sometimes impractical or unobtainable through existing or possible experimentation.

Medical practitioners and etiologists rarely, if ever, hesitate to form conclusions about disease causation for want of more specific knowledge of mechanistic understanding.

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Scientists do not understand exactly how tobacco smoke causes cancer, yet tobacco smoke is a long-recognized cause of cancer.

In the same way, an exposure may be identified as the "sole" cause of a disease, though it is in fact a part of a constellation of causes.

A bullet wound to the chest may damage many different organs while causing the death of a person who is shot.

Though damage to the heart, lung or pancreas may have been the mechanism of death, no doctor would refrain from concluding that the bullet was the cause of death.

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"Coherence" addresses the issue of consistency between the causal theory and that which is already known about the exposure or disease.

Coherence deals with the known facts, in contrast to the previously mentioned biological plausibility, which deals with theories of disease causation.

When little is known about a condition, coherence is easily satisfied.

However, in such cases, meeting this aspect of association does not tell much about the association.

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"Strength of association" is a reflection of the power of a study.

Strength of association is not a measure of the importance of a particular factor in causation.

It is a gauge of potential errors due to confounding or bias.

Studies with large rate ratios are less likely to contain errors attributable to bias or confounding.

Causal factors with "relatively low rate ratios" may be equally or more important than strong associations from a public health perspective.

In addition, a rate ratio of two is not required to establish that a factor contributed to a disease in a particular individual (specific causation).

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"Consistency" inquires as to whether or not a proposed effect has been or can be observed repeatedly under different circumstances.

This consideration is useful, and many different conditions and types of study can meet it.

However repetition of findings under similar conditions is not necessarily supportive of this consideration.

Similar biases (or confounding) occur under similar conditions.

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"Biologic gradient" for the cause-effect link in question, asks whether a dose-response relationship, or biologic gradient exists.

A common fallacy occurs when scientists limit consideration of dose-response to linear relationships between the proposed cause-effect link.

Hemoglobin oxygenation provides a simple example of a common non-linear dose-response curve.

As more oxygen is added to a hemoglobin molecule its affinity for oxygen increases in a non-linear fashion.

Hence the dose-response relationship for hemoglobin oxygenation produces a sigmoidal or S-shaped curve.

A dose-response relationship is not always necessary in order to establish causation.

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"Experimental evidence" includes studies of mechanisms of disease causation, which use experimental evidence and observation as the basis for their conclusions.

The data may be derived from animal studies, laboratory studies, controlled clinical trials, or observational pathology studies.

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Animal studies are relevant to human inference. Animal studies are performed for application to human health, not to animal health. Animal studies are not conducted to determine health risks to mice, rats, dogs or cats. They are not conducted out of concern for mouse or rat health. They are conducted because it is generally felt that inferences about human risks can be drawn from animal studies.

If scientists argue that animal studies are irrelevant to human inference, they should explain why inferences are not to be drawn since many animal studies indicate that illnesses in humans (especially cancer) can be reproduced in animals.

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"Analogy" takes in to consideration epidemiological and other studies to determine if analogous substances caused adverse health effects.

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"Specificity" asks if each cause has single or logically related similar effects.

This is rarely a useful consideration because many causes have multiple effects.

Asbestos causes asbestosis, lung cancer, mesothelioma and other cancers.

Smoking causes heart disease, lung cancer, oral cancer, etc.

Trauma from a car accident can cause many different injuries.

The analysis of specificity can be recast as the exclusion of a group of diseases in which the exposure is not associated with the disease.

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"Temporality" considers whether or not the cause precedes the effect.

While this is generally relevant to cause effect determination, there will be some cases where strict temporality is not necessary in order to evaluate etiologic relationships.

Temporality is most commonly established through non-epidemiological evidence.

Tobacco companies argue correctly that the current body of epidemiology literature cannot distinguish temporality from a genetic link between the tendency to smoke and risk factors for cancer.

Conclusive support for the temporal relation of smoking and cancer is derived from molecular and animal data.

Chrysotile Causes Mesothelioma: Hill's Considerations for Determining Causality

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Biological plausibility:

- Is a theory
- in this case is it possible that chrysotile causes mesothelioma?

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965).

