Chrysotile causes mesothelioma:

Hill’s Considerations
Hill’s Considerations for Determining Causality

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?
“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.
Hill’s Considerations for Determining Causality

Plausibility
Coherence
Strength of Association
Consistency of Observed Association
Biological Gradient
Experiment
Analogy
Specificity of the Association
Temporality

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.
“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.
### Hill’s Considerations for Determining Causality

<table>
<thead>
<tr>
<th>Plausibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coherence</td>
</tr>
<tr>
<td><strong>Strength of Association</strong></td>
</tr>
<tr>
<td>Consistency of Observed Association</td>
</tr>
<tr>
<td>Biological Gradient</td>
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<tr>
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<tr>
<td>Analogy</td>
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<tr>
<td>Specificity of the Association</td>
</tr>
<tr>
<td>Temporality</td>
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</tbody>
</table>

“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).
“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.
“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 into 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.
Hill’s Considerations for Determining Causality

“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?

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.
Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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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.


Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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

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**Coherence**

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

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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**Strength of Association:**
- rate ratio
- can we expect that anything exposed will experience the same effect?
Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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### Table 2: Epidemiologic studies Chrysotile alone or combined

<table>
<thead>
<tr>
<th>Study (Authors)</th>
<th>Year</th>
<th>Population Size Studied</th>
<th># of Years Studied</th>
<th># of Meso Cases</th>
<th>R.R. &gt;2 (Y/N)</th>
<th>Stat. Sig. (Y/N)</th>
<th>Rate Ratio*</th>
<th>Expected</th>
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<tbody>
<tr>
<td>Cullen, MR and Baloyi, RS</td>
<td>1991</td>
<td>51</td>
<td>21</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>2,801</td>
<td>0.001071</td>
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<tr>
<td>Camus, M, Siemiatycki, J and Meek, B</td>
<td>1998</td>
<td>11,651</td>
<td>19</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>32</td>
<td>0.221369</td>
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<tr>
<td>Baloyi</td>
<td>1989</td>
<td>300</td>
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<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>1,111</td>
<td>0.0027</td>
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<tr>
<td>Enterline, PE, Hartley, J, and Henderson, V</td>
<td>1987</td>
<td>1,074</td>
<td>39</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>143</td>
<td>0.041886</td>
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<td>Nokso-Koivisto, P and Pukkala, E</td>
<td>1994</td>
<td>8,391</td>
<td>38</td>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>25</td>
<td>0.318858</td>
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<tr>
<td>Borrow, M et al</td>
<td>1973</td>
<td>600</td>
<td>14</td>
<td>10</td>
<td>Yes</td>
<td>Yes</td>
<td>1,190</td>
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<td>Morinaga et al</td>
<td>1989</td>
<td><strong>50,000</strong></td>
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<tr>
<td>Strum et al</td>
<td>1993</td>
<td><strong>50,000</strong></td>
<td>30</td>
<td>67</td>
<td>Yes</td>
<td>Yes</td>
<td>45</td>
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<tr>
<td>Rogers AJ, et al</td>
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<td><strong>50,000</strong></td>
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<td>0.25</td>
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</table>
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**Table 2: Epidemiologic studies Chrysotile alone or combined contd.**

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Year</th>
<th>Cases</th>
<th>Relative Risk</th>
<th>RR</th>
<th>CI</th>
<th>Outcome</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Hughes, JM and Weill, H</td>
<td>1986</td>
<td>5,500</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
<td>44</td>
<td>0.275</td>
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<tr>
<td>Begin R et al</td>
<td>1992</td>
<td>50,000</td>
<td>35</td>
<td>Yes</td>
<td>Yes</td>
<td>11</td>
<td>1.75</td>
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<tr>
<td>Doll, R and Peto, J</td>
<td>1985</td>
<td>4,022</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>60</td>
<td>0.2011</td>
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<tr>
<td>Feingold, A. citation from depositions about mesothelioma in Quebec workers</td>
<td></td>
<td>10,000</td>
<td>50</td>
<td>Yes</td>
<td>Yes</td>
<td>76</td>
<td>0.5</td>
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<tr>
<td>Berry</td>
<td>1996</td>
<td>10</td>
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<td>#DIV/0!</td>
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<tr>
<td>Stayner, LT, Dankovic, DA, and Lemen, RA</td>
<td>1996</td>
<td>45</td>
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<td>#DIV/0!</td>
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### Chrysotile and Mesothelioma - Not an issue until the late 1970s

<table>
<thead>
<tr>
<th>Article</th>
<th>Year</th>
<th>Fiber Type Mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wedler</td>
<td>1943</td>
<td>No</td>
</tr>
<tr>
<td>Wedler</td>
<td>1944</td>
<td>No</td>
</tr>
<tr>
<td>Mallory et al.</td>
<td>1947</td>
<td>No</td>
</tr>
<tr>
<td>Chief Inspector of Factories</td>
<td>1949</td>
<td>No</td>
</tr>
<tr>
<td>Wyers</td>
<td>1949</td>
<td>No</td>
</tr>
<tr>
<td>Doig</td>
<td>1949</td>
<td>No</td>
</tr>
<tr>
<td>Smith</td>
<td>1952</td>
<td>Yes Chrysotile [Data from Cartier]</td>
</tr>
<tr>
<td>Cartier</td>
<td>1953</td>
<td>No</td>
</tr>
<tr>
<td>Weiss</td>
<td>1953</td>
<td>No</td>
</tr>
<tr>
<td>Leicher</td>
<td>1954</td>
<td>No</td>
</tr>
<tr>
<td>Bonser et al.</td>
<td>1955</td>
<td>No</td>
</tr>
<tr>
<td>Doll</td>
<td>1955</td>
<td>No</td>
</tr>
<tr>
<td>Bohlig and Jacob</td>
<td>1955</td>
<td>No</td>
</tr>
<tr>
<td>Francia and Monarca</td>
<td>1956</td>
<td>No</td>
</tr>
<tr>
<td>Braun and Truan</td>
<td>1958</td>
<td>No</td>
</tr>
<tr>
<td>Konig</td>
<td>1960</td>
<td>No</td>
</tr>
<tr>
<td>Keal</td>
<td>1960</td>
<td>No</td>
</tr>
<tr>
<td>Eisenstadt and Wilson</td>
<td>1960</td>
<td>No</td>
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Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

<table>
<thead>
<tr>
<th>Strength of Association</th>
<th>Publication Year</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Eisenstadt and Wilson</td>
<td>1960</td>
<td>No</td>
</tr>
<tr>
<td>Wagner et al.</td>
<td>1960</td>
<td>Yes Crocidolite and chrysotile</td>
</tr>
<tr>
<td>Schepers</td>
<td>1960</td>
<td>No</td>
</tr>
<tr>
<td>Sleggs</td>
<td>1961</td>
<td>No</td>
</tr>
<tr>
<td>Frenkel and Jager</td>
<td>1961</td>
<td>No</td>
</tr>
<tr>
<td>Heard and Williams</td>
<td>1961</td>
<td>No</td>
</tr>
<tr>
<td>McCaughey et al.</td>
<td>1962</td>
<td>No</td>
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<tr>
<td>Eisenstadt</td>
<td>1962</td>
<td>No</td>
</tr>
<tr>
<td>Thompson</td>
<td>1962</td>
<td>No</td>
</tr>
<tr>
<td>Wagner</td>
<td>1962</td>
<td>Yes Crocidolite and chrysotile</td>
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<tr>
<td>Smither et al.</td>
<td>1962</td>
<td>No</td>
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<tr>
<td>Enticknap</td>
<td>1962</td>
<td>No</td>
</tr>
<tr>
<td>Mancuso and Coulter</td>
<td>1963</td>
<td>Yes Chrysotile</td>
</tr>
<tr>
<td>Thomson et al.</td>
<td>1963</td>
<td>No</td>
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<tr>
<td>Thomson</td>
<td>1963</td>
<td>No</td>
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<tr>
<td>Enticknap and Smither</td>
<td>1963</td>
<td>Yes Crocidolite and chrysotile</td>
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<tr>
<td>Hourihane</td>
<td>1964</td>
<td>No</td>
</tr>
<tr>
<td>Owen</td>
<td>1964</td>
<td>No</td>
</tr>
<tr>
<td>Gafafer</td>
<td>1964</td>
<td>No</td>
</tr>
<tr>
<td>Elwood and Cochrane</td>
<td>1964</td>
<td>No</td>
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Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

**Strength of Association**

<table>
<thead>
<tr>
<th>Article</th>
<th>Fiber Type</th>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appel JD, Eady JM, Kohtz DS, Kohtz JD, Johnson EM</td>
<td>chrysotile</td>
<td>1988</td>
<td>chrysotile mediates damage enabling transfected plasmid to be replicated.</td>
</tr>
<tr>
<td>Bolton RE, Davis JMG, Donaldson K, Wright A</td>
<td>chrysotile, amosite</td>
<td>1982</td>
<td>chrysotile samples found to be more carcinogenic than the amosite.</td>
</tr>
<tr>
<td>Davis JMG, Beckett ST, Bolton RE, Collings P, Middleton AP</td>
<td>chrysotile, crocidolite, amosite</td>
<td>1978</td>
<td>chrysotile samples were the most fibrotic and the most tumorigenic.</td>
</tr>
<tr>
<td>Jauret MC, Kheuang L, Magne L, Bignon J</td>
<td>chrysotile</td>
<td>1986</td>
<td><em>in vitro</em> 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.</td>
</tr>
<tr>
<td>Libbus BL, Craighead JE</td>
<td>crocidolite, chrysotile</td>
<td>1988</td>
<td>rat mesotheliomas induced by crocidolite or chrysotile. Loss of chromosomes and translocations observed.</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>作者</th>
<th>研究</th>
<th>年份</th>
<th>发现</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund LG, Aust AE</td>
<td>crocidolite, amosite, chrysotile, or tremolite</td>
<td>1992</td>
<td>chrysotile induced single strand breaks in DNA, percent of DNA with SSB directly related to its iron content.</td>
</tr>
<tr>
<td>Osgood C, Sterling D</td>
<td></td>
<td>1991</td>
<td>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.</td>
</tr>
<tr>
<td>Suzuki Y, Kohyama N</td>
<td>amosite, chrysotile, and zeolite</td>
<td>1984</td>
<td>chrysotile and amosite had the highest tumor incidence</td>
</tr>
<tr>
<td>Valerio F, de Ferrari M, Ottagio L, Repetto E, Sant L</td>
<td>chrysotile, crocidolite</td>
<td>1983</td>
<td>statistically significant increase in chromosome and chromatid damage were present after treatment with chrysotile fibers. Anomalies most frequently chromatid breakage.</td>
</tr>
<tr>
<td>Dumas L, Page M</td>
<td>chrysotile, crocidolite, amosite</td>
<td>1986</td>
<td>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.</td>
</tr>
</tbody>
</table>
Consistency:

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

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.
Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

“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.”

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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.

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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.”

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.

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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.

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

(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.

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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.
Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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.

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:

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.

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.


Plausibility

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.

Coherence

Consistency of Observed Association

Biological Gradient

Experiment

Analogy

Specificity of the Association

Temporality

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.
Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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.”

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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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.”

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

“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.”

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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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. . . .”

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

“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.”

Plausibility
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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.

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.

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

Plausibility
Coherence
Strength of Association
Consistency of Observed Association
Biological Gradient

**Experimental evidence**
- what do the studies show?

Experiment
Analogy
Specificity of the Association
Temporality

## Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plausibility</td>
<td>“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.””</td>
</tr>
<tr>
<td>Coherence</td>
<td></td>
</tr>
<tr>
<td>Strength of Association</td>
<td></td>
</tr>
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<td>Specificity of the Association</td>
<td></td>
</tr>
<tr>
<td>Temporality</td>
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</tbody>
</table>

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Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

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“…[I]ngestion by human beings of any 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.
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.

Chrysotile Causes Mesothelioma: Hill’s Considerations for Determining Causality

Plausibility
Coherence
Strength of Association
Consistency of Observed Association
Biological Gradient
Experiment

**Analogy**

- Do other substances cause mesothelioma?

Specificity

• is there only a single effect of exposure?

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**

• did the exposure occur before the disease?

<table>
<thead>
<tr>
<th>Hill’s Criteria</th>
<th>Chrysotile does not cause mesothelioma</th>
<th>Chrysotile does cause mesothelioma</th>
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</thead>
<tbody>
<tr>
<td>Plausibility</td>
<td>Does not meet standard</td>
<td>Meets standard</td>
</tr>
<tr>
<td>Coherence</td>
<td>Does not meet standard</td>
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</tr>
<tr>
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<tr>
<td>Specificity</td>
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<td>Not applicable</td>
</tr>
<tr>
<td>Temporality</td>
<td>Does not meet standard</td>
<td>Meets standard</td>
</tr>
</tbody>
</table>
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: