July 7th, 2008

Ms. Vivian Turner
EPA Science Advisory Board
Room 3610B U.S. Environmental Protection Agency
1025 F Street, N.W.
Washington, DC 20004 USA
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Re: EPA's Office of Solid Waste and Emergency Response
"Proposed Approach for Estimation of Bin-Specific Cancer
Potency Factors for Inhalation Exposure to Asbestos."

Dear Ms. Turner,

These comments, and the attached draft paper[1], are for consideration by the special committee of the Science Advisory Board considering the risk assessment for asbestos inhalation.

Richard Wilson, Mallinckrodt, Research Professor of Physics at Harvard University and immediate past Director of the Regional Center for Global Environmental Change at Harvard University. He is an Affiliate of the Center for Science and International Affairs and of the Center for Middle Eastern Studies at Harvard. Professor Wilson was Chairman of the Department of Physics at Harvard University and past Chairman and currently a member of the Cyclotron Operating Committee. He is a founder of the Society for Risk Analysis. He is and has been a consultant to the United States government and the governments of numerous foreign countries on matters of toxicology, epidemiology, public health and safety, nuclear safety, and risk assessment. Professor Wilson's areas of expertise include ground water pollution by arsenic, and human rights. He is the author of many scientific articles on high energy physics, environmental pollution and risk analysis including *Particles in Our Air and Health Effects* (with John Daniel Spengler) (Harvard University Center for Risk Analysis, 1986) and *Risk Benefit Analysis* (2 ed.) (with Edmund Crouch) (Harvard University Center for Risk Analysis, 2001). Professor Wilson is the author or co-author of more than 880 published papers on subjects including atomic particles, radioactive particle decay, acute toxicity and carcinogenic risk, carcinogenic bioassays, statistical distribution of health risks, public health, cancer risk management, shielding of particle accelerators and nuclear reactors, nuclear energy production, health risk of nuclear power plant accidents, health effects of electromagnetic fields, risk and health impacts of radiation, risk of nuclear proliferation, risk benefit analysis and global energy use and global warming. He has been given numerous awards and medals in recognition of his work including the Medal as "Chernobyl Liquidator" USSR (1987), Society for Risk Analysis Distinguished Achievement Award (1993) and a Honorary Doctorate from the International Sakharov Environmental University (2001).

[1]We refer the SAB to the attached draft paper by the authors of these comments and the references therein, and ask that the attachment be made part of the record.

Robert P. Nolan, the Deputy Director of the Center for Applied Studies of the Environment and a member of the doctoral faculty in Chemistry and Earth and Environmental Sciences at The Graduate School and University Center of The City University of New York. He received a Ph.D. degree in chemistry from The City University of New York in 1986. He was awarded fellowships from the Stony-Wold Herbert Foundation, National Research Council, Fulbright Program, and International Union for Pure and Applied Chemistry. He is the author of more than fifty scientific papers and is internationally recognized as an expert in the characterization and health hazard evaluation of asbestos and other minerals[2].

We are concerned about the way in which the request for comments has been posed implies a prior decision on how the risk assessment should proceed. The "Proposed Approach" poses a number of detailed questions, but this should be preceded by a discussion of the way in which EPA has handled the problem in the past, the successes and failures of the prior approach[es], and the way the scientific data suggest a better approach.

(1) The 1986 EPA report on cancer risks from asbestos exposure had several virtues and several faults (U.S. EPA. 1986. Airborne Asbestos Health Assessment Update. Prepared by the Environmental Criteria and Assessment Office, Research Triangle Park, NC 600/8-84-003F). The virtue is that it was a report to which everyone could refer, which gave definite answers to questions. We have ourselves used it in this way, pointing out the places and reasons where our scientific judgments differed from that of EPA. The 1986 report should have clearly described, in appropriate places, what assumptions were being made pending further scientific information. Unfortunately, many people have used the 1986 report as the "true word". The risk assessment used a model – rather two models one for lung cancer and another for mesothelioma – and the numerical results depend upon the validity of the model predictions. We remind the SAB of the old dictum: "All models are wrong: some models are useful".

While in many places, such as Congressional testimony, EPA officials have stated that, they feel it their duty to err, if at all, on the side of caution (using what Europeans call the "Precautionary Principle"). The places where this Precautionary Principal was used should have been specified in the 1986 report and should be made clear in every report, including any which emanate from the current process. Unfortunately, this was not done in the 1986 report. Precautionary planning has been appropriate, and consequently, manufacturing processes involving amphibole asbestos have been abandoned, and the use of serpentine asbestos has dropped to less than 1/2% of the amount in 1970.

However, the report has also been used incorrectly for assigning medical causation in many situations, including assigning fault and awarding billions of dollars in damages. The result has been described by some as a 'random redistribution of wealth". While the EPA itself is not culpable of such misuse, the tone of the 1986 report encouraged it. It is vital that the EPA carefully word any future report, on asbestos or indeed any other subject to avoid such misunderstandings and misuse.

(2) The 1986 report deliberately treated all asbestos as the same even though there was already in 1986 more than sufficient scientific evidence to show that the various types of asbestos had a

[2]Professors Wilson and Nolan submit these comments in their personal capacities, and the comments do not reflect the views of the educational institutions with which they are affiliated.

range of potencies for causing asbestos-related diseases. There is anecdotal evidence that this was well understood by EPA officials at the time, but the treatment of all "asbestos" in the same way perhaps because the phase-contrast light microscopy technique used to monitor asbestos in the workplace could not distinguishing among the various asbestos fiber-types and relying on transmission electron microscopy is problematic. As all of the asbestos risk assessments are benchmarked to the earlier optical method. This should have been stated in the 1986 report to avoid the problems noted in section (1) of our comments. It was later made clear by EPA in its 2003 report (U.S. EPA, Final Draft: Technical Support Document for a Protocol to Assess Asbestos-Related Risk, EPA #9345.4-06, Executive Summary at 1.4(6)(October 2003))("EPA 2003 Report").

(3) The 2003 report to EPA, and the document which the SAB is now called upon to consider, is complex and seems to imply more than the data allow us to consider. It takes a long time to read and longer to understand. We suspect that the output may well be a complex computer program that few people will understand and yet will dominate EPA decision making for decades. We *strongly* urge the SAB to make simple recommendations, clearly stating the assumptions that could be modified later as further information becomes available. It should also make clear whether the particular recommendations are for proceeding with caution, or for assigning blame for past conduct.

(4) The initial issue is the definition of asbestos. This must be clearly stated and if there are, variants of different fiber-types that must be clearly stated and the limitations of the report accordingly made clear[3]. In 1986, it was not. The effective definition in 1986 was any material that could be used in this way and was available commercially. Asbestos is a commercial term to describe a group of minerals with a common uses. Analogs of asbestos minerals occur with similar chemical formulae but crystallizing in geological processes different from asbestos. For each of these non-asbestos analogs the scientific evidence available indicates they are not nearly as carcinogenic as asbestos (if carcinogenic at all). There is a difference between cleavage fragments that form by breaking massive rock and the asbestiform fibers that grow as polyfilamentous fibers under special geological conditions. There is strong evidence that the length to diameter ratio is important in distinguishing asbestos from other fibrous minerals. Now that asbestos is almost all removed from the market place, there is time to ponder these matters and understand the differences.

(5) It was already known to many scientists in 1986, and is now certain, that there is a big difference between the group of "amphiboles' and "serpentine" asbestos minerals. In his submission to the SAB Dr. David Bernstein has emphasized the structural distinction between these two groups of minerals. We argue that the distinction may well be responsible for the differences in toxicological behavior that have been increasingly reported.[4] We suggest that there currently may be too little information to subdivide these classes further. The scientific reason for the toxicological differences should be noted for future consideration with respect to asbestos, but also with respect to other substances which may be examined in the future -such as carbon nanotubes –

[3] One of the signatories (Professor Wilson) emphasizes that the definition from the ancient Greek "it will not burn", is more appropriate than most. The first large scale modern use of asbestos was from taking natural mineral fibers, and weaving them into fire resistant cloth

[4] In the attached draft paper by the authors of these comments.

and which may exhibit similar characteristics and effects. This explicit realization by EPA might also go some way toward undoing the random financial damage caused by the failure, without explanation, to make the distinction in the 1986 report and the misuse of that report in adversarial proceedings. We submit that the following differences between amphibole asbestos and serpentine asbestos that seem to be agreed by the best scientists:

(a) Chrysotile, the only serpentine asbestos, is less potent in causing lung cancer than amphibole asbestos. The factor is uncertain but is probably about a factor of five although equality cannot be completely excluded.

(b) Epidemiological studies indicate that chrysotile is *much* less potent in causing pleural mesothelioma than the amphibole asbestos (amosite, crocidolite, tremolite, and actinolite) minerals and no evidence that chrysotile can cause peritoneal mesothelioma. The factor is uncertain but at least a factor of 50 times less and maybe an infinite factor less. This has been widely discussed, and is explained in the attached paper.

(c) The carcinogenic potency of asbestos depends on the shape and size and is greatest for fibers 10 microns or greater in length having widths of 0.2 microns or less yielding aspect ratios of 50 or more.

(d) It is widely believed that the latency for causing mesothelioma is longer than for lung cancer. This needs to be reexamined. Indeed, in the EPA 1986 risk assessment different models were used for each disease. For lung cancer, a model based on the work of Siedman and Selikoff with cancers beginning to appear 20 years after first exposure and continuing to appear for 40 years. For mesothelioma, a model was developed by Peto *et al. 1982* assuming that mesotheliomas begins decades after first exposure and the probability increases rapidly until death (Peto J, Seidman H, Selikoff IJ(1982). Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. British Journal of Cancer 45 124-135). We urge the SAB to be explicit about the definition of latency. Many epidemiologists define it as the time between the first exposure in a cohort and the first incidence of the disease. For the same data, it is evident that this varies with the size and duration of exposure in the cohort.

(e) Items (a) through (d) suggest that differences in biopersistence between the asbestos types would be an important factor and support a claim for chrysotile being less potent a carcinogen this has not been confirmed. Nonetheless, chrysotile may be removed from the lung more readily than amphibole asbestos.

(f) An implication is that any artificial fibers that have a similar shape and size distribution as asbestos, and do not disintegrate, must be viewed with suspicion as candidates for causing mesothelioma. Carbon nanotubes have these characteristics and EPA should view them with appropriate suspicion.

(g) Toxicologists have depended for a century on data on laboratory animals (mostly rats and mice) on warning of potential carcinogens. These ratios of potency between species, and in particular between animal and man seemed to be quantitative as expressed for example by Crouch

and Wilson in 1979. "Interspecies Comparison of Carcinogenic Potency,", *J. Tox. and Environ. Health*, 5:1095-1118, 1979. However, a major exception was apparent. When the world ignored this exception, incorrect public health recommendations were made and over 35 million people in Bangladesh alone are exposed to excessive levels of arsenic.

(h) While the animal to man comparison works (with the exceptions for arsenic noted above) no one has any real idea on the expected animal to man comparison for fibers. For fibers, structural details make a big difference in the carcinogenic potency. As nanotechnologies develop, and new products enter the market, understanding these will become ever more important.

The major lesson for the future is that we must watch carefully for any exceptions to established dogma. Any judgments such as these should be explicitly stated with a clear statement that if new data appear, the conclusions may be altered appropriately.

Yours sincerely,

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The Causes of Mesothelioma

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Introduction

Human mesothelioma can be caused by exposure to some types of asbestos and also by exposure to other naturally occurring fibers, erionite and asbestiform fluoro-edenite (Hodgson and Darnton 2000, IARC 1987, Paoletti *et al.* 2000). Most mesotheliomas with no exposure history to these particular fiber-types are background cases of mesothelioma for which no cause(s) has yet been identified. Asbestos is either an amphibole asbestos or serpentine asbestos. Four amphibole asbestos minerals – crocidolite, amosite, tremolite and actinolite - are well established causes of mesothelioma while anthophyllite is not. Asbestos is a term used in commerce, and hence by regulators since 1971, to describe a group of minerals used worldwide for their physical properties, which include fire protection. Indeed the very name comes from the Greek - "will not burn". Mineralogically, it is categorized into two mineral groups: serpentine (chrysotile) and amphibole asbestos.

Each asbestos type has a distinct chemical formula. Amphiboles are among the most common minerals in the earth's crust generally occurring in a massive nonasbestos form but under rare geological conditions these minerals can form as finely fibrous minerals called asbestos. The asbestos (fibrous) type damages the lung and related tissue while the nonasbestos analog has been shown to be markedly less hazardous, if it is hazardous at all. Chrysotile is a sheet silicate that rolls into nano-sized tubular structures possessing a hollow core, whereas amphiboles are double chain silicates (Bernstein and Hoskins 2006). Chrysotile was the most commonly used asbestos fiber-type and the only one of the six left in commerce. It is not surprising that the amphiboles and serpentine forms should also behave differently.

Asbestos minerals as a group have been causally associated with three diseases, asbestosis, lung cancer and mesothelioma. When we look at the mesothelioma causation evidence of each asbestos type separately, we find that four of the *amphibole* asbestos *can and have* caused mesothelioma. Nevertheless, chrysotile, a form of serpentine asbestos is different. There are now adequate data to suggest that the response of humans to chrysotile asbestos exposures of is very different from the response to the four-

amphibole asbestos types, especially for mesothelioma (Hodgson and Darnton 2000, Yarborough 2006). Whereas chrysotile can cause, and has caused, both asbestosis and lung cancer the proof that it causes human mesothelioma is limited to miners and millers with high occupational exposure in certain geological locales.

Exposure to which Amphibole Asbestos Mineral Increase Mesothelioma Mortality?

The first cluster of 33 mesotheliomas was found in a hospital in South Africa (Wagner *et al.* 1960). A careful examination of the limited lung parenchyma revealed the presence of asbestosis and asbestos bodies indicating asbestos might be the etiological agent in this cluster. A crocidolite asbestos mine, was found to be the source of the exposure. Sixty percent of the cases occurred among workers in the mine, 40% simply lived in the environment of the mine, and mill where exposures were lower, but a greater number of people were exposed. In another crocidolite mining area, Wittenoom, Australia there was a similar pattern of mesothelioma risk again predominantly after occupational exposure and some non-occupational cases (Hodgson and Darnton 2000, Reid *et al.* 2007, Table 1). Factories producing cigarette filters and military gas masks using crocidolite were also experiencing markedly increased risk of mesothelioma compared with the expected background described later (Talbott *et al.* 1989, Hodgson and Darnton 2000, McDonald *et al.* 2006).

The first report of mesothelioma among amosite-exposed workers occurred when Selikoff *et al.* 1972 reported five mesotheliomas among 105 deaths among Paterson, NJ factory workers producing amosite insulation products for the US Navy. In 1954 the factory moved to Tyler, Texas where a new workforce was occupationally exposed to amosite resulting in a similar excess mesothelioma mortality (Levin *et al.* 1998, Table 1). Occupational amosite exposures in a factory in Uxbridge, UK also caused increased mesothelioma mortality (Acheson *et al.* 1981, Acheson *et al.* 1984, Table 1).

The effect of non-occupational amosite exposure has only been studied in two Paterson, New Jersey groups – household contacts and those living in the neighborhood

of the factory. Among the household contacts four mesotheliomas developed among 115 deaths or 3.5% (Joubert *et al.* 1991). The mesothelioma mortality among the household contacts (with lower amosite exposures) is higher than any of the four cohorts with occupational exposure to amosite (Table 1). Mesothelioma mortality was 3.5% among the household contacts while in the general population it is 0.1%. No mesotheliomas occurred among the wives of the asbestos workers thought from earlier studies to be the contact with greatest risk of developing mesothelioma (Nolan *et al.* 2007).

The other non-occupational group to be studied was those who simply lived in the neighborhood of the Paterson amosite factory. The neighborhood cohort was restricted to males for ease of tracing. Mesothelioma mortality in the neighborhood of the amosite factory is less than the background in the United States general population (Table 1). Unlike crocidolite exposure, neighborhood exposures to amosite have not been associated with an increased risk of developing mesothelioma.

Finland was the major producer of anthophyllite asbestos from 1918 to the close of the mines in 1977. Epidemiological studies of these miners and millers did not find an increased risk of mesothelioma although the cohort did experience increased risk of lung cancer and asbestosis (Muerman *et al.* 1974). Timbrell *et al.* (1971) hypothesized; based on anthophyllite asbestos having fiber diameters greater than amosite and much greater than crocidolite, that exposure to anthophyllite asbestos would rarely, if ever, produce human mesotheliomas (see Timbrell 1989, for further discussion).

Evidence for anthophyllite asbestos-related mesothelioma is limited to case reports in which higher than expected amounts of anthophyllite asbestos were found in the lung parenchyma of individuals with mesothelioma. Initially the reports were of individuals occupationally exposed to asbestos but not as anthophyllite asbestos miners and millers. Lung content analysis revealed that in addition to anthophyllite asbestos other asbestos types more commonly associated with mesothelioma were also present (Tuomi *et al* 1989). By 1994, four mesothelioma cases were reported among anthophyllite asbestos miners and millers (Karjalainen *et al* 1994). All four had

exposures sufficient to induce asbestosis, which is consistent with the evidence that anthophyllite asbestos is weakly
mesotheliomagenic. This is the most persuasive evidence that uncontrolled exposure to anthophyllite asbestos may result in mesothelioma, particularly if the fibers are very thin. A mesothelioma case has recently been reported in a 38-year old male without asbestosis from neighborhood exposure (Rom *et al,* 2001). We remain skeptical about etiology in this case report.

Four Types of Amphibole Asbestos Have Been Shown Unequivocally to Cause Mesothelioma

The four-amphibole asbestos minerals – crocidolite, amosite, tremolite and actinolite - are known to cause human mesothelioma. We have quantitatively established the risk by developing Risk Ratios (RR) for the various asbestos types. Ideally, this would be done using a dose-response relation within the cohort studies for each asbestos type (Hodgson and Darnton 2000). Another approach is to compare the mesothelioma mortality in the exposed population to the general background of mesothelioma at the same time and in the same region. This introduces a source of uncertainty in addition to the statistical uncertainty that is hard to estimate and all too often ignored. In the USA for mesothelioma, the background rate (or rate in the general population) is about 0.1% among all persons with 0.17% among males and 0.045% among females (Table 2). Mesothelioma is 3.8-fold more common among males than females. One hypothesis for this observation is that males at work are more commonly exposed to asbestos than females.

In this paper, we examine the mesothelioma risk for each asbestos type separately. We list the data for the amphibole asbestos types in Table 1. For crocidolite, the Risk Ratio (RR) is 48 for the two mining and three manufacturing cohorts. All the cohorts independently show unequivocally that exposure to crocidolite can cause mesothelioma.

The result for amosite is less dramatic with a RR of 9.4 based on six cohort studies (Table 1).

Tremolite and actinolite are both calcium-rich amphiboles differing only in the amount of iron in an otherwise identical structure forming a solid-solution series (Ross and Nolan 2003, Hawthorne and Oberti 2007). These two types of asbestos were not widely used in commerce and were first associated with increase risk of human mesothelioma after environmental exposure rather than occupational exposure (Brown and Wagner 2001). Numerous case reports starting with Yazicioglu *et al.* 1980 describe an increased risk of mesothelioma from environmental exposure to tremolite asbestos particularly in whitewashes or stuccos (Ross and Nolan 2003).

Proportional mesothelioma mortality has only been reported in one cohort of miners exposed to tremolite-actinolite asbestos found in the vermiculite mine near Libby, Montana. The calcic amphiboles from this vermiculite mine contain sodium and potassium in sufficient amount to be called winchite and richterite (Hawthorne and Oberti 2007). McDonald *et al.* 2004 reported 12 mesotheliomas had occurred in 286 deaths or 4.2%. The calculated Risk Ratio for these tremolite asbestos exposed miners is 24.7. In a recent update Sullivan (2007), 15 mesotheliomas have now occurred among 767 deaths. Just three additional mesotheliomas (among them the first peritoneal mesothelioma death in the cohort) have occurred after an additional 481 deaths reducing the RR to 12 (Table 1). This trend is consistent with lower asbestos exposures in the younger workers in this cohort. Tremolite asbestos and the entire solid-solution series of tremolite-actinolite asbestos can cause mesothelioma.

Has Chrysotile Caused Mesothelioma?

Since exposure to four amphibole asbestos minerals discussed *supra* causes mesothelioma, analogy suggests that exposure to chrysotile can also cause mesothelioma. This common argument can be provisionally accepted for preventive public policy, *with a large uncertainty attached*, until there is more direct information on mesothelioma mortality among chrysotile-exposed populations. We show in this paper, that there are such chrysotile-exposed populations available and the evidence does *not* show an unambiguous increase in the risk of developing mesothelioma.

We specifically address the situations where there has been high exposure to chrysotile asbestos but only general background exposure to amphiboles (Table 3). The highest exposures occur among chrysotile miners and millers. We compare the fraction of male chrysotile miners and millers who develop pleural mesothelioma to the fraction of males in the same region, and at the same time period, who develop pleural mesothelioma in the general population. The number of females who develop mesothelioma is smaller, and their inclusion would only dilute the already weak evidence that chrysotile causes mesothelioma among males, so we restrict the calculations to males. For the same reason we restrict the calculation to pleural mesothelioma.

The crucial step in this discussion is to estimate the background pleural mesothelioma mortality in the general population of Quebec where the principal mining cohorts are located. We do so in three ways:

1. Health Canada reports the Standard Incidence Rates (SIR) for both Quebec and the US, which are 100 and 79 respectively. The rate is for males and females. In the US 0.1% of all deaths are from mesothelioma that by proportionality would be 0.126% in Quebec. Mesothelioma (pleural and peritoneal) is 26% more common in Quebec than in the US. We estimate that 0.17% of all US male deaths are from mesothelioma (Table 2), then Quebec 0.21% of all Quebec males deaths would be from mesothelioma.
2. Secondly, the incidence rates of mesothelioma per 100,000 living people each year in Canada are:

Site	**Males**
Pleural	1.7
Peritoneal	0.06

Quebec has a population of 7,492,100 and the Canadian death rate is 720 per 100,000. Recently about 54,000 deaths occur each year in Quebec and we assume 27,000 male deaths. If 64 male mesotheliomas were occurring among 27,000 deaths, the percentage of mesothelioma deaths among all male deaths in

Quebec is 0.236%.

3. Health Canada reports 1,210 male mesotheliomas cases in Quebec from 1982 to 2002 or on average about 57 cases per year if we again assume 27,000 deaths each year than 0.213% of all deaths among all males in Quebec is from mesothelioma.

Averaging the three estimates, we get 0.22% of all the deaths among males in Quebec are from mesothelioma. There are 0.44% male mesothelioma deaths among the Quebec chrysotile-mining cohorts. The ratio, the Relative Risk equals 2.0 (Table 3). Since the number of cases is 33, and the lower 90^{th} percentile of an "expected" 33 is about 23. This would be a risk ratio of 1.4, which satisfies our criterion that the confidence interval should not include one.

That this general line of reasoning is consistent and correct can be gleaned from the previous calculation for amphibole asbestos in Table 1. We found a Risk Ratio of 50 for a crocidolite based cohort. Since any effect of a pollutant will be proportional to RR-1, chrysotile asbestos is at least 25 times less likely to cause mesothelioma than amphibole asbestos. If we note also that, the exposure in the chrysotile mines is nearly 20 times higher than in the amphibole cohorts, the difference is even more dramatic.

Thus, the evidence that chrysotile asbestos can cause mesothelioma is marginal, and is statistically significant if the uncertainty of comparing miners and the general population is ignored. Some confounding must be added to the uncertainty in the general comparison between the workers in the mines and the general population. However, it is very likely that in the mining cohorts that there is confounding with other mineral fibers. Any such confounding would inevitably reduce the relative risk, and the evidence for general causation (see below) would then be inadequate.

Although the amount of confounding, and its uncertainty is hard to determine, no statement of risk is complete without a statement of uncertainty. The present authors make an estimate, based upon our professional judgment, that the number of cases in the

Quebec cohorts must be reduced by 10% with an uncertainty of 30% (90th percentile). This reduces the risk ratio for this cohort to 1.8, with a lower limit that embraces unity. This is discussed in detail in the next section.

Evidence of Confounding in Chrysotile Exposed Mining Cohorts

There is little, if any, disagreement that amphibole asbestos can, and has, caused both pleural and peritoneal mesothelioma. However, there is a considerable body of opinion, Hodgson and Darnton 2000, that chrysotile asbestos does not cause mesothelioma to the same extent, and indeed some claim that it may not cause mesothelioma at all (Yarbrough 2006). It seems likely on general theoretical grounds, that it can cause mesothelioma but with a much lower potency than the four-amphibole asbestos minerals.

We discuss confounding factors in the two chrysotile-exposed cohorts (Quebec miners & millers and the South Carolina textile workers). First, the largest number of chrysotile mesotheliomas, 33 cases, occurred among 7,456 deaths in the Quebec chrysotile mines (Hodgson and Darnton, 2001). The average exposure for these miners was 600 fiber/milliliter x years. Of the two major Quebec, mining areas the percentage of deaths from mesothelioma is 0.6% in the Thetford area and 0.2% in the nearby mining complex in the city of Asbestos.

The evidence that chrysotile has caused mesothelioma rest primarily on the high mesothelioma mortality in the Thetford area. But that may be confounded by the presence of fibrous tremolite in the chrysotile mine and/or other amphibole asbestos fiber-types (McDonald and McDonald 1995). These additional fibrous minerals are not present in chrysotile from South Africa or the Russian Federation (Rees *et al.* 1999, Rees *et al*. 2001, Nolan *et al*. 2006, Shcherbakov *et al*. 2001) and no increased risk of mesothelioma *has been reported* among these two cohorts of chrysotile miners and millers. Among Italian chrysotile miners a three mesotheliomas have been reported by Silvestri *et al.* 2001, the miners had a mean cumulative exposure of 570 fiber/miller x

years slightly less than the Canadian miners. The data therefore fail the consistency attribute suggested by Sir A. Bradford Hill to establish causation (Hill 1965).

Secondly, the South Carolina chrysotile cohort has recently been updated and 3 mesotheliomas have now occurred among 1,841 deaths or 0.16% of all deaths identical to the males in the US general population (Hein *et al.* 2007). The cohort is reported to have a strong exposure-response relationship between cumulative exposure to chrysotile and mortality from asbestosis and lung cancer. One hundred and ninety-eight lung cancers occurred where only 102 were expected and 36 asbestosis cases where none should have occurred. About 7% of the deaths in the Charleston cohort are from asbestos-related disease yet we cannot use this cohort to establish general causation for chrysotile exposure increasing the risk of developing mesothelioma. Hein *et al.* 2007 presented evidence of an exposure-response relationship for asbestos-related lung cancer and asbestosis in South Carolina cohort. The number of mesothelioma deaths in the cohort was too few for such an analysis.

Two mesotheliomas had been reported earlier within this group while the new case occurred in a short-term worker with 2.5 years of exposure and 50 years of latency. The complete occupational history in these three mesothelioma cases is not available and there are no lung content analyzes in these three cases to establish the concentration(s) and asbestos fiber-type(s) to which they were exposed.

The South Carolina factory did use a small amount of crocidolite 2,000 pounds or less than 0.03% the balance being chrysotile (Hein *et al.* 2007). Chrysotile was the most common asbestos fiber-type found in the lungs of deceased South Carolina workers consistent with the factory's asbestos consumption. An incidental and unexpected finding of lung content study was almost 12% of the asbestos fibers found in the pulmonary tissue of South Carolina chrysotile factory workers were crocidolite that represented less than 0.03% of the consumption (Pooley and Mirtha 1986).

Similar concentrations of crocidolite in the pulmonary tissue of other mesothelioma cases from South Africa have been shown to be associated with increased risk of human mesothelioma (Nolan *et al*. 2006). The available evidence supports a claim that the South Carolina workers had a significant crocidolite exposure but still the RR for the male workers is 1.5, higher than would be expected in the general population but values inconsistent with a claim for general causation of an increased risk of mesothelioma by this asbestos type (Table 1).

The chrysotile-exposed cohorts have either a small numbers of mesotheliomas or none, and this is not due to differences in the cohort size, insufficient latency, or exposure intensity. Among 28 deaths of workers exposed manufacturing crocidolite containing cigarette filters 5 mesothelioma cases were found. In the studies used to establish general causation for the four-amphibole asbestos types contained 5,337 deaths while the chrysotile-exposed cohort contained 10,540 deaths.

Although manufacturing workers in the United States are less exposed than the Quebec miners and millers, we also examine these cohorts (Table 3)**.** Among the general male US population, 0.17% will die from mesothelioma (Table 2). Three mesotheliomas occurred among 2,002 male deaths in the US cohort manufacturing chrysotile containing-products. The Risk Ratio (RR) for mesothelioma among the males in these three cohorts is 0.15/0.17 or 0.88, less than the general male population (Table 2). From this simple argument, it can be seen that averaging these manufacturing workers with the mining and milling workers would weaken the argument for general causation.

The cumulative exposures in the chrysotile user industries are lower than mining and milling that may also be an explanation for users industries having a lower proportional mesothelioma mortality. The chrysotile user industries either have slightly lower proportional mesothelioma mortality to the general population of the United States (Table 3). For the user industries and miners and millers the RR is 1.5.

Wagner *et al.* 1960 were able to readily identify 33 mesothelioma cases (40% having only non-occupational exposure) from crocidolite exposure while it took more than 30 years to find a similar number among the Quebec miners and millers with a paucity of non-occupational cases. Although the United States has consumed at least 24.5 million tons of chrysotile asbestos since 1931, the epidemiology available indicates there may be small excess of mesothelioma associated with high cumulative exposure with the confounding factors described *supra.*

We note that many scientists argue that one should compare the proportionate mortality in the high exposure cohort to a calculated historical background of mesothelioma in the period before there was widespread asbestos use from 60 years ago to about 20 years ago (Welch 2007). This is logically incorrect. Whatever the cause of the background exposure, the *background incidence* at the appropriate period of time and appropriate place must be subtracted from the *total incidence* in this cohort to arrive at the mesothelioma incidence from chrysotile alone. This is independent of whether the present background exposures are largely due to past asbestos exposures as we and others believe. Nevertheless, these past exposures included exposures to the four more potent types of amphibole asbestos.

General Causation

Unless a Risk Ratio (RR) is greater than 2 than the general belief that the postulated exposure is the cause of the effect is not generally accepted by scientists (Taubes, 1995). The data for chrysotile causing mesothelioma is marginal. If no account is taken of the uncertainty of the comparison of the miners and the background population, the Risk Ratio in the most important cohorts, the mining cohorts, is just 2 and the lower limit exceeds one. But in our view the confounding and other uncertainties both reduce the central value of the Risk Ratio and increase the uncertainty so that the lower 90^{th} percentile embrace unity. This is in stark contrast with the data for amphiboles, calculated similarly, where a comparison between Tables 1 that shows the Risk Ratio can be 50 times larger. The authors conclude that General Causation is not met for chrysotile causing mesothelioma.

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Table 1. Mesothelioma mortality in 13 epidemiologic cohort studies of individuals exposed to crocidolite, amosite, anthophyllite asbestos and tremolite-actinolite asbestos. The average cumulative exposures are from Hodgson and Darnton, 2000. Occupational exposures in all the amphibole asbestos cohorts (except anthophyllite) had increased risk of mesothelioma while the non-occupational cohort studies and the anthophyllite-exposed miners were either negative or suggestive.

Asbestos Fiber-Type	**Cohort Name**	**Total № of Mesotheliomas/ Deaths (%)**	**Mean Cumulative Exposure f/ml x Years§**	**Risk Ratio (>2)**
Crocidolite	**Miners**			
	South Africa(SA)	20/423 (4.7%)	16.4	28(4.7/0.17*)
	Wittenoom, Australia	231/2,549(9.1%)	23	54(9.1/0.17)
	Factory Workers			
	Gas Mask Canada	9/56(16.1%)		94(16.1/0.17)
	Gas Mask UK	5/219(2.3%)		13.5(17.8/0.17)
	Massachusetts	5/28 (17.8%)	120	104(17.8/0.17)
	Occupational Cohorts	***270/3,275(8.3%)***	***53***	**48 (8.3/0.17)**
Amosite	**Miners**			
	South African Miners	4/648(0.6%)	23.6	3.5(0.6/0.17)
	Paterson, NJ			
	Factory Workers	17/740(2.3%)	65	13(2.3/0.17)
	Household	4/115 (3.5%)	Unknown	35 (3.5/0.1)
	Neighborhood	1/780(0.12%)	Unknown	0.7(0.12/0.17)
	Factory Workers			
	Tyler, TX	6/222(2.7%)		16(2.7/0.17)
	Uxbridge, UK	5/333(1.5%)		6(1.5/0.17)
	Occupational Cohorts	**32/1,943 (1.6%)**		**9.4(1.6/0.17)**
	Miners			
Tremolite-Actinolite Asbestos‡	**Libby, Montana**	**15/767(2.0%) †**		**12(2.0/0.17)**
Mean for four amphibole asbestos minerals		**313/5,337(5.9%)**	**49**	**34(5.9/0.17)**
Anthophyllite Asbestos	**Miners**			
	Paakkila & Maljasalmi Finland	0/248(0%)	Unknown	

§ Hodgson and Darnton, 2001.*Background % of mesothelioma deaths in US general male population. † Sullivan, 2007. ‡Calcic amphiboles with increased sodium and potassium.

Table 2. The percentage of deaths due to mesothelioma in the United States in 2003 is given for the general population and the specifically males and females. About 2,560 mesotheliomas occurred in the United States in 2003 where the disease was about 4-fold more common in males (♂**)** than females (♀**).** A total of 2,448,288 deaths occurred in the US that year with 1,201,964 in males. US males in 2003 are expected to have 1 mesothelioma in 600 deaths. Recently in the US general population mesothelioma accounts for 1 death in 1, 000 deaths in the general population and 1 in 600 and 2,000 for males and females respectively.

Asbestos Fiber-Type	Mesothelioma Deaths Per 1,000 in General Population	Total № of Mesotheliomas/ Deaths (%) §	Average Cumulative Exposure f/ml x Years
United States	**1**	**2,560(0.1%)**	***Bkgd***†
Males	**1.7**	**2,000(0.17%)** ♂	***Bkgd***
Females	**0.45**	**560(0.045%)** ♀	***Bkgd***

†World Health Organization (1986) estimated the global background for asbestos in the ambient air to be between 0.001 and 0.01 fibers/milliliter and chrysotile is the predominant fiber-type.

§Mesothelioma as a percentage of all deaths.

Table 3. Data for the four chrysotile-exposed cohorts all the mesotheliomas are pleural. General causation (doubling the background risk of pleural mesothelioma) due to chrysotile asbestos exposure is marginal among the Quebec miners and millers. It critically depends upon the estimate of background mesotheliomas. Adding in manufacturing workers makes the evidence weaker.

Asbestos Fiber-Type	**Cohort Name**	**Total № of Mesotheliomas/ Deaths (%)**	**Mean Cumulative Exposure f/ml x Years§**	**Risk Ratio (>2)**
	Miners & Millers			
	Canadian Mines	33/7,456 (0.44%)	600	**2.0 (0.44/0.22*)**
	Manufacturers			
Chrysotile	**Charleston South Carolina** *Males only in Charleston SC*	3/1,186 (0.25%) §	28	**1.5** (0.25/0.17)
Chrysotile	**New Orleans, LA**	0/259 (0%)	22	**0**
Chrysotile	**Connecticut**	0/557 (0%)	46	**0**
	All Males Manufacturers	***3/2,002 (0.15%)***		**0.88 (0.15/0.17)**
	TOTAL all studies	***39/10,540 (0.37%)***	***170***	**1.5**

*Background % of mesothelioma deaths in Quebec general male population
§ Hein *et al.* 2007 the other data are from Hodgson and Darnton, 2000.