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The shape of the fiber is the key factor in assessing a substance's potential to induce mesothelioma. Chrysotile like crocidolite can be found as extremely thin fibers. It is universally accepted that chrysotile is a cause of cancer in the lung. In addition, chrysotile migrates to and is concentrated in the pleura to a much greater extent than amphibole fibers.

Suzuki and Kohyama, "Translocation of Inhaled Asbestos Fibers from the Lung to Other Tissues," Am. J. Ind. Med., 19:701-704 (1991)

Kohyama and Suzuki; "Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers," Ann. NY Acad. Sci., 643:27-52

Sebastien, Janson, Gaudichet, Hirsch and Bignon, "Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura," IARC Sci. Pub., 30:237-246 (1980).

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Since chrysotile is carcinogenic and is present in high concentrations in the pleura where the mesothelioma is induced, it is biologically plausible that it causes or contributes to the development of mesothelioma.

Suzuki and Kohyama, "Translocation of Inhaled Asbestos Fibers from the Lung to Other Tissues," Am. J. Ind. Med., 19:701-704 (1991)
Kohyama and Suzuki; "Analysis of asbestos fibers in lung parenchyma, pleural plaques, and mesothelioma tissues of North American insulation workers," Ann. NY Acad. Sci., 643:27-52
Sebastien, Janson, Gaudichet, Hirsch and Bignon, "Asbestos retention in human respiratory tissues: comparative measurements in lung parenchyma and in parietal pleura," IARC Sci. Pub., 30:237-246 (1980).

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Chrysotile penetrates the cell, enters the nucleus and induces abnormal chromosome formation in dividing cells.

Levresse, Renier, Fleury-Feith, Levy, Moritz, Vivo, Pilatte, Jaurand, "Analysis of Cell Cycle Disruptions in Cultures of Rat Pleural Mesothelial Cells Exposed to Asbestos Fibers," Am. J. Respir. Cell Mol. Biol., 17:660-671 (1997).

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Coherence

- deals with the known facts about chrysotile
- assess how well the facts fit the theory

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965)

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Strength of Association:

- rate ratio
- can we expect that anything exposed will experience the same effect?

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Table 2: Epidemiologic studies Chrysotile alone or combined

Study (Authors)	Year	Population Size Studied	# of Years Studied	# of Meso Cases	R.R. >2 (Y/N)	Stat. Sig. (Y/N)	Rate Ratio*	Expected
Cullen, MR and Baloyi, RS	1991	51	21	3	Yes	Yes	2,801	0.001071
Camus, M, Siemiatycki, J and Meek, B	1998	11,651	19	7	Yes	Yes	32	0.221369
Baloyi	1989	300	9	3	Yes	Yes	1,111	0.0027
Enterline, PE, Hartley, J, and Henderson, V	1987	1,074	39	6	Yes	Yes	143	0.041886
Nokso-Koivisto, P and Pukkala, E	1994	8,391	38	8	Yes	Yes	25	0.318858
Borrow, M et al	1973	600	14	10	Yes	Yes	1,190	0.0084
Morinaga et al	1989	***50,000***	18	6	Yes	Yes	2	0.9
Strurm et al	1993	***50,000***	30	67	Yes	Yes	45	1.5
Rogars AJ, et al	1991	***50,000***	5	2	Yes	Yes	2	0.25

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Table 2: Epidemiologic studies Chrysotile alone or combined contd.

Hughes, JM and Weill, H	1986	5,500	***50***	12	Yes	Yes	44	0.275
Begin R et al	1992	***50,000***	35	20	Yes	Yes	11	1.75
Doll, R and Peto, J	1985	4,022	***50***	12	Yes	Yes	60	0.2011
Feingold, A. citation from depositions about mesothelioma in Quebec workers		10,000	***50***	38	Yes	Yes	76	0.5
Berry	1996			10			#DIV/0!	
Stayner, LT, Dankovic, DA, and Lemen, RA	1996			45			#DIV/0!	

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Chrysotile and Mesothelioma – Not an issue until the late 1970s

Article	Year	Fiber Type Mentioned
Wedler	1943	No
Wedler	1944	No
Mallory et al.	1947	No
Chief Inspector of Factories	1949	No
Wyers	1949	No
Doig	1949	No
Smith	1952	Yes Chrysotile [Data from Cartier]
Cartier	1953	No
Weiss	1953	No
Leicher	1954	No
Bonser et al.	1955	No
Doll	1955	No
Bohlig and Jacob	1955	No
Francia and Monarca	1956	No
Braun and Truan	1958	No
Konig	1960	No
Keal	1960	No
Eisenstadt and Wilson	1960	No

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Eisenstadt and Wilson	1960	No
Wagner et al.	1960	Yes Crocidolite and chrysotile
Schepers	1960	No
Sleggs	1961	No
Frenkel and Jager	1961	No
Heard and Williams	1961	No
McCaughey et al.	1962	No
Eisenstadt	1962	No
Thompson	1962	No
Wagner	1962	Yes Crocidolite and chrysotile
Smither et al.	1962	No
Enticknap	1962	No
Mancuso and Coulter	1963	Yes Chrysotile
Thomson et al.	1963	No
Thomson	1963	No
Enticknap and Smither	1963	Yes Crocidolite and chrysotile
Hourihane	1964	No
Owen	1964	No
Gafafer	1964	No
Elwood and Cochrane	1964	No

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Table 3: Animal Studies Chrysotile and mesothelioma - *in vitro* studies

Article	Fiber Type	Year	
Appel JD, Fasy JM, Kohtz DS, Kohtz JD, Johnson EM	chrysotile	1988	chrysotile mediates damage enabling transfected plasmid to be replicated.
Bolton RE, Davis JMG, Donaldson K, Wright A	chrysotile, amosite	1982	chrysotile samples found to be more carcinogenic than the amosite
Davis JMG, Beckett ST, Bolton RE, Collings P, Middleton AP	chrysotile, crocidolite, amosite	1978	chrysotile samples were the most fibrotic and the most tumorigenic.
Jaurand MC, Kheuang L, Magne L, Bignon J	chrysotile	1986	*in vitro* treatment of rat pleural mesothelial cells with chrysotile fibers. At 7 micrograms/ml, induction of 21% abnormal metaphases. Aberrations were primarily of chromatid type, also breaks and fragments.
Korkina LG, Durner AD, Suslova TB, Cheremisina ZP, Daugel-Dauge NO, Afanas'ev IB	chrysotile	1992	mutagenic action probably mediated by iron-oxygen complexes plus hydrogen peroxide.
Libbus BL, Craighead JE	crocidolite, chrysotile	1988	rat mesotheliomas induced by crocidolite or chrysotile. loss of chromosomes and translocations observed.

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Table 3: Animal Studies Chrysotile and mesothelioma - *in vitro* studies

Lund LG, Aust AE	crocidolite, amosite, chrysotile, or tremolite	1992	chrysotile induced single strand breaks in DNA. percent of DNA with SSB directly related to its iron content.
Mochaux G, Bichon J, Jaurand MC, Lafuma J, Sebastien P, Masse R, Hirsch A, Goni J	chrysotile, crocidolite	1981	mesotheliomas in rats, chrysotile more carcinogenic than crocidolite.
Osgood C, Sterling D		1991	chrysotile and amosite induced sex-chromosome aneuploidy, which is associated with development and/or progression of cancers. chrysotile appeared to be the more effective agent.
Suzuki Y, Kohyama N	amosite, chrysotile, and zeolite	1984	chrysotile and amosite had the highest tumor incidence
Valerio F, de Ferrari M, Ottagio L, Repetto E, Santi L	chrysotile, crocidolite	1983	statistically significant increase in chromosome and chromatid damage were present after treatment with chrysotile fibers. Anomalies most frequently chromatid breakage.
Dumas L, Page M	chrysotile, crocidolite, amosite	1986	chrysotile was the most cytotoxic of all the fibers tested. chrysotile increased the maximum cell density of fibroblasts, which may be one step in carcinogenesis.

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Consistency:

- Are the studies reproducible in different people, animals, and populations?

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Among 5,681 female workers, a total number of 858 death cases by all cases were found. The analysis of the percentage of specific causes of death showed that cancer (24.83%) was the first cause of death, and that lung cancer (40.85%) was the most prevalent. SMR's for all cancers (1.35) and for lung cancer (3.88) were significantly elevated than those of the control group.

King Zhang et al. Survey on the Mortality of Malignant Tumors in Asbestos Manual Spinning Female Workers.

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"The actual relative risk was probably higher because a review of death certificates for the entire cohort revealed an additional four deaths from pleural mesothelioma as contributory causes during the observation period and a fifth death after the study had closed."

Dell, L. and Jane Teta. Mortality among workers as a plastics manufacturing and research and developments facility: 1946-1988.

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"The focus of the study is on mesothelioma among railroad machinists employed in the steam locomotive era who were exposed to chrysotile. The findings demonstrated an extremely high relative risk for machinists exposed to chrysotile for the induction of mesothelioma… In terms of relative risk in the development of mesothelioma from exposure to chrysotile asbestos, what is most striking is the occurrence of mesothelioma in such a small number of deaths and cohorts in each respective individual year of hire.

Source: Mancuso, Relative Risk of Mesothelioma Among Railroad Machinists Exposed to Chrysotile (1988) 2.

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"There is strong support for the proposition that chrysotile is a potent causative factor in producing mesothelioma and that the risk associated with exposure to chrysotile in producing mesothelioma is similar to that of amosite on a per fiber exposure basis."

Nicholson, William J. The Carcinogenicity of Chrysotile Asbestos—A Review. Industrial Health 2001.

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82 cases of mesothelioma of residents of the town of Manville, New Jersey, who had never worked at the abets products manufacturing plant located there. These data indicate that residents of Manville had an extremely elevated risk of developing mesothelioma….This study suggests a major community impact by a facility using primarily chrysotile fibers.

Source: Berry. Mesothelioma Incidence and Community Asbestos Exposure (1996). New Jersey Dept. of Public Health. 69.

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In the German Federal State of Saxony-Anhalt, Strum and his colleagues reviewed 843 cases of "proven asbestos-accepted mesotheliomas" and determined that 67 of the cases were related to exposure to only chrysotile asbestos.

Strum, W. et al. Use of asbestos, health risks and induced occupational diseases in the former East Germany. Toxicology letters 72 (1994) 317-324.

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(1) chrysotile asbestos is a potent cause of pleural mesothelioma; (2) the large majority of mesothelioma is attributable to asbestos exposure; and (3) chrysotile asbestos has been the major type used. Based on this evidence, we conclude that chrysotile asbestos is by far the main contributor to pleural mesothelioma causation in the United States and other countries in which it has been the predominant fiber. Crocidolite may be 2-4 times more potent, but there is no valid evidence that amosite is more potent than chrysotile. Even considering an extreme that crocidolite and amosite were two times more potent than chrysotile, the extent of use of chrysotile means that it would still be the main contributor of pleural mesothelioma causation.

Smith, A. and Catherine C. Wright. Chrysotile Asbestos is the Main Cause of Pleural Mesothelioma. AJIM 30:252-256 1995.

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Due to the exact knowledge of the conditions of production it is possible for 481 cases exposed to asbestos to provide detailed information about the relevant types of asbestos. On this basis the sole exposure to chrysotile asbestos was determined to be the cause of the disease in 67 cases which corresponds to a share of 14%.

We are of the opinion that even though the persistence of the chrysotile fiber in the human organism may be shorter than that of the amphibole fibre, it may obviously be long enough to cause chronic and progressive processed, including mesothelioma.

Source: Strum, Menze et al. Asbestos-related diseases and asbestos types used in the former GDR (1995) 68.

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Cases of mesothelioma have been observed in chrysotile asbestos in:

Mechanics who installed chrysotile asbestos brake linings in Canada, United States, England, and Denmark; railroad workers using chrysotile insulation on locomotives in the United States, Italy, and Switzerland; an Italian worker in the wine filter industry.

McDonald, Harper, Attar and McDonald, "Epidemiology of Primary Malignant Mesothelial Tumors in Canada," Cancer, 26(4):914-919 (1970).
Langer and McCaughey, "Mesothelioma in a Brake Repair Worker," The Lancet, November 13, 1982, pages 1101-1103.
Kagan and Jacobson, "Lymphoid and Plasma Cell Malignancies: Asbestos-related Disorders of Long Latency," American Journal of Clinical Pathology, 80(1):14-20(1983).
Huncharek, Muscat and Capotorto, "Pleural mesothelioma in a brake mechanic," Brit. J. Indus. Med., 46:69-71 (1989)
Greenberg and Davies, "Mesothelioma Register 1967-68," Brit. J. Indus. Med., 31:91-104 (1974)
Hansen, "Mortality of auto mechanics, a ten year follow-up," Scand. J. Work Environ. Health, 15:41-46 (1989)
Mancuso, "Relative Risk of Mesothelioma Among Railroad Machinists Exposed to Chrysotile," Amer. J. Indus. Med., 13:639-657 (1988)
Maltoni, Pinto and Mobiglia, "Mesotheliomas due to Asbestos Used in Railroads in Italy," The Third Wave of Asbestos Disease: Exposure to Asbestos in Place, Annals of the New York Academy of Sciences, 643:347-415 (1991)
Discussion: Part II, Annals of the New York Academy of Sciences, 643:415 (1991).
Scansetti, Mollo, Tiberi, Andrion, and Piolatto, "Pleural Mesothelioma After a Short Interval From First Exposure in the Wine Filter Industry," Amer. J. of Indus. Med. 5:335-339 (1984).

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Cases of mesothelioma have been observed in chrysotile asbestos in:

Wives of workers who manufactured chrysotile textiles and friction products in New York State, and individuals who simply lived in close proximity to a chrysotile asbestos textile and friction products plant have all developed mesothelioma.

Vianna and Polan, "Non-Occupational Exposure to Asbestos and Malignant Mesothelioma in Females," The Lancet, May 20, 1978, pp. 1061-1063.
Lieben and Pistawka, "Mesothelioma and Asbestos Exposure," Arch. Environ. Health 14:559-566 (1967)
Wolf, Piotrowski, Engel, Bekeris, Palacios and Fisher, "Malignant Mesothelioma With Occupational and Environmental Asbestos Exposure in an Illinois Community Hosptial," Arch. Intern. Med. 147:2145-2149 (1987).

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Cases of mesothelioma have been observed in chrysotile asbestos in:

Workers manufacturing textiles containing chrysotile asbestos in North Carolina and New Jersey, workers who manufactured chrysotile asbestos friction products in Connecticut, England and in Germany.

Dement, Harris, Symons and Shy, "Exposures and Mortality Among Chrysotile Asbestos Workers. Part II: Mortality," Amer. J. Indus. Med., 4:421-433 (1983).
Borrow, Conston, Livornese and Schalet, "Mesothelioma following Exposure to Asbestos: A Review of 72 Cases," Chest, 64(5):641-646 (1973).
Teta, Lewinsohn, Meigs, Vidone, Mowad and Flannery, "Mesothelioma in Connecticut, 1955-1977," Journal of Occupational Medicine, 25(10):749-756 (1983).
Newhouse and Sullivan, "A mortality study of workers manufacturing friction materials: 1941-86," Brit. J. of Indus. Med., 46:176-179 (1989).
Konetzke, Beck and Herold, "Asbestos-Induced Mesotheliomas - Results of a Retrospective Study," Proceedings of the International Symposium on the Prevention of Occupational Cancer, Helsinki, Finland (1981)

Chrysotile Causes Mesothelioma: Hill's Considerations for Determining Causality

Plausibility

Coherence

Strength of Association

Consistency of Observed Association

Biological Gradient

Experiment

Analogy

Specificity of the Association

Temporality

Cases of mesothelioma have been observed in chrysotile asbestos in:

Chrysotile miners in Canada, and in Zimbabwe. Workers exposed during the manufacture of chrysotile asbestos cement in Louisiana.

"Survey of Some Current British and European Studies of Occupational Tumor Problems," Arch. Industr. Hyg. 5:262 (1952)(Abstract of Discussion by Paul Cartier).
Champion, "Two Cases of Malignant Mesothelioma after Exposure to Asbestos," American Review of Respiratory Disease, 105:821-826 (1971).
Cullen and Baloyi, Chrysotile Asbestos and Health in Zimbabwe, American Journal of Industrial Medicine (1991).
Hughes, Weill and Hammad, "Mortality of workers employed in two asbestos cement manufacturing plants," Brit. J. Indus. Med., 44:161-174 (1986).

Chrysotile Causes Mesothelioma: Hill's Considerations for Determining Causality

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Examination of all pertinent studies makes it clear that chrysotile asbestos is similar in potency to amphibole asbestos. Since asbestos is the major cause of mesothelioma, and chrysotile constitutes 95% of all asbestos used world wide, it can be concluded that chrysotile asbestos is the main cause of pleural mesothelioma in humans.

Source: Smith & Wright, 1996. Chrysotile Asbestos is the main cause of pleural Mesothelioma. 40.

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Two mesothelioma death cases were found among 132 deaths of employees of a factory using chrysotile asbestos that contained a negligible amount of tremolite, less that .001 percent. The authors stated that they found, "no evidence in support of the amphibole contaminant hypothesis. To the contrary, a strong potential for chrysotile asbestos alone to cause lung cancer and mesothelioma was suggested."

Yano et al. Cancer Mortality Among Workers Exposed to Amphibole-free chrysotile Asbestos. Am. J. of Epidemiology: (154:6).

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"Because of its rarity, this tumor [Diffuse Malignant Mesothelioma (DMM)] is said to be a signal tumor of asbestos exposure…In 1943, Wedler first associated DMM with asbestos exposure, and in 1947 the first case in an asbestos worker in the United States was described in the Case Records of the Massachusetts General Hospital."

Rom, W.N. (ed.), Environmental and Occupational Medicine, Little, Brown, and Company, Boston, 1983.

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"The most important item here is the incrimination of all major types of asbestos as causal agents for carcinoma, particularly mesothelioma. Most of the other items only confirm or substantiate previous conclusions."

"Since most of us use substantial amounts of Chrysotile asbestos in our formulations, association of this material with mesothelioma and other types of cancer is of serious concern."

Address of I. W. Weaver, "Asbestos and the Friction Material Industry," given at the Annual Membership of the Asbestos Textile Institute on Wednesday morning, June 27, 1973.

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"All major commercial types of asbestos cause cancer…"

"Evidence has been greatly strengthened that all commercial types of asbestos except Anthophyllite may be responsible for mesothelioma. . . ."

Address of I. W. Weaver, "Asbestos and the Friction Material Industry," given at the Annual Membership of the Asbestos Textile Institute on Wednesday morning, June 27, 1973.

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"Our review of both the toxicologic and epidemiologic literature strongly supports the view that occupational exposure to chrysotile asbestos is associated with an increased risk of both lung cancer and mesothelioma."

Stayner, L.T. *et al*., *Occupational Exposure to Chrysotile Asbestos and Cancer Risk: a Review of the Amphibole Hypothesis*, American Journal of Public Health. 1996, 86:179-186. Smith *et al*., *Chrysotile Asbestos, the Main Cause of Pleural Mesothelioma*, American Journal of Industrial Medicine, 1996, 30:252-266.

Chrysotile Causes Mesothelioma: Hill's Considerations for Determining Causality

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A majority of the researchers and physicians that have addressed the issue agree that chrysotile, as sold and used in the United States, is a cause of mesothelioma and that the pattern of disease induction has a dose-response relationship.

Rogers, Leigh, Berry, Ferguson, Mulder, Ackad, "Relationship between lung asbestos fiber type and concentration and relative risk of mesothelioma," Cancer, 67:1912-1920 (1991).

Chrysotile Causes Mesothelioma: Hill's Considerations for Determining Causality

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Biologic gradient asks whether a dose-response relationship, or biologic gradient exists.

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965).

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Experimental evidence

- what do the studies show?

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965).

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"Neoplasms of rodents and other animals are…fundamentally similar in nature, and there are many examples of chemicals that cause tumors in both humans and animals. It is a fundamental principle…that 'in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as they presented a carcinogenic risk to humans."

Wilbourn J., Haroun L., Heseltine E., Kaldor J., Partensky C., Vainio H. "Response of experimental animals to human carcinogens: An analysis based on the IARC monographs programme." Carcinogenesis 7:1853-1863. (1986).
Rice, J. M., Wilbourn, J. D. "Tumors of the nervous system in carcinogenic hazard identification" Toxicologic Pathology vol. 28 (1), 202-214. (2000).

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"…[I]ngestion by human beings of <u>any</u> amounts of a compound shown to be carcinogenic in test animals must be regarded as a threat to human health."
-Paul Kotin, former medical director for Johns-Manville

Statement of Paul Kotin, FIFRA 293 (Mirex), November 12, 1973.

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Heintz et al., conducted a tissue culture study of the effects on the expression of two proto-oncogenes of crocidolite and chrysotile asbestos on rat pleural mesothelial cell lines (RPM) and HTE cell lines, progenitor cell types of bronchogenic carcinoma. The researchers found that both fibers increased the expression of these two genes, in similar rates in proportion to dose in grams.

Heintz NH, Janssen YM, Mossman BT, Persistent induction of *c-foc* and *c-jun* expression by asbestos. Proc Natl Acad Sci USA 90:3299-3303, 1993.

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Analogy

- Do other substances cause mesothelioma?

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965)

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Specificity

•is there only a single effect of exposure?

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965).

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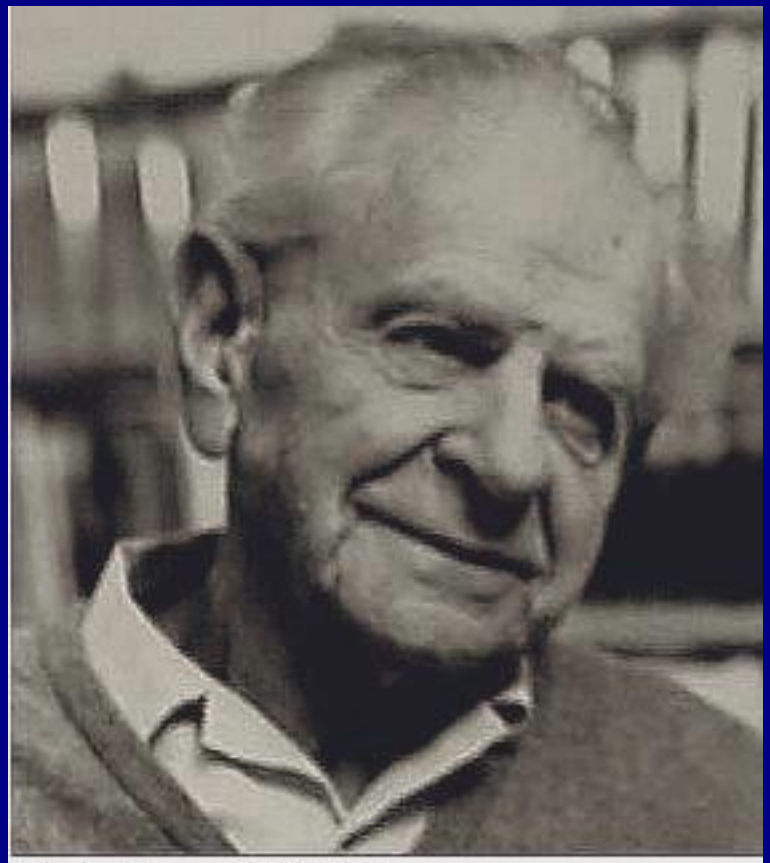
Temporality

- did the exposure occur before the disease?

Hill, A.B.. the Environment and disease: association or causation? 58(5) Proc. Royal Soc'y Med. 295, 299 (1965).

Hill's Criteria	Chrysotile does not cause mesothelioma	Chrysotile does cause mesothelioma
Plausibility	Does not meet standard	Meets standard
Coherence	Does not meet standard	Meets standard
Strength of Association	Indeterminate	Meets standard
Consistency	Does not meet standard	Meets standard
Biological Gradient	Does not meet standard	Meets standard
Experimental Evidence	Indeterminate	**Meets standard**
Analogy	Does not meet standard	Meets standard
Specificity	Not applicable	Not applicable
Temporality	Does not meet standard	Meets standard



Sir Karl Popper (1902-1994)

Science is the Art of Disproving Hypotheses

White Swan Hypothesis:

Chrysotile does not cause mesothelioma

The White Swan Hypothesis:

Chrysotile does not cause mesothelioma

Is disproved by the finding of Black Swans:

Studies that conclude that exposure to chrysotile causes mesothelioma

Agencies which DO SUPPORT the "Chrysotile causes mesothelioma" position: