Health Canada Santé Canada

Chrysotile Asbestos Consensus Statement and Summary

Chrysotile Asbestos Expert Panel

Montreal, Quebec
November 13–14, 2007

This report was written by the Chair and members of the Expert Panel, and the opinions expressed therein do not necessarily reflect the views of Health Canada.

Canada

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Dear Ms Lloyd

I have pleasure in presenting to Health Canada the two reports of the Expert Panel on Chrysotile Asbestos, which met in Montreal, November 13-14, 2007 to consider at the request of Health Canada the relationship of lung cancer, pleural mesothelioma, and peritoneal mesothelioma to exposure to chrysotile asbestos.

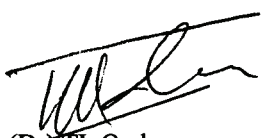
The reports are:
Summary Proceedings of the Panel Meeting. This is a chronological summary of the discussions, with some extra material which the panel agreed should be prepared and added.
Consensus Statement and Summary. This is a summary of the conclusions which the Panel felt that they could agree.

The Panel supported the approach of two major reviews, which give information on the relationship of the cancers to chrysotile exposure. Generally these show a strong relationship of exposure with lung cancer, but a much less certain relationship with mesothelioma. However, the Consensus Statement and Summary should be consulted for details.

All six panellists signed the Consensus Statement and Summary, but two attached reservations. The main points of these concerned: (1) whether chrysotile can be realistically distinguished from amphiboles in risk of lung cancer; (2) the unexplained and apparently much higher carcinogenicity of chrysotile in one textile plant; (3) the likelihood that risk may not be detectable at modern Canadian exposure levels.

The Panel included members who in the past have expressed strongly opposed views on this subject. Thanks are due to them for their willingness to work to find a common position as far as possible. Getting them to participate at fairly short notice was itself a significant achievement, for which Dr Michel Camus and Health Canada staff deserve major credit.

Yours sincerely



~~(Dr)~~ TL Ogden
Panel Chairman

Table of Contents

1 Panel assignment, and the evidence used..... 1

2. Mechanisms of Toxicity, and implications for risk evaluation..... 2

3. Use of the Major Epidemiological Reviews..... 3

4 Some limitations of meta-analyses in occupational asbestos studies..... 4

5 Cancer risk..... 6

6 Relative risk elicitation..... 11

Reservations with the Consensus Statement – Leslie Stayner..... 13

Reservations Concerning the Consensus Statement and Summary – G.W. Gibbs..... 15

Chrysotile Asbestos Consensus Statement and Summary

1 Panel assignment, and the evidence used

1.1 Health Canada convened the expert panel to assess cancer risks associated with today's typical chrysotile asbestos exposure in Canada, and to give an opinion on how the proportion of tremolite in commercial chrysotile influences the exposure-response relationship between chrysotile and risk. The panel was also asked to qualify risk estimates by putting a figure on their uncertainty, such as credibility ranges or, where possible, a probabilistic representation of plausible values.

1.2 *Meaning of terms in this Consensus Document.*
"Typical exposures in Canada" were stated to the Panel to be occupational exposures up to 0.5 fibre/ml (by phase contrast optical microscopy), and environmental exposures up to 0.0005 fibre /ml (by transmission electron microscopy).
"Tremolite" means fibrous forms of minerals in the tremolite-ferroactinolite series .
"Amphiboles" means tremolite, crocidolite and amosite.
As mined and used, chrysotile often contains a small amount of tremolite. This document uses "tremolite-free chrysotile" where it is necessary to distinguish chrysotile without tremolite, although tremolite-free chrysotile can vary slightly in its elemental composition.

1.3 In assessing the risks for chrysotile exposure, participants were instructed to consider tremolite-free chrysotile, even though it may not exist naturally. Likewise, when considering the role of tremolite in exposure risks, it was acknowledged that data on the extent of tremolite contamination is often unavailable. Therefore, participants were instructed to give estimates based on current information and knowledge

1.4 The panel met on November 13 and 14 at the Bonaventure Hilton in Montreal, Quebec, Canada, with Dr. Trevor Ogden in the chair. The panelists were Dr. David Bernstein, Dr. Kenny S. Crump, Dr. Nicholas De Klerk, Dr. Bice Fubini, Dr. Graham Gibbs, and Dr. Leslie Stayner. Dr. Michel Camus was present as the Health Canada panel organizer.

1.5 For convenience and to meet a tight timescale, Health Canada proposed that the panel focus on two recent meta-analyses of the relation of lung cancer and mesothelioma with asbestos exposure. One, by Berman and Crump[1], referred to here as B&C, was commissioned by the US

[1] Berman DW, Crump KS. Final Draft: Technical support document for a protocol to assess asbestos-related risk; Prepared for: Office of Solid Waste and Emergency Response U.S. Environmental Protection Agency Washington, DC. Report EPA # 9345.4-06. October 2003. The panel also had access to some material for the peer review of this document, and from three journal papers based on the work which are currently in preparation.

Environmental Protection Agency. The other, by Hodgson & Darnton[2], referred to here as H&D, is by two members of staff of the British Health and Safety Executive, and has been used by HSE in proposing asbestos regulations. However, some 60 relevant, mostly recent, papers were submitted by and distributed to members of the panel, and some members of the panel also made individual presentations.

2. Mechanisms of Toxicity, and implications for risk evaluation

2.1 The panel heard and discussed presentations on factors that elucidate the risks of the different types of asbestos and their different uses.

Mineral type and determinants of toxicity

2.2 There are two broad classes of commercial asbestos fibres: (1) amphiboles, which include crocidolite and amosite; and (2) the serpentine mineral chrysotile. Tremolite is an amphibole which is not deliberately mined, but often occurs in close association with chrysotile.

2.3 It is accepted that tremolite-free chrysotile and amphiboles are natural fibrous silicates with similar overall chemical compositions, but differing in crystal structure and therefore in fibre structure. Based on current research it is believed that geometric shape and size, surface chemistry, and biopersistence (which modulates cumulative exposure) are the primary factors which may influence the range of toxicities of fibres. However it should be kept in mind that issues related to how fibre concentrations are measured can also affect the apparent toxicity of fibres.

Biological effect and persistence

2.4 After inhalation, both classes of asbestos can interact with bodily defences in ways which may lead to cancer. The different crystal structures and compositions mean that amphibole fibres can stay in the lung much longer than tremolite-free chrysotile, and this may lead to amphiboles having greater biological effect. Well-conducted animal experiments which avoid the problems of overload have found that tremolite-free chrysotile disappears from the lung in a relatively short time, but nevertheless chrysotile is found in or near the lung of exposed individuals many years after their main exposure. The lungs of workers exposed to chrysotile contaminated with a small proportion of tremolite, which is an amphibole, typically contain a much higher proportion of tremolite than in the original asbestos. This raises the question of

[2] Hodgson JT, Darnton AJ, The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. *Annals of Occupational Hygiene* (2000); vol. 44(8):565–601

whether the greater biopersistence of the tremolite makes it more likely to be the cause of the disease than the inhaled tremolite-free chrysotile.

Fibre size

2.5 Various toxicological studies have found that longer and possibly finer fibres are more carcinogenic, and this is supported by Stayner et al's (2007) recent epidemiological study.[3] These differences may lead to some sources of exposure being riskier than others. Moreover, the conventional optical microscope method of measuring airborne asbestos gives equal weight to all fibres longer than 5 micrometres, does not count fibres shorter than this, and cannot see fibres thinner than about 0.25 micrometres. This means that exposure measured by the optical microscope method correlates imperfectly with risk, and may have a different relation with risk in different studies, because the asbestos size distribution depends on fibre type and process. Transmission electron microscopy can measure all fibre sizes.

3. Use of the Major Epidemiological Reviews

3.1 Over the course of the panel meeting, participants referred often to the H&D and B&C reviews, debating the merits and drawbacks of each one. Discussions frequently revolved around whether one analysis presents, or interprets, the data better than the other analysis. Overall, participants said that the two studies are generally in agreement with each other: both represent the situation fairly accurately, but in both studies Quebec chrysotile mining seems to have less disease than would be expected and the South Carolina textile manufacture seems to have more. This problem of heterogeneity is discussed in para 5.1.

3.2 It was recognised that new studies are always being published, and the discussion could only reflect what is available now, and mainly depended on work available to B&C and H&D.

3.3 The major differences in the approaches of the two reviews are as follows.

- 3.3.1 B&C took account of the estimated proportions of tremolite in the chrysotile exposures in each study, to try to isolate the effect of tremolite-free chrysotile. H&D did not take tremolite contamination into account, so that H&D's risk estimates assign effects to "chrysotile" which may be partially due to the tremolite component.
- 3.3.2 B&C modelled the relationship between exposure and disease within each study, whereas H&D used the mean result of each study. This means that the B&C approach could better adjust for different baseline risks of lung cancer (e.g. due to different smoking patterns) and different exposure histories of different cohorts, but was more

[3] Stayner LT, Kuempel E, Gilbert S, Hein M, Dement J. An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers . *Occ Env Med, on-line advance publication*, Dec 2007, doi:10.1136/oem.2007.035584

liable to effects resulting from important exposure misclassification within cohorts. H&D approach could use more studies, because they could include some with less detailed exposure-effect data.

- 3.3.3 B&C pooled the amphibole results, but H&D considered crocidolite and amosite separately. (H&D found crocidolite to give more mesothelioma than amosite, with no appreciable difference in lung cancer.)
- 3.3.4 B&C pooled peritoneal and pulmonary mesothelioma, and H&D considered them separately. (H&D found different relationships between the two for amosite and crocidolite.)
- 3.3.5 B&C assumed linear relationships between exposure and disease, and H&D allowed non-linear relationships. The major effect of this is at the low exposures where there is little or no data, and where H&D's model predicted greater risk for mesothelioma and smaller risk for lung cancer.
- 3.3.6 B&C used the limited data which is available to consider whether changing the measured fibre size range improved the correlations; H&D did not.

4 Some limitations of meta-analyses in occupational asbestos studies

Measures of risk

4.1 Meta-analyses and risk assessments are limited by the number of studies available for review, and the statistical power of these studies. Study design issues are also important, such as: knowledge of potential cofactors that cause diseases of interest of their own (e.g. smoking and lung cancer); effect modifiers that multiply or attenuate the effect of the exposures of interest (e.g. smoking and asbestos exposures are more potent jointly than separately); the capacity to identify outcomes clearly (e.g. diagnosis of mesothelioma has long been very uncertain, especially in studies based on death certificates); and, particularly for observational human studies, the capacity to characterize and quantify exposures adequately (see next sub-section).

Errors in exposure assessment

4.2 Epidemiological studies always state confidence limits reflecting the statistical errors for the risk term, but often cannot specify so clearly the errors in the estimate of exposure, and this is a serious problem in historical asbestos cohort studies. These errors will not generally produce an apparent risk where none exist if they are non-differential, ie if they are unrelated to the

disease status of the workers. On the other hand, even non-differential exposure misclassification usually leads to underestimation of the true magnitude of exposure-effect relationships, and can distort the shape of a relationship, making a linear relationship appear non-linear. The error can differ from study to study, from fibre type to fibre type, and from process to process. Sources of exposure misclassification can include the following.

- 4.2.1 Exposure concentrations estimated in published epidemiological studies were mostly determined by area monitoring, rather than personal monitoring, and this usually underestimates personal exposure and can miss short periods of high exposure.

- 4.2.2 Published epidemiological studies differ in the frequency and time period over which sampling was conducted. Little or no sampling was conducted prior to the 1950s, when exposure concentrations were probably higher than more recently. The early exposures must be estimated by extrapolation, an uncertain process.

- 4.2.3 Studies vary in the degree to which the various operations were directly sampled, and the degree to which exposures at unmeasured operations were estimated.

- 4.2.4 Laboratories often do not agree with one another when they measure the same environment, and this particularly affects measurements before modern quality checks became common in about 1980.

- 4.2.5 Exposure estimates from before about 1970 may have involved conversion from particle counts to fibre counts, a very uncertain process whose effect will have varied from environment to environment.

- 4.2.6 Optical microscopy as used for counting cannot distinguish between asbestos and non-asbestos materials, and it is possible that in some particularly dusty environments a significant amount of material counted was not asbestos, which would lead to variable underestimates of risk per unit of exposure in the different environments. Also many workers were exposed to asbestos other than the main type used in their job, and this may not be apparent in the measurements.

- 4.2.7 Changes in optical microscope methods have meant that modern exposure measurements will generally be higher than old measurements in the same environment, and the difference may be several-fold. This will affect comparisons between more recent and older studies, and between younger and older groups of workers.

- 4.2.8 As mentioned in paragraph 2.5, the fibre size range counted is often not identical with the size range of pathogenic fibres.

- 4.2.9 Individual samples can be subject to substantial random errors, particularly when small numbers of fibres are counted, but most data points in an epidemiological study pool many samples, which will reduce the random errors.

- 4.2.10 Exposures will be overestimated if workers wear protective equipment. This is more likely in the dustiest jobs, but the equipment was not widely used in some of the earlier cohorts..

- 4.2.11 Chrysotile as mined and used usually contains some tremolite, so disease due to one component may be misattributed to the other. B&C estimated the fraction of total asbestos exposure due to tremolite in different studies in order to estimate risks of tremolite-free chrysotile, and estimating this fraction is a further source of possible error.

5 Cancer risk

Heterogeneity and the two meta-analyses

5.1 Neither H&D nor B&C were able to resolve the heterogeneity in lung cancer response between the South Carolina textile workers and the Quebec miners and millers. Among Charleston (South Carolina) textile workers there was substantially more lung cancer risk per unit of exposure than in the other studies, and in Quebec miners and millers there was less, although the Quebec study is within the confidence limits of the overall relationship. The lung cancer risk in the Charleston cohort seems to be about seventy times the risk in the Quebec mining and milling study. This must be taken into account in applying the overall relationships to particular situations. (The recent reanalysis of the Charleston data by Stayner et al, referred to above, has shown that correlation between exposure and disease is improved by using a different fibre size fraction, analysed by TEM. The panel recommends that these techniques should be applied to the Quebec data and to other studies. This should clarify how the overall relationship should be applied to particular groups of workers, and should improve agreement of the different studies and narrow the confidence limits of the overall relationship.)

General statement

5.2 Some participants stated that presenting single-risk estimates would "gloss over" important nuances in the data. So at the end of the two-day panel, participants after much discussion agreed to offer Health Canada a general approach using a the following narrative statement

based on the two models. They suggested that Health Canada could use this information to tailor risk estimates for specific scenarios.

> *We believe that the approaches of Berman and Crump and Hodgson and Darnton are reasonable for estimating risk for mesothelioma and lung cancer in the light of present knowledge, subject to the following serious reservations. Application of the models to particular environments must take into account 1) and 2) in particular.*
>
> > *1) The lung cancer risks in chrysotile textile manufacturing at Charleston were higher than those predicted by these and other models. Further research may elucidate the reason for this.*
> >
> > *2) The lung cancer risks in chrysotile mining and milling are less than those predicted by these models. Further research may elucidate the reason for this.*
> >
> > *3) We are inclined to favour the linear approach of Berman and Crump.*
> >
> > *4) New data are likely to require updating of the models.*

5.3 Reservations 1 and 2 reflect the important heterogeneity referred to in paragraph 5.1. This means that caution must be used in applying the general relationship (using conventional phase contrast optical microscopy) to particular groups.

5.4 Reservation 3 reflects the fact that B&C assumed that the risk was proportional to cumulative exposure (fibre/ml.years), but H&D estimated non-linear relationships. The panel preferred the linear approach on the principle that a linear model is to be preferred unless data are available which reliably demonstrate non-linearity. (However, in B&C mesothelioma risk is linearly related to exposure intensity, and a given cumulative exposure resulting from an exposure of long duration has somewhat less effect than the same cumulative exposure resulting from a very short exposure.)

5.5 Reservation 4 reflects the fact that new studies are always being published, and should be taken into account in risk assessment.

Particular environments

5.6 The panel recommended that Health Canada should use the risk estimates applicable to particular relevant environments, where these are available, rather than rely on the general relationships.

Potency of tremolite-free chrysotile relative to amphibole

5.7 One of the Panel's objectives was to estimate the impact of tremolite content on the toxicity of chrysotile. This implies being able to estimate the relative toxicities of tremolite (an amphibole) and tremolite-free chrysotile. We therefore summarise the findings of the two meta-analyses on this relative potency.

Lung cancer.

5.8 For lung cancer, B&C found that, for results measured with the normal optical method, the best estimate of the potency of tremolite-free chrysotile relative to amphibole was 0.48 (ie the amphibole: chrysotile potency ratio was about 2:1), but the hypothesis that the two forms are equally potent could not be rejected (p=0.51). The hypothesis that tremolite-free chrysotile had zero potency was rejected (p=0.001). If different size ranges are evaluated, these conclusions are unchanged, although best value of relative potency and the p values are changed.

5.9 H&D's estimates for lung cancer give a much higher estimate of relative potency of amphiboles. At an exposure of 1 f/ml.yr, their best estimates of risk for the different types yield an amphibole: chrysotile ratio of about 40:1, with a possible range of 1:1 upwards. However, B&C's method allows different cohorts to have different background lung cancer rates, for example due to different smoking habits, so that B&C's estimate of relative potency may be better. Also, as noted above, H&D did not attempt to remove the effect of tremolite, so their estimates are for chrysotile as used, not for tremolite-free chrysotile.

5.10 Because the risk of chrysotile appears much greater in South Carolina textile workers than in Quebec miners and millers (para 5.1), excluding either of these cohorts will strongly influence the calculated potency of chrysotile relative to amphibole.

Mesothelioma.

5.11 B&C found that for results measured with the normal optical method, the best estimate of the potency of tremolite-free chrysotile relative to amphibole was 0.0033 (amphibole: tremolite-free chrysotile = 300:1), and the hypothesis that the two forms are equally potent was rejected (p=0.0007). The hypothesis that tremolite-free chrysotile had zero potency could not be rejected (p=0.61). If different size ranges are evaluated, these conclusions are unchanged, although best value of relative potency and the p values are changed.

5.12 What H&D refer to as their "best estimates" at 1 f/ml.yr yield a crocidolite: chrysotile ratio of 130:1, and amosite: chrysotile 18:1, but the uncertainty of the estimates leads to a very wide possible range of ratios. (Also, as already noted, H&D did not attempt to remove the effect of tremolite.)

Numerical estimates of risk given by B&C and H&D

5.12 For information, the overall risk estimates from the two meta-analyses are summarised in Table 1. These estimates are quoted here for information only, and were not discussed in detail or endorsed by the panel.

Table 1. Risk estimates for chrysotile as given by B&C and H&D. **This table is included for information only – the panel did not discuss specific estimates and therefore did not endorse these figures.** See paragraph 3.3 for important factors which affect comparison of the two sets of estimates. The figures in **bold** are Maximum Likelihood Estimates (B&C), or the "best estimates" (H&D). The figures flanking them are calculated confidence limits (B&C), or "cautious" or "arguable" figures (H&D). For lung cancer, H&D also give a higher "exceptional" figure (not shown) calculated from the Charleston study. The H&D" risk estimates for chrysotile include any contribution to risk by fibrous tremolite contamination (see para 3.3.1). The cumulative exposure levels in the table are for occupational exposure (assumed to be 8 hours per day, 240 days per year). The typical occupational exposure stated to the panel (0.5 f/ml) would give a cumulative exposure of 10 f/ml.yr if it lasted for 20 years. The typical environmental level (0.005 f/ml) for 168 hours a week for 50 years would give an occupational-equivalent cumulative exposure of about 0.1 f/ml.yr. by TEM, equivalent to a lower value by PCOM.)

Cumulative exposure (occupational exposure pattern: 8 hr/day, 240 days/yr)	Lung Cancer *Deaths per 100,000 exposed*	Mesothelioma *Deaths per 100,000 exposed*
0.01 f/ml.yr	B&C: 0.028 **0.083** 0.21 H&D: Possibly 0 **Very probably <1** Possibly 1.	B&C: 0 **0.01** 0.082 H&D: **Probably <1.** Highest arguable 1
0.1 f/ml.yr	B&C: 0.28 **0.83** 2.1 H&D: Possibly 0 **Probably <1** "Cautious estimate 3"	B&C: 0 **0.1** 0.82 H&D: **Probably <1** "Highest arguable 4"
1 f/ml.yr	B&C: 2.8 **8.3** 21 H&D: Possibly 0 **2** 30	B&C: 0 **1** 8.2 H&D: 1 **5** 20
10 f/ml.yr	B&C: 28 **83** 210 H&D: (no figure given) **50** 300	B&C 0 **10** 82 H&D: 6 **20** 60

Note on effect of smoking on these figures (by Dr K Crump). Among the issues that must be considered in interpreting the results of Table 1 is that these estimates of risk are for a general population that includes both smokers and non-smokers. Smoking is an independent risk factor for lung cancer and other diseases, but not mesothelioma, and a synergistic relationship has been found between smoking and asbestos in causing lung cancer. As a result, compared to the figures in Table 1 the asbestos-related risk of lung cancer would be smaller in non-smokers and higher in smokers. The reverse would be true for mesothelioma due to the fact that smokers have shorter life spans than non-smokers, although this effect is considerably smaller than the effect on lung cancer. B&C provide smoking-specific estimates of risk for both lung cancer and mesothelioma.

6 Relative risk elicitation

6.1 Exposure risks were discussed in general terms throughout the panel. On the second day, participants took part in a more formal relative risk uncertainty elicitation exercise. This was to obtain an indication of the panel's wide range of opinions. Lung cancer risk estimates were the most contentious, whereas mesothelioma risk estimates were more consistent. Because of the range of opinions, it was suggested that to come up with "average" risk estimates would be misleading. Instead participants offered statements of risk estimates. Some participants expressed concern over the small sample size of the exercise, noting that in the case of mesothelioma risks, for example, only four participants took part in the exercise.

Lung cancer

6.2 There was a wide and essentially irreconcilable range of opinions between participants on the exposure-specific risk for lung cancer. On the difference between amphiboles and chrysotile, panellists' "best estimates" ranged from a no difference to a 100-fold ifference. However, the uncertainty of each panellist was large and their uncertainty intervals did not all overlap.

6.3 Three panel members believed there was 0% and no more than 5% chance that chrysotile was at least as potent as amphiboles for lung cancer, one panellist gave a 10% chance, one gave it a 36% chance, and one gave it an 80% chance.

6.4 The heterogeneity and large uncertainty of expert opinions about fibre type differential for lung cancer prevented blending or pooling the panellists' probabilistic estimates. This is consistent with the heterogeneity of epidemiological observations aforementioned.

Mesothelioma

6.5 In regard to exposure-specific risks for both peritoneal and pleural mesothelioma, the relative risk uncertainty elicitation exercise seemed to suggest a possibility that chrysotile by itself may not cause mesothelioma. However, participants were unable to reach agreement on that statement in subsequent discussions.

6.6 Only four panellists gave an individual opinion of the relative amphibole/chrysotile potencies for mesothelioma. For either peritoneal or pleural mesothelioma, their best estimates concurred around an approximate 500-fold difference between amphiboles and chrysotile, with a 95% uncertainty interval of between 20 and 1000.

6.7 Some panellists expressed the opinion that a larger dose of asbestos is required for peritoneal mesothelioma compared to pleural mesothelioma, and one participant believed that exposures to chrysotile contaminated with tremolite did not cause any risk of peritoneal mesothelioma in the Quebec mines and mills.

6.8 Participants noted that for risk of mesothelioma, for each class of asbestos, the best-estimate predictions of H&D and B&C's models were within a factor of ten , for exposures above 0.1 f-yr/ml. The models also agreed that mesothelioma risk increases with increased exposure intensity.

6.9 No mesotheliomas were found at the lowest exposures in some studies and some panellists considered this to provide evidence of a threshold. However, other panellists noted this lack of response could be explained by the inevitable limitation of study power at the lowest exposure levels in a study.

6.10 It was proposed that following the panel, participants could add individual statements based on their own knowledge and experience. Several participants identified the need to clearly identify qualifying statements under headings, such as chrysotile and lung cancer or chrysotile and mesothelioma, for the sake of clarity.

Reservations with the Consensus Statement – Leslie Stayner

My primary disagreement with the consensus statement is with the following conclusion "*We believe that the approaches of Berman and Crump and Hodgson and Darnton are reasonable for estimating risk for mesothelioma and lung cancer in the light of present knowledge*..." I do not believe that either the Hodson and Darnton (2000) or the Berman and Crump (2008) reports provide reasonable models for predicting lung cancer risk for several reasons.

First the models from both analyses predict slightly lower lung cancer risk for chrysotile than to amphibole asbestos. The difference in risk in the Berman and Crump analysis is only 25 to 50% which is a trivial difference in risk assessment terms. More importantly having fiber type specific risk predictions for lung cancer is inconsistent with the findings from these analyses, which have failed to demonstrate clear statistical evidence for a difference in lung cancer risk by fiber type. In Berman and Crump (2008a) the hypothesis that the potency for lung cancer of chrysotile was different than the potency of amphiboles was strongly rejected in all of their models (p=0.23 to p=0.51). In Hodgson and Darnton (2000) the average lung cancer slope for chrysotile was similar to the slope for amphiboles when the studies of Quebec miners were excluded, and about an order of magnitude lower when the South Carolina textile cohort was excluded.

The lack of evidence for a difference in lung cancer potency for different fibre types is consistent with an analysis of rat inhalation bioassay data (Berman and Crump 1995), and of previous quantitative and qualitative analyses of the epidemiologic data (Lash et al. 1997, and Stayner et al. 1996). The fact that chrysotile is less biopersistent in the lung than amphiboles is frequently cited as a reason for assuming that the potency for lung cancer potency should be lower for chrysotile than for amphiboles. However, this reasoning rests on the assumption that residence time in the lung is an important determinant of lung cancer risk. The empirical evidence based on analyses of both the toxicologic and epidemiologic data simply does not support this assumption. This assumption also appears to conflict with the findings from the recent analyses of Berman and Crump (2008b) that demonstrated that the relative risk of lung cancer does not decrease after the cessation of exposure to chrysotile. If the limited biopersistence of chrystotile was a determinant of lung cancer risk then one would expect the risk to drop off rapidly after the cessation of exposure.

Second as both analyses report, and as acknowledged in the consensus statement, there is strong evidence that there was heterogeneity in the findings for lung cancer. As many authors have stressed it is generally not useful to present a summary estimate from a meta-analysis when there is substantial heterogeneity in the data [Rothman and Greenland 1998]. Rather than producing a summary estimate of risk the goal in this situation should be to search for an explanation for the heterogeneity. As noted in the consensus statement, the heterogeneity in this case appears to be largely (but not entirely) due to the large difference in slopes for lung cancer risk that have been derived from the studies of chrysotile exposed miners and millers in Quebec [Liddell et al. 1997], and the textile workers in South Carolina [Hein et al. 2008]. However, this is not really an explanation of the heterogeneity since it does not explain why these studies have produced such different findings for lung cancer risk. In a previous meta-

analysis Lash et al [1997] reported that the heterogeneity in the findings for lung cancer was explained by difference related to industry type, methods used for measuring asbestos, tobacco habits, and standardisation procedures. A similar search for the causes of the heterogeneity was lacking in the reports produced by Hodson and Darnton and Berman and Crump.

Finally, I am concerned that in order for the meta-analyses to "represent the situation fairly accurately updated" they should be updated with the most recently published epidemiologic studies. Several relevant studies have been published since these reports including one study that my colleagues at NIOSH have just recently published [Stayner et al. 2007], which would be highly relevant particularly for the fiber size specific approach that was used by Berman and Crump [2008a].

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Reservations Concerning the Consensus Statement and Summary – G.W. Gibbs

Precision is sometimes lost in consensus documents. This is logical because an attempt is being made to accommodate sometimes quite diverse opinions. I believe this to be the case in a number of instances in this document. Thus, my comments are made to ensure somewhat greater precision concerning matters where my interpretation of what is written may differ from that of another reader. My comments are as follows:

Paragraph 2.2

The statement is made that "tremolite is an amphibole which is not deliberately mined, but often occurs in close association with chrysotile."

In fact tremolite and actinolite have been sporadically mined in various parts of the world.

Paragraph 2.3

The statement is made that tremolite-free chrysotile and amphiboles are natural fibrous silicates with similar overall **chemical** compositions…

This is incorrect: The elements that are essential to the various minerals are as follows:

Chrysotile - magnesium silicon oxygen and hydrogen.
Tremolite - calcium, magnesium, silicon, oxygen and hydrogen.
Amosite - ferrous iron, magnesium, silicon, oxygen and hydrogen
Crocidolite - sodium, ferrous iron, ferric iron, silicon, oxygen and hydrogen.

The main silicate component of all the amphiboles is $Si_8O_{22}(OH)_2$ while the silicate component of the chrysotile is $Si_2O_{5.}(OH)_4$

I would not consider these to have "similar overall compositions".

Paragraph 3.3.5

The statement is made that: "The major effect of this is at the low exposures where there is little or no data….

I do not agree with the statement concerning the "little or no data".

First, low is not defined in this context.

Second, exposure-response relationships such as that based on the Quebec chrysotile mining and milling cohort rely on relative levels of exposure. That is, the risk increases in relation to increasing levels of exposure. The lowest categories of exposure in these relationships could be quite high by today's standards but might be considered low if they do not increase risk and the population in those levels of exposure can be quite large. For example, Liddell et al (Annals of Occup Hyg 41; 13-36 1997) reported that in their cohort there were 51.30 thousand person years at risk in men from the age of 55 on with exposure to that age of less than 300 mppcf-years of exposure (estimated to be about 900 f/cc-years). These workers showed no increase in risk in relation to increasing exposure up to this level of exposure. However, there was a definite increase in the risk of lung cancer above this level and that increased with increasing exposure. The number of person-years represented in the part of the exposure-response curve where the lung cancer risk did increase with exposure was 8.6 thousand person years. If low exposure is defined as levels at which risk does not increase with exposure then the Quebec mining study included large numbers of such persons. Of course the exposures were enormous compared to the levels that we are concerned about today. Liddell concluded: "These findings indicate that except at very high levels of exposure, several orders of magnitude higher than any presently permitted, adverse effects on health will not occur". It seems reasonable to conclude that when there are no exposure-related increases in risk at levels orders of magnitude above levels of concern today, that there are unlikely to be any detectable risks at present day exposure levels. There are data in some studies.

Paragraph 4.2.6

The statement is made that: "Also many workers were exposed to asbestos other than the main type used in their job".

I do not know whether this is correct or not. We do know, from lung burden studies that some workers were exposed to fibre types other than those with which they worked, but whether this is "many" I do not believe we have the evidence to support this generality.

Paragraph 5.1

A. The statement is made: "Among Charleston (South Carolina) textile workers there was substantially more lung cancer risk per unit of exposure than in the other studies and in Quebec miners and millers there was less, although the Quebec study is within the confidence limits of the overall relationship."

This term "overall relationship" is not clear to me.

The Quebec chrysotile mining and milling cohort results for lung cancer are clearly within the confidence intervals of B&C for all the chrysotile industry sectors and all the predominantly chrysotile industry sectors, but do not overlap with those for the Charleston cohort (See Fig 1 B&C paper 2).

The Charleston cohort confidence intervals are barely within the confidence intervals of the other chrysotile industry sectors and do not overlap at all with those of the Connecticut friction or Quebec mining industry cohorts.

The H& D report (Figure 3) includes more cohorts than B&C. Their results make it even clearer as the Quebec mining and milling confidence intervals are within those of all the chrysotile only cohorts except for the cohort from the Carolina textile cohort. The latter's confidence intervals only just overlap with the intervals from one of other sector chrysotile plants and not the others..

This may assist Health Canada in deciding which industry sector chrysotile data apply in Canada as textile operations no longer exist here.

B. In the same paragraph, the statement is made that: "This should clarify how the overall relationship should be applied to particular groups of workers, and should improve agreement of the different studies….".

While I am optimistic that this may improve agreement between studies, I believe the wording is too strong for the current level of evidence. However, I do believe that examining the long fibers (>40 micrometers) as well as the composition of those long fibers in the textile and mining industry sectors is important.

Paragraph 5.8

This low amphibole: chrysotile potency ratio results from the inclusion of the Charleston cohort data in determining the overall potency for chrysotile. In section 5.10 that cohort is acknowledged as showing a considerable greater lung cancer risk than cohorts in the chrysotile mining and other chrysotile industry sectors. What we know is that two well conducted studies (the Quebec mining and the Charleston textile) give quite different lung cancer risks. In my view, the heterogeneity renders the comparison in 5.8 inappropriate and potentially quite misleading in that we think we know the precise lung cancer risks associated with chrysotile but we do not. Completely different ratios are obtained depending on which of the chrysotile industry ratios is used in the comparison with the amphiboles.

Paragraph 5.10

Based on our current knowledge, the risk of lung cancer in the Charleston cohort per f/cc-year **is** much greater than that in the Quebec chrysotile mining and milling cohort. While these may be prove to be same or similar if, in the future, we are able to find the parameter/exposure/factor that is responsible for the difference, on present evidence the Charleston cohort, in my opinion more than "appears" to present a higher risk of lung cancer. The 95% confidence intervals in all studies show the Charleston and Quebec risk estimates are not the same. That is what we currently know.

GW Gibbs
March 4, 2008.

Health Canada Santé Canada

Chrysotile Asbestos Expert Panel

Health Canada

Summary Proceedings of the Panel Meeting, Montreal, Quebec November 13–14, 2007

This report was written by the Chair and members of the Expert Panel, and the opinions expressed therein do not necessarily reflect the views of Health Canada.

Canada

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Ms. Karen Lloyd, Acting Director General
Safe Environments Programme
Healthy Environments and Consumer Safety Branch
Health Canada

18 March 2008

Dear Ms Lloyd

I have pleasure in presenting to Health Canada the two reports of the Expert Panel on Chrysotile Asbestos, which met in Montreal, November 13-14, 2007 to consider at the request of Health Canada the relationship of lung cancer, pleural mesothelioma, and peritoneal mesothelioma to exposure to chrysotile asbestos.

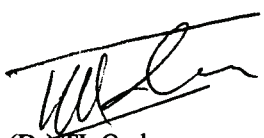
The reports are:
Summary Proceedings of the Panel Meeting. This is a chronological summary of the discussions, with some extra material which the panel agreed should be prepared and added.
Consensus Statement and Summary. This is a summary of the conclusions which the Panel felt that they could agree.

The Panel supported the approach of two major reviews, which give information on the relationship of the cancers to chrysotile exposure. Generally these show a strong relationship of exposure with lung cancer, but a much less certain relationship with mesothelioma. However, the Consensus Statement and Summary should be consulted for details.

All six panellists signed the Consensus Statement and Summary, but two attached reservations. The main points of these concerned: (1) whether chrysotile can be realistically distinguished from amphiboles in risk of lung cancer; (2) the unexplained and apparently much higher carcinogenicity of chrysotile in one textile plant; (3) the likelihood that risk may not be detectable at modern Canadian exposure levels.

The Panel included members who in the past have expressed strongly opposed views on this subject. Thanks are due to them for their willingness to work to find a common position as far as possible. Getting them to participate at fairly short notice was itself a significant achievement, for which Dr Michel Camus and Health Canada staff deserve major credit.

Yours sincerely



~~(Dr)~~ TL Ogden
Panel Chairman

Table of Contents

Participants **1**

Day 1: Welcome; Presentation of the Panel: Mandate, Agenda, and Procedures **3**

Discussion of Comparative Mineralogy and Toxicology of Chrysotile Asbestos Relative to Amphibole Fibres **5**

Physicochemical Characteristics and Mechanisms of Asbestos Toxicity **5**

The Toxicity of Chrysotile and Amphibole Asbestos **8**

Discussion 10

Discussion of Comparative Mineralogy and Toxicology of Chrysotile Asbestos Relative to Amphibole Fibres (Continued) **15**

Epidemiological Evidence on Chrysotile Asbestos Exposure-Response Models **16**

Effect of exposure errors upon risk estimates 27

Exposure-Specific Risk Estimates for Peritoneal and Pleural Mesotheliomas **27**

Day 2: Epidemiological Evidence for Lung Cancer **28**

Exposure-Specific Estimates for Typical Exposure Models and Exposure-Specific Risk Estimates for Lung Cancer **35**

Continuation of Dose Response Estimation; Indication of the Degree of Confidence of the Individual Panelists' Estimates; Synthesis of Main Areas of Agreement and Disagreement **38**

Conclusion, Thanks, Homework Directives, Deadlines **47**

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Day 1:
Welcome; Presentation of the Panel:
Mandate, Agenda, and Procedures

Patricia Hoes introduced Dr. Michel Camus, the meeting's organizer. Dr. Camus welcomed participants to Montreal and thanked them for taking time from their busy schedules to join the panel. "This issue is challenging and controversial," he said, explaining that Health Canada sees the panel as a key source of information to guide decisions from a policy perspective in the future.

"We all have different opinions," he said. "We want to have a fair discussion and debate." One of the meeting's goals was to define areas of agreement and disagreement. Dr. Camus also advised participants that they would need to supply risk estimates by the end of the day on Wednesday, November 14; they should keep this in mind over the next two days.

Dr. Camus referred to background material that had been distributed prior to the meeting, in particular the Hodgson and Darnton paper, telling participants they did not necessarily have to align their recommendations with these materials, as they were simply intended as a starting point. More important was to understand any divergences and uncertainties of opinion. "Uncertainty should be your middle ground and we should discuss from there," he said.

Canada is not the only country in the process of reassessing its risk estimates for asbestos, said Dr. Camus, but it is one of the first. He explained that the United Kingdom and the United States are undergoing similar exercises in a similar manner. "So you're trendsetters, coming here," he said.

Dr. Camus reminded participants that he needed Declarations of Interest and summaries of their biographies before the end of the meeting. He also advised participants that the meeting was being recorded, but the tapes would not be made public. The Conference Publishers (Ottawa, Ontario) would use the tapes to generate a report of the meeting. The report will be submitted to participants for revisions before the final draft is produced for them to sign. Participants will be free to append their own comments to the report if they disagree with any parts of it. Dr. Camus said the personal risk assessments requested prior to the meeting would be kept confidential, and participants should inform him if, at any time, they wished to speak "off the record."

Following this review of the mandate and procedures for the panel, Dr. Camus introduced Dr. Trevor Ogden, chair of the meeting.

Dr. Ogden expressed his thanks and said he would be "pushing" participants over the course of the meeting to reach consensus, or at least a reasonable common opinion, so Health Canada could start its policy processes from a sound basis.

Introductions of panel members

- Dr. Ogden introduced himself as an aerosol scientist, not an expert on asbestos; however, he has handled policy on asbestos, headed research on hazardous dusts, and chaired a British panel on exposure limits.
- Dr. Leslie Stayner is currently a Professor of Epidemiology at the University of Illinois at Chicago. He was previously the Chief of the Risk Evaluation Branch at the National Institute for Occupational Health and Safety (NIOSH), where he conducted research on asbestos and acted as an advisor to other agencies developing policies on asbestos, including the World Health Organization and the US Environmental Protection Agency (EPA).
- Dr. Nicholas de Klerk has over 25 years of experience in asbestos-related epidemiology. He has published numerous papers on asbestos-related diseases and has been an advisor to the World Trade Organization (WTO) on asbestos-related issues.
- Dr. Bice Fubini is a chemist by trade, has published several papers on asbestos-related topics, and, as head of an interdepartmental centre for the study of asbestos, has been involved in several multidisciplinary projects in asbestos research.
- Dr. David Bernstein was originally a physicist before re-educating in toxicology. He has been working in the field of fibres and asbestos since 1977, and has published several papers on the differences between chrysotile and amphibole asbestos.
- Dr. Graham Gibbs started work in this field in 1959. He has many publications on asbestos and he has organized international workshops on chrysotile asbestos and chaired several committees.
- Dr. Kenny Crump has worked in the fields of risk assessment and asbestos for 30 years. He has a fellowship with the EPA and has published several papers on the topic of asbestos.
- Dr. Morley Brownstein is a research chemist who has been involved in asbestos regulation since the 1970s. He was responsible for developing most of Canada's restrictions on asbestos under its Hazardous Products Act.

Dr. Ogden also introduced the observers in the room: Greg Paoli, Simon Pietrocatelli, Bernardo Li, Patrick Chevalier, Caroline Gratton, Tamara Trudeau, Sheryl Bartlett, Patricia Hoes and Jacinta Aungier.

Mandate, agenda, and procedures

Following the introductions, the agenda for the next two days was distributed. Participants were told that the timing on the agenda was not fixed, but all points needed to be covered. Dr.

Ogden said, "The purpose is not to solve all outstanding problems … but to focus on Health Canada's needs in this area." He also reminded participants that the key focus for the meeting was to provide direction to help Health Canada assess the risk for particular chrysotile asbestos exposures, in particular pure chrysotile and tremolite-contaminated chrysotile.

"I think ideally Health Canada would like to know what the role of tremolite is in asbestos-related disease," Dr. Camus said, adding that not much information is available on the extent of contamination, and participants would have to make decisions based on the information and knowledge they had currently.

Discussion of Comparative Mineralogy and Toxicology of Chrysotile Asbestos Relative to Amphibole Fibres

Physicochemical Characteristics and Mechanisms of Asbestos Toxicity

Dr. Bice Fubini
Professor
Faculty of Pharmacy
University of Turin, Italy

Dr. Fubini outlined the three areas she would cover in her presentation:

- Accepted mechanisms and physicochemical features involved
- Mineral structure, fibre dissolution and leaching, and fragmentation
- Surface chemistry

Past research on fibre toxicity has shown that the three major determinants of toxicity are form and size, surface chemistry, and biopersistence. "Those three things all together are responsible for the extent of toxicity of fibres," said Dr. Fubini. In particular, crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, can change surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids will influence their biopersistence, a factor that modulates cumulative exposure.

There are two broad classes of commercial asbestos fibres: (1) amphiboles, which include crocidolite and amosite; and (2) the serpentine mineral chrysotile. All are crystalline silicates. Tremolite is an amphibole which is not deliberately mined, but occurs in close association with chrysotile, and so is usually a minor constituent of commercial chrysotile.

The fibres interact in many ways with body defences. Upon inhalation, the fibres react with the extracellular matter. Some fibres are immediately cleared by the mucociliary escalator or phagocytosed by alveolar macrophages (AM), "but very often, they don't make it," said Dr. Fubini. This leads to macrophage activation and release of oxidants, cytokines, and growth

factors in the surrounding medium. This ultimately leads to AMs' death, release of the engulfed fibres, establishment of a continuous ingestion re-ingestion cycle with consequent damage to epithelial and mesothelial target cells. The fibres themselves may also act directly on the target cells and cause damage. Reactions between cells and fibre products may occur.

As a result of these processes, several things occur. First, the antioxidant defences of the cell, such as ascorbic acid and GSH, become depleted. Next, oxidation stress, inflammation, and fibrosis may increase. Primary genotoxicity occurs where the fibres act directly on the cells, and secondary genotoxicity may be caused by cell products and their interactions with the fibres. The result of all these stresses is mesothelioma or lung cancer.

"Each step [in this process] is governed by a different physicochemical feature of the fibre," said Dr. Fubini. Reactive metal ions on the surface of the fibre trigger the antioxidant defences. The fibre shape and size results in "frustrated phagocytosis" and the release of reactive oxidation species (ROS) and many other AM-derived factors. The length of the fibre also plays a role. Phagocytosis may clear short fibres more easily than longer ones. "But fibre-derived free radical release is the major reason why damage occurs," Dr. Fubini said.

Dr. Fubini summarized this part of the presentation with a quote from Kamp and Weitzman (*Thorax*, 1999; 54, 638-652): "...no single mechanism fully accounts for all the complex biological abnormalities caused by asbestos."

The next part of the presentation compared amorphous synthetic fibres with crystalline mineral fibres. Chrysotile is an inorganic, crystalline, natural fibre. The European Community directive on synthetic vitreous silicate fibres is largely based on biopersistence data for synthetic vitreous fibres (SVFs). However, the extent to which biopersistence data from SVFs may be extended to other fibres remains unknown, and thus cannot be generalized to other fibres, like the organic and the mineral crystalline ones (Bernstein *et al.*, *Inhal Toxicol* 2005; 17; 1-41). "More research is needed," said Dr. Fubini, adding that in fact, chrysotile and vitreous fibres are quite different.

In natural mineral fibres like chrysotile, the mineral spontaneously crystallizes into fibres because of constraints of the structure; in contrast, vitreous artificial fibres are obtained in fibrous form by forced extrusion of a melted silicate mixture through a small hole. The dissolution properties of the two types of fibres are also different. Chrysotile has relatively poor solubility, selective leaching, and incongruent dissolution, which ultimately leaves a fibrous structure even if mainly made up by the silica framework. This fibrous habit is retained even under strong mechanical and chemical attack. Fibres may also split into smaller fibrils yet retain a fibrous structure. In contrast, SVFs have congruent dissolution, solubility depends on the individual chemical compositions, and when ground, lose fibrous habit and become an isometric particle dust. Dr. Fubini presented transmission electron microscopy (TEM) images from various publications, demonstrating what happens to chrysotile fibres in high temperature

and acidity, compared with SVFs. "They are still fibrous," she said, "whereas with SVF, they break down into isometric particles."

In cross-section, chrysotile fibrils have a spiral structure because of a mismatch in spacing between the magnesium and hydrated silica layers. In contrast to the strong covalent bonds connecting these layers, the van der Waals inter-particle forces holding together different fibrils are weak. Consequently, when chrysotile breaks, it does not disperse into isometric particles; but instead gives rise to a large number of fibrils. When amphiboles break, they do so along planes within the crystal structure, and the pieces generally retain fibrous aspect. The resulting product of both classes of asbestos therefore is always in fibrous form. In contrast, SVFs break into progressively smaller pieces, and lose their fibrous form.

Past and recent literature data report that selective leaching of chrysotile occurs in strong acidic or chelating conditions, resulting in removal of Mg^{2+} ions and eventually some silica moieties. As far as the actual dissolution mechanism is concerned, the dissociation kinetics varies according to origin of the material, mechanical treatments, and associated contaminants. First, acids remove the exposed Mg^{2+} ions, which weakens the fibrils. Next, H^{+} ions bind to the hydrated silica sheet, resulting in the very slow removal of silicic acid. In the natural environment, chrysotile does not dissolve, said Dr. Fubini, adding that chrysotile nanofibres have been identified in weathered soil debris from the Balangero mine.

Surface reactivity plays a major role in fibre toxicity. An active surface site converts various molecules into free radicals. In traces, transition metals, namely iron (Fe^{2+}, Fe^{3+}), react at the fibre surface. Iron is always present in asbestos, either as a constitutive element or as Fe^{2+} substitute for Mg^{2+} ions, as in chrysotile and tremolite. "In nature, you don't find a chemically pure chrysotile," said Dr. Fubini. "All mineral fibres contain some chemical contaminant."

To test whether chemically pure chrysotile posed the same cytotoxicity and genotoxicity as natural chrysotile, Dr. Fubini and her associated groups prepared a pure synthetic chrysotile and tested it. "We had no chemical activity and no cellular damage," said Dr. Fubini. This does not mean it is not dangerous, she cautioned, but rather suggests that iron-free chrysotile does not induce *in vitro* cell and DNA damage. In contrast, all responses typical of natural forms are restored when the synthetic chrysotile is doped with iron traces, including fibre-derived ROS production. (Gazzano *et al., Toxicol Appl Pharmacol* 2005; 206:356-364)

Dr. Fubini concluded her presentation with four points:

- Synthetic vitreous fibres have different leaching and breaking patterns from natural crystalline fibres.
- Amphiboles are more stable and biopersistent than chrysotile.
- Chrysotile fibres split into smaller fibres and fibrils, which retain fibrous characteristics even at the nanoscale.

- Pure chrysotile is a "Utopia."

In the discussion period following the presentation, Dr. Fubini clarified that the single chrysotile fibrils, although never measured in length within the pristine mineral, when in soils or living matter are generally shorter t hen the fibre bundle , usually less than five microns and seldom longer than 20 microns. "They are persistent," she said "and there are no data stating how dangerous they are".

The Toxicity of Chrysotile and Amphibole Asbestos

Dr. David Bernstein
Consultant in Toxicology
Geneva, Switzerland

Dr. Bernstein explained that biopersistence is one of four criteria the European Community uses for classification of synthetic vitreous fibres (SVFs), and that it is an area that he had been asked to coordinate. He and his colleagues looked at the biopersistence of fibres and determined that there was a strong correlation of the biopersistence of the longer fibres (> ~ 20 μm) with fibrosis as a precursor to tumours following inhalation, and with tumour incidence following intraperitoneal injection studies.

Before describing his toxicity data, Dr. Bernstein reviewed the physical properties of chrysotile and amphiboles and the difference between the two, which included many of the points already covered by Dr. Fubini.

Dr. Bernstein described a typical biopersistence study in rats, which followed the protocol established by the European Commission. The rats were exposed to commercial fibres from Canada, the United States, and Brazil, not the artificially prepared fibres created by grinding that have been commonly used in previous animal-model experiments. Grinding can change the fibre structure and can contaminate the material with stainless steel. "So [studies which have used this ground material do] not have anything to do with what is sold commercially," said Dr. Bernstein, "[and] have little validity because it was ground so finely."

In one of the biopersistence studies that is representative, Dr. Bernstein explained that the rats were exposed to 14,805 fibres/cm^3, of which 200 fibres/cm^3 were greater than 20 microns in length. This was a high exposure to longer fibres, which was important, according to Dr. Bernstein, because macrophages cannot carry away fibres longer than 20 microns. However, he added that surprisingly, these long fibres still disintegrate or dissolve. To find out where the fibres deposited in the lung, Dr. Bernstein used confocal microscopy to image in 3D the lung, identifying the length and diameter of the fibres, and where the fibres are within the lung. This procedure permitted quantification without bias as the confocal microscopy allowed examination of a cube of the lung without the need for sectioning.

The longer amphibole fibres were quite biopersistent, staying in the lung without dissolving. In contrast, the longer chrysotile fibres were cleared from the lung with a half time ranging from 0.3 to 11.4 days. Even the shorter fibrils were cleared in all cases with clearance half times similar or faster than those for insoluble dusts.

"There is a radical difference in how the lung handles [chrysotile versus amphibole]," said Dr. Bernstein. He said he believes macrophages play an important role in this difference. Chrysotile dissolves readily in acid *in vitro*. This has been documented by Pundsack, *J Phys Chem* 1955; 59: 892-895. In contrast, tremolite and amosite show very little dissolution even in hot acid. Dr. Bernstein used transmission electron microscopy to measure the clearance of fibres from the lung, using confocal microscopy to confirm this independently and to show the fibre location. He was able to show that after 90 days, no fibres remained, but some small pieces could be seen in macrophages. Most of the pieces were under five microns, and none was longer than 20 microns.

Within macrophages, chrysotile is exposed to a pH of about four, which appears to be sufficient to begin breaking apart the fibres. Once the fibre is "broken up," the macrophages take it away. In the particles that remained, Dr. Bernstein and colleagues saw by TEM-EDAX only silica without magnesium; Dr. Bernstein added that this confirms leaching.

If this is the case, the next question is how to explain all the older inhalation studies that showed chrysotile is carcinogenic. Dr. Bernstein said he believes the problem lies with the dosing used in the earlier studies. Studies performed between 1960 and 1985 exposed animals to enormous fibre concentrations, up to 1 million fibres/particles per cubic centimetre of air, whereas the workplace TLV is 0.1 fibres/$cm^{3.}$ The lungs of the rats, which are considerably smaller than those of humans, were therefore overloaded.

"Putting so much material in the lung causes the macrophage system to break down due to overload," said Dr. Bernstein. Under these conditions, insoluble particles have been shown to be carcinogenic, stemming from the retarded macrophage clearance. These impaired macrophage-mediated alveolar clearances at high dose are not observed at lower doses in rats. Oberdörster (*Inhal Toxicol* 2002; 14; 29-56) proposed two high-dose effects and two thresholds: the first is a threshold in pulmonary dose that results in a reduction of macrophage-mediated clearance; and the second, at higher doses, occurs when antioxidant defences become overwhelmed and tumours develop.

A similar overload effect is seen in cell culture studies, in which calculations show that cells were exposed to up to 250 fibres per cell, compared to a typical workplace exposure in humans of 0.0005 fibres per cell. "If you have 1,000 times or 10,000 times [exposure], maybe we could start to extrapolate human hazard," Dr. Bernstein said, but he questioned performing *in vitro* studies at 28 million times human exposure.

In a 90-day sub-chronic inhalation toxicity study, rats were exposed to commercial Brazilian chrysotile for six hours per day, five days per week, for 13 weeks. This was followed by 13 more weeks of observation. At 5,000 times the US workplace limit of 0.1 fibres/cm3, no fibrosis or other pathological endpoint was observed at any time point. At 15,000 times the US limit, an exposure calculated to be approaching overload, minimal fibrosis was observed. Chrysotile also produced a less inflammatory response in a similar 90-day study than a synthetic mineral fibre, CMS, which is not considered a carcinogen.

Dr. Bernstein also presented data from an earlier study that examined lung histopathological sections, following exposure to filtered air, and following inhalation exposure to chrysotile (for 90 days) or amphibole (for 5 days). After 90 days' exposure to chrysotile, the sections looked very similar to the control lung samples at the bronchiolar-alveolar junction. "You see more macrophage but no pathology," Dr. Bernstein said. In contrast, following five days of exposure to amphibole, interstitial fibrosis and pathology are clearly visible within 28 days.

Dr. Bernstein concluded that the difference in histopathological response is clear: the longer chrysotile fibres clear rapidly and do not result in a pathological response. Tremolite following early tracheo-bronchial clearance does not clear from the lung, and initiates a rapid and severe inflammatory response leading to interstitial fibrosis within a few weeks

Discussion

Following the presentation, Dr. Ogden asked whether Dr. Bernstein was proposing that fibrils were broken up due to the pH generated by the macrophage inside the lung. "Whether it is just the acidic environment or other things, I can't tell you. No one has looked at them separately," Dr. Bernstein replied. "It may be pH 4 or enzymes." Dr. Fubini said that in her opinion, a pH of four would not be enough to dissolve the fibres.

"If the chrysotile fibres dissolve into fibrils, aren't fibrils still small fibres?" asked Dr. Stayner, who suggested that perhaps the chrysotile does not disappear from the lung, but is simply undetectable. Dr. Bernstein responded that a transmission electron microscope was used and no lower limit was set; thus, the resolution was sufficient to see all fibrils. He added that he agrees with Dr. Fubini that chrysotile has been seen in human lungs, and that it is clear that these short little pieces get into lymphatic tissue, and can be stored in other compartments.

He believes, however, that current lung sampling methods used in biopsy samples can preferentially sample areas in which short fibres can accumulate. His studies show that the small fibres enter the interstitial area, but then leave. Also in the lymphatics, his team found many free fibres floating through the channels. "So lots of stuff is being washed down this drainage system without macrophage," he said. "They get stopped in lymphatic tissue and probably dissolve over time, but in a slower time than in the lung."

Dr. Gibbs asked whether Dr. Bernstein had looked to see if the fibres really entered the lung and if he was confident he would have seen the fibrils if they were there. Dr. Bernstein replied that they used TEM, and he was confident it would have captured the fibrils. "But even if we didn't, there was no pathology," he added.

Dr. de Klerk said to Dr. Bernstein, "You said shorter fibres had a longer clearance but […] you showed a noticeable difference between US, Canadian, and Brazilian clearance, [which] seemed to be the opposite." Dr. Bernstein responded that it is possible that the Canadian textile sample had more long fibres, so it took a little longer for them to clear. When the longer fibres break up, they contribute to the number of shorter fibres present. Thus, the clearance of the shorter fibres represents not only the clearance of those shorter fibres deposited but also the accumulation of shorter fibres that result when the longer fibres break apart.

Dr. Crump raised the issue of total fibre load versus fibre length, saying they had carried out a meta-analysis about 10 years ago and found that lung cancer risk did not correlate at all with total fibres, but did correlate with long fibres. "That doesn't seem to work with overload theory," Dr. Crump said. Dr. Gibbs asked why "we only get 20% tumours" with amphiboles, because the histological evidence from the slide presented by Dr. Bernstein would seem to suggest a higher expected incidence.

On the subject of fibre length, an unidentified panel member added that in a six-month study done by Wagner with a lower total fibre load, 80% of rats had developed tumours. The discrepancy would only make sense if fibre size were taken into account.

Dr. Stayner added that 0.1 fibres/cm^3 is a regulatory standard, but actual exposures in the epidemiologic investigations has generally been 10 to 100 times that concentration. Moreover, much of the exposure in these environments is not to chrysotile fibres, but rather to dust. "In South Carolina, 95% of stuff that was in the air was dust, not fibre," he said, "so doesn't this also impact overload?" He added he is not certain that overload does not occur in humans, particularly when other exposures, like smoking, are taken into account. "I think it is wrong to say that we know that lung overload doesn't happen in humans," he concluded.

Dr. Ogden said it was difficult to ascertain the other cofactors in exposure. In some studies, chrysotile accounted for only 1% of total dust exposure. Unfortunately, few, if any, studies have actually characterized that dust, he said. Dr. Ogden also agreed that very high exposures to any kind of dust could be dangerous and cause lung cancer. Dr. Gibbs added that dust exposure levels are much lower today than in the past. He recalled that in the 1960s, dust was cleaned from machines using compressed air. The resulting dust was so thick it obscured visibility past a few feet.

Dr. Ogden raised a point of discrepancy between Dr. Fubini's and Dr. Bernstein's presentations. In her presentation, Dr. Fubini had said that if fibrils persisted, this would suggest they should "resist the break-up [Bernstein] described," Dr. Ogden said. Dr. Bernstein replied that it was

unclear whether the fibrils are actually broken down or are removed from the lung. He said the shorter fibrils might be transported to the lymphatic system, where they are deposited into a neutral compartment in the lung that does not produce disease.

Dr. Ogden said many reports exist showing that chrysotile persists in human lungs for a long time. "That seems to be inconsistent with your picture," he said. Dr. Bernstein suggested that what were being measured were the chrysotile fibres that have been transported to other compartments like the lymphatics; once the fibres are in this compartment they are not associated with disease process: "Most people have huge dust exposures. […] What you are seeing is the 1% remaining in compartments, which I believe aren't doing anything at all."

Dr. Fubini said she thought the various types of chrysotile behave quite differently. Furthermore, in contrast to Dr. Bernstein, she said the UICC standard would be expected to be less dangerous because of the extensive amount of grinding the samples underwent "This may explain [why Dr. Bernstein's] data is not representative of all exposures," she said. She also expressed surprise over the half times presented by Dr. Bernstein, challenging that he had only used his own data and not the other present in the literature. Dr. Bernstein responded, "No one else has done studies."

In terms of overload, Dr. Fubini said, with chrysotile fibrils, the exposed surface area should be a better metric than the number of fibres and fibrils.

"The term 'solution' of chrysotile seems rather difficult for me to accept," said Dr. Fubini. Her team has been able to destroy chrysotile only through a combination of ultrasound and high acidic or chelating media, yet a solid phase persisted, and she said she doubted that in the lung, macrophages could do what her team could not do in the laboratory. Dr. Fubini also said the dissolution of chrysotile in a strong acid medium could not be compared with the disappearance of fibres longer than 20 microns from the lung. Dr. Bernstein said that about 10% of fibres in his study were longer than 20 microns. "Those longer than 20 are falling apart using some mechanism," he said. Macrophages pick up fibres in the range of five to 20 microns and break them down into particles of less than five microns. Since this results in the creation of more small fibres, it appears that fibres less than five microns are clearing more slowly than they actually are.

Addressing Dr. Fubini's point regarding the UICC standard, Dr. Bernstein said it was designed as a reference sample, not a commercial product. "What we study are commercial products, not reference products," he said. He added that although he had shown only one set of data in his overload presentation, five or six other studies appear to support the model, although fibre count needed to be back-extrapolated in these. "I understand that you disagree about the mechanism," he said. "To me the mechanism is not important. What is important is that the animals clear it."

Dr. Ogden asked Dr. Fubini and Dr. Bernstein if they felt Dr. Bernstein's work undermined the two mechanisms that might lead to inflammatory response or carcinogenesis proposed by Dr. Fubini in her presentation. Dr. Fubini replied that the question was hard to answer since inflammatory response is not necessary for mesothelioma. "We are confusing overload, reported for an excess of dust," which would in any case only concern lung cancer, she said. While mesothelioma is another story, overload effects have never been related to mesothelioma. While this is not really her field, Dr. Fubini said she understood that two different processes yield the two diseases.

Dr. Stayner questioned whether fibrosis is necessary for cancer, saying this is an unresolved question. "Just the fact that there is a lot less fibrosis in Dr. Bernstein's experiments doesn't necessarily suggest that there will be less lung cancer," said Dr. Stayner.

Dr. Bernstein replied that in every animal study his lab had examined, fibrosis was a prerequisite to developing lung cancer; however, he was uncertain whether fibrosis was causal or parallel. Dr. de Klerk said people who die from mesothelioma often do not have fibrosis. Dr. Bernstein said he was talking specifically about lung cancer.

Another point of contention regarding Dr. Bernstein's presentation related to evidence from Suzuki, which both Dr. Fubini and Dr. Stayner had mentioned. Suzuki autopsied the lungs of North American insulation workers and reported a higher percentage of chrysotile fibres compared to amphiboles in pleural plaques. Dr. Bernstein responded that he has concerns regarding Suzuki's methodology. "When you open the lung cavity at autopsy, everything just falls out," he said. "The fluids are all over the place."

Dr. Bernstein also spoke about autopsy analyses that were negative for fibrosis. He said these studies could easily have missed fibrosis, probably because they took only small samples of the lung and not enough locations were sampled. "The lung is not homogeneous," he said.

Animal models often differ from epidemiological observation, said Dr. Gibbs, who added he was not sure if researchers even know what is taking place in the animal models. "I think it's come a long way [in terms of improving our] understanding, but in terms of mechanisms, we are still at the hypothesis stage," he said.

Summarizing the discussions, Dr. Ogden said the overload theory does convincingly undermine a great deal of the earlier animal work. He added that although participants disagreed on the mechanism, chrysotile does appear to clear rapidly from lungs. On the other hand, chrysotile is still found in the lungs post-mortem and participants are unsure how mesothelioma supposedly caused by chrysotile fits into the picture.

Dr. Gibbs said Dr. Pooley had looked at lung fibre burden in mesothelioma cases and controls. "Their results are quite telling," he said. The study suggested no link between chrysotile and

mesothelioma, because the lungs of exposed workers did not show a higher fibre burden compared to controls.

Referring to the earlier discussion on exposure levels in studies, Dr. Stayner said he wondered whether data obtained from epidemiological studies with high exposure levels might also be less relevant. Dr. Bernstein said he thought these studies were useful but had limitations. "If you go too high, then you change the mechanism," he said. "Once you pass certain levels [of exposure], the lung reacts differently."

Dr. Crump said a clear dose-response relationship exists with long structures; however, he was unsure how that related to overload. He also cautioned against drawing conclusions from the amount of chrysotile seen in lungs at death, because that makes assumptions about the time course of disease. Dr. Crump said if chrysotile does its damage fairly soon after entering the body, whether it is lung cancer or mesothelioma, there might be little difference in fibre load between exposed individuals and controls. Moreover, it is not possible to know whether the fibres found in the compartments in the lungs are there due to recent exposure or previous exposure.

Dr. Gibbs said evidence from cumulative lifetime exposure in miners shows that higher exposure means higher lung burden (Rowlands N., Gibbs G.W., McDonald A.D. "Asbestos fibres in the lungs of chrysotile miners and millers--a preliminary report." *Ann Occup Hyg.* 1982;26: 411-415). He added that the data was "very crude and limited," however. Dr. Stayner said studies suggest that fibrous tremolite lung burden is a better marker of chrysotile exposure than chrysotile lung burden. Dr. Gibbs said this is true, but chrysotile burden is related to cumulative exposure as well.

Dr. Camus asked participants if they thought chrysotile and amphiboles affect cell health differently, especially in light of the biopersistence data and surface reactivity, and in terms of their effects on the lung or the pleura. Dr. Crump replied, "Just because amphiboles reside in the lung a long time doesn't mean that they don't do their work early on."

Dr. Fubini said she thought most participants agreed that differences exist in biopersistence, but they did not agree on the extent of the difference. In terms of surface chemistry, she said little difference exists between amphiboles and chrysotile, and added, "There is much more iron in some amphiboles, [but] as far as our lab tests can tell, there is not much difference in surface reactivity mechanisms." She also said she did not know whether fibres or fibrils were more important in terms of their effects on the lung, and that she believed macrophages played a role in the pathology. Dr. Ogden added that the duration of the persistence of the fibres might also be pertinent.

Discussion turned again to the validity of studies using UICC samples. Dr. Bernstein said he felt the grinding process changes the reactive process and adds metal contaminants to the sample.

Dr. Fubini argued that she would expect the UICC samples to be less active than the commercial samples because of the grinding; consequently, data from these studies are important and should be considered. Dr. Bernstein said he agreed the samples would have a different potency, but did not agree this would be less than commercial samples.

Discussion of Comparative Mineralogy and Toxicology of Chrysotile Asbestos Relative to Amphibole Fibres (Continued)

Following the lunch break, Dr. Ogden asked the panel members to wind up the morning's discussion on the comparative mineralogy and toxicology of chrysotile asbestos relative to amphibole fibres. The panel would then discuss the epidemiology of mesotheliomas.

The panel discussed the biopersistence of chrysotile in the lungs. Dr. Ogden said that this persistence, years after exposure, seems to be an important factor in determining the toxicological properties of the fibres. The panel members agreed, but suggested interpreting this observation cautiously.

Dr. Stayner said the chrysotile in the lung might have been sequestered in some way, or rendered harmless, meaning that its presence would not have an effect. Dr. Gibbs said it had been suggested in the 1950s that chrysotile fibres sequestered within ferruginous bodies could presumably become potentially potent if the ferruginous bodies ruptured.

Earlier, Dr. Fubini had presented data from studies showing the differences in the mineralogy and chemistry of amphibole and chrysotile. Dr. Ogden asked Dr. Fubini if amphibole and chrysotile fibres affected cells with the same mechanisms.

Dr. Fubini said the surface chemistry mechanism might be the same, but other mechanisms, including translocation and macrophage clearance, would be different. She said the presence of iron ions in all mineral chrysotiles might influence its biological response, since synthetic chrysotile without iron contamination does not induce chemical and cellular responses. The iron content of asbestos fibres may be involved in the generation of reactive oxygen species that lead to pulmonary and pleural toxicity. "The absence of iron could stop one component of the toxic mechanism," said Dr. Fubini.

In summary, Dr. Ogden said the presence of iron in chrysotile might affect its toxicity, but that it is not the only component of the toxic mechanism.

Epidemiological Evidence on Chrysotile Asbestos Exposure-Response Models

Dr. Kenny S. Crump
Research Professor
Mathematics and Statistics
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The panelists moved on to discussing the epidemiology of chrysotile asbestos exposure-response models and exposure-specific risk estimates for peritoneal and pleural mesotheliomas. Dr. Crump presented the results from three papers he co-authored with Dr. Wayne Berman, an environmental scientist at Aeolus, Inc. in Albany, California. The three studies, listed below, were originally developed for the US Environmental Protection Agency (EPA):

- "The Effects of Time and Exposure Concentration on Asbestos-Induced Lung Cancer and Mesothelioma"
- "Update of Potency Factors for Asbestos-Related Lung Cancer and Mesothelioma"
- "New Metrics for Assessing Asbestos-Related Cancer Risk that Address Fiber Size and Mineral Type"

The EPA assessment of asbestos potency, developed in 1986, considers asbestos and amphibole equally hazardous in the development of lung cancer and mesothelioma. Dr. Crump presented the results of the first paper, which assessed the adequacy of the EPA models. They developed a new model in which they assigned different potencies to amphibole and chrysotile, and to different-sized fractions.

According to the EPA model for mesothelioma, the mortality rate at time *t* from the beginning of exposure is given by:

$$I_M(t) = 3 \times K_M \times \int_0^{t-10} E(u) \times (t-u-10)^2 \, du$$

where E(u) is the exposure (f/ml) at a time u, and K_M is a proportionality factor called the mesothelioma potency factor. (The factor 3 is required for K_M to have the same meaning as used in the 1986 EPA document.)

One implication of the model is that even with short-term exposure, the risk of mesothelioma continues to increase. "We addressed whether this was an adequate representation of what we see in the epidemiological studies," Dr. Crump said.

Working from three sets of raw data from cohorts from South Carolina, Wittenoom, and Quebec, and one data set from a detailed report from a New Jersey cohort, Berman and Crump

plotted mesothelioma deaths against cumulative exposures for each cohort and compared the agreement between the observed number of deaths and the number predicted by the EPA model.

The EPA model states that mesothelioma risk depends on intensity of exposure, duration of exposure, and time since exposure. For the Wittenoom and Quebec cohorts, the model underestimates the number of deaths at low exposure intensities and overestimates the number of deaths at high exposure intensities. Dr. Crump said the curves suggested a supralinear dose-response for mesothelioma. However, inaccurate exposure estimates could also generate a similar curve.

Berman and Crump also compared the fit of the EPA model with the observed data on mesothelioma mortality after exposure ended. The risk continued to increase up to 50 years following exposure in the Wittenoom, Quebec, and New Jersey cohorts. "Mesothelioma risk increased in a supralinear fashion with increased exposure intensity after controlling for duration of exposure and time since last exposure," said Dr. Crump.

(A supralinear relationship is one that predicts higher risk at low exposures, and lower risk at high exposures, than a linear relationship through the data; for example risk proportional to exposure raised to a power less than one.)

Dr. Stayner said random exposure misclassification might cause the supralinear curve. The model would also generate a supralinear curve if the highest exposures were underestimated. Dr. Crump agreed.

Dr. Crump presented a meta-analysis that evaluated the mesothelioma potency of different-sized amphibole and chrysotile fibres. In the current EPA approach, amphibole and chrysotile fibres longer than five microns are considered equally potent. Dr. Crump said data limitations and uncertainty made interpretation of the analysis difficult in some cases. He also expressed interest in adding the data from the South Carolina cohort that Dr. Stayner had mentioned earlier in the day.

In their studies, Berman and Crump developed three models based on the width of the asbestos fibres:

- A "Thin" model with lengths equal to or greater than five microns and widths equal to or less than 0.4 microns.
- A "PCME Widths" model with lengths equal to or greater than five microns and widths equal to or greater than 0.2 microns.
- An "All Widths" model with lengths equal to or greater than five microns and all widths.

The Berman-Crump analysis assigned no potency to fibres shorter than five microns, found a much higher potency for amphibole than chrysotile in causing mesothelioma, and found no

significant difference in potency of fibres of different widths. However, he expressed doubt about the last conclusion, because of the problems with the exposure data. "Our data doesn't discriminate width, but personally, I don't believe that. I think there are problems with the exposure data," he said. Dr. Ogden said the panel was more interested in the conclusions regarding fibre potency than size effects. Dr. Crump said size may sometimes be important because it could affect the potency, but agreed that in the analysis he and Berman had been able to carry out thus far, width did not seem to have influenced potency. "We just don't have the data," he said.

Dr. Ogden and Dr. Gibbs said Dr. Crump's meta-analysis did not differentiate between peritoneal and pleural mesotheliomas. Dr. Gibbs said this is important to remember when considering the results, because the risks of mesothelioma at these two sites are not equal.

The panel members discussed amphibole contamination of chrysotile and its influence on mesothelioma risk. In their analysis, Crump and Berman set amphibole contamination of chrysotile at values ranging from 0.3% to 1%. Dr. Stayner said he had a study in press in which amphibole represented 0.01% of the fibres in the South Carolina chrysotile study.

Future analyses should include newly available data from their study, said Dr. Stayner. Since the collection of the data used by Berman and Crump and Hodgson and Darnton, researchers have developed powerful new techniques for counting asbestos fibres. Phase contrast optical microscopy (PCM) is less powerful than electron microscopy, but was used to count the fibres of most of the samples evaluated in both the Hodgson and Darnton and the Berman and Crump studies. Dr. Stayner said new transmission electron microscopy (TEM) data from a South Carolina cohort indicated more long fibres than had previously been observed with PCM.

He said a new Chinese study might be useful for including in an updated analysis.

The panelists discussed the relative potency of amphibole and chrysotile for mesothelioma. In the *WATCH* paper[1], Darnton compared the relative potency for mesothelioma in the Berman and Crump study with the Hodgson and Darnton study. For exposures between 0.1 and 10 fibre-years per millilitre, the ratio of amphibole to chrysotile was 300 to 1 in the Berman and Crump study. It was 150 to 1 in the Hodgson and Darnton paper. Dr. Crump said the confidence intervals in his study might encompass the values obtained in the Hodgson and Darnton analysis, and vice versa. (It was later pointed out that Hodgson and Darnton's "chrysotile" included chrysotile contaminated with tremolite, but Berman and Crump's "chrysotile" was tremolite-free.)

1 *The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure – a comparison of risk models based on asbestos exposed cohorts*, by Andrew Darnton. Paper prepared for the British Health and Safety Commission's WATCH Committee, Nov 2007, and made available to the Panel

The panel talked about the differences between the Berman and Crump and Hodgson and Darnton papers, and their possible causes.

Hodgson and Darnton used cohort means for exposure and overall response in their calculations, whereas Berman and Crump evaluated the dose-response within each cohort. Hodgson and Darnton's approach meant that people with very low exposure were grouped with those more highly exposed to produce one data point, so that the risk at very low exposures could not be determined. Berman and Crump's approach did not have this problem.

Dr. Ogden said the averaging out of minimally exposed individuals in the Hodgson and Darnton evaluation is an issue for Health Canada because the agency is interested in the risks of mesothelioma at low cumulative exposure. At 0.01 fibre-years per millilitre, the Darnton model gives 15 times the risk of mesothelioma mortality given by the Berman and Crump model. Dr. Ogden said there was not much data on the mesothelioma risk at low exposure. “Tell me if you disagree, but neither of you have actual information at that level,” he asked. Dr. Crump said he agreed there is not a lot of data at low exposure levels.

The Berman and Crump analysis generated a supralinear dose-response curve for mesothelioma mortality. The panelists discussed whether there were biological grounds for choosing a supralinear model over a linear one, or whether Dr. Crump’s preference for a linear model lay in its simplicity. Dr. Crump said he believes it is biologically implausible for a supralinear model to extend across all doses. At lower doses the dose response should become linear.

Dr. Gibbs said there is data to support non-linearity at very low doses. For example, in the Quebec chrysotile cohort, no mesotheliomas were detected among miners with less than two years’ exposure in the industry. (Concentrations in this industry were up to three orders of magnitude higher than current OELs.) This data supported the hypothesis that a threshold exposure is necessary to develop mesothelioma. “But I’m not saying there is one,” said Dr. Gibbs, “although there may well be a practical one.”

Dr. Crump said examples like Dr. Gibbs’ add little to the discussion because it is possible not to find any effects of a substance at very low doses in any assumed dose-response situation. “The data [isn’t] good enough to make those distinctions,” he said. Dr. Ogden asked if data from animal toxicology studies could help to clear up the effect of chrysotile at low exposure doses, but Dr. Crump pointed out that toxicologists would encounter the same interpretation problems at low doses.

Parsimony is an important principle in modelling, said Dr. Camus. The simplest model is often the most robust, due to a tendency to over-fit the data when adopting a complex model. Poor exposure data from historical studies means that a high rate of misclassification among the workers must be expected, and could explain the discrepancies between the model and the epidemiological data in the high- and low-exposed groups. “Should you not then assume a

linear model and presume that most of the effect is seen due to exposure misclassification?" Dr. Camus asked. Dr. Crump said he and Berman hoped to investigate this issue within each cohort in the future.

Dr. Camus asked Dr. Crump if there were significant differences between the Berman and Crump and the Hodgson and Darnton reports, even though each group had used different data and approaches. Dr. Crump said the relative potency for chrysotile and amphibole were comparable. In Dr. Crump's opinion, the biggest difference between the two studies was the type of model each group used. Hodgson and Darnton recommend using a non-linear model at low doses, whereas Berman and Crump do not.

Dr. Stayner said supralinear dose-response curves are common in studies of occupational exposures and are observed in exposures to dioxin and radiation (Stayner et al. *Scand J Work Environ Health* 2003;29(4):317-24). He added that supralinear curves might be due to biases in the data, exposure misclassification, and/or the healthy-worker survivor effect, where only the healthiest workers will live long enough to receive the highest exposures. The experience of friction product manufacturing was mentioned, where several independent studies and reports have concluded that there has been no chrysotile-linked increased risk of mesothelioma or lung cancer.

Dr. Ogden asked if the Hodgson and Darnton and the Berman and Crump studies were in agreement with respect to the relative risk of mesothelioma mortality from different types of asbestos. He said the Hodgson and Darnton study showed that the relative risk of mesothelioma mortality from chrysotile, amosite, and crocidolite was 1:100:500. In other words, amosite is 100 times as potent as chrysotile, and crocidolite is 500 times as potent as chrysotile. Dr. Crump said there was good agreement between the two studies.

Dr. Bernstein asked that the panel spend some time discussing the exposure estimates on which the models are based and the lack of consideration of uncertainty in exposures used in the models.

Dr. Ogden asked Dr. Crump to talk about the quality of the exposure estimates in his studies, and how he distinguished between the amphibole and chrysotile studies. Dr. Crump said there have always been issues with the chrysotile exposures of some cohorts. Some of the exposure estimates in the Berman and Crump model came from the literature, while others were assumed, he said. Dr. Stayner asked if it was fair to say that none of the analyses takes into account the uncertainty of exposure. Dr. Crump said in their analysis, he and Berman had subjectively included the limitations in exposure information.

Dr. Gibbs raised some concerns over the ability to detect fibres of different lengths and widths and, therefore, different asbestos types when using PCM. Nearly all amosite fibres will be counted because "we see virtually all of them on a filter," he said. Most chrysotile fibres from mining samples will be detected, but not all. Most chrysotile fibres will also be counted in the

textile industry, but many textile fibres which are slightly longer than the measurement limit (five microns) may also be thin and may not be counted . Many crocidolite fibres, which are long and narrow, will not be counted at all. "Even though we are talking about the same denominator, they really are quite different. I don't think there is anything we can do about it in the short term, but it is something to realize," he said.

Dr. Gibbs' comments sparked discussion over the accuracy of the exposures in Berman and Crump's analysis. "How much do we really know about what they were exposed to?" asked Dr. Bernstein.

The majority of the panel expressed confidence in the accuracy of the fibre types to which each cohort was exposed in the Berman and Crump and the Hodgson and Darnton studies. The Hodgson and Darnton studies distinguish between exposures to chrysotile, mixed fibres, amphiboles, and amosite. "We know the South Carolina people were exposed to chrysotile, and in Wittenoom it was crocidolite," said Dr. Ogden.

However, amosite had been found in the lungs of the South Carolina cohort. "How do you factor this in?" Dr. Bernstein asked. Crump and Berman's calculations assumed the South Carolina cohort had been exposed to a certain amount of amphibole, but Dr. Crump could not recall the value. Dr. Stayner referred to a study by Bruce Case, a pathologist at McGill University, which found low concentrations of amosite in some lungs and higher concentrations in the cohort of Quebec miners. He attributed its presence to a small use of amosite at the plant or to exposure during prior employment. "I suspect that if you took all of our lungs and you sampled them, you would find amosite. It is ubiquitous," said Dr. Stayner.

Dr. Bernstein raised a statistics issue regarding the Case study (Case, B.W. *et al*. *Inhalation Toxicology* 12 {Supplement 3}, 2000: 411–418). He referred to conclusions that had been drawn after counting an average of only eight fibres on a filter. "With eight fibres, you have no power at all.... There is no statistical power," Dr. Bernstein said.

But do these observations undermine the apparent differences between chrysotile and amphibole in causing mesothelioma? Historical records can reveal the type of asbestos used at an individual plant. However, if the chrysotile sample is contaminated by amphibole, the difference in the potency between chrysotile and amphibole will appear smaller than it is. Dr. Ogden said this could not explain away the 100- to 300-fold difference between chrysotile and amphiboles to which Dr. Crump was referring.

Dr. Stayner said it would be useful to have the confidence intervals for the relative potency of the asbestos fibres from the Berman and Crump study, since the panel had been asked to give a range of potency estimates. Dr. Bernstein concurred.

Dr. Gibbs said the panel should also consider changes to the methodology of measuring fibre concentrations. The membrane filter method, which allows for the measurement of the airborne

fibre number concentration, has existed since the 1960s. Rickards showed that successive improvements to the counting method have had a major impact on the measured concentration (Rickards, A.L."Levels of workplace exposure." *Ann Occ Hyg* 1994:38:469-475). "[Rickards] reckons there is an enormous difference between what was measured then and what is measured now. Risk based on past measurements but measured against concentrations today may look like it is hundreds of times greater than what it looked like originally," said Dr. Gibbs.

Dr. Ogden invited the panelists to structure their estimates of mesothelioma risks based on Table 11 in the paper by Hodgson and Darnton (2000), which summarizes the quantitative mesothelioma risk from asbestos exposure at different levels of cumulative exposure. He asked Dr. Crump how the relative risk values tied into the absolute risk estimates provided in Table 11 (reproduced below as Table 1). Dr. Crump agreed to discuss this point the next day.

TABLE 1. *Summary statements of the quantitative mesothelioma risks from asbestos exposure at different levels of cumulative exposure (modified from Hodgson and Darnton)*

Fibre	Mesothelioma
Risk summaries for cumulative exposures between 10 and 100 fibre/millilitre.years	
Crocidolite	Best estimate about 400 deaths per 100,000 exposed for each f/ml.yr of cumulative exposure. Up to two-fold uncertainty.
Amosite	Best estimate about 65 deaths per 100,000 exposed for each f/ml.yr of exposure. Two- to four-fold uncertainty.
Chrysotile	Best estimate about two deaths per 100,000 exposed for each f/ml.yr of exposure. Up to three-fold uncertainty.
Risk summaries for cumulative exposures of one fibre/millilitre.years	
Crocidolite	Best estimate about 650 deaths per 100,000 exposed. Highest arguable estimate 1,500; lowest 250.
Amosite	Best estimate about 90 deaths per 100,000 exposed. Highest arguable estimate 300; lowest 15.
Chrysotile	Best estimate about five deaths per 100,000. Highest arguable estimate 20; lowest one.
Risk summaries for cumulative exposures of 0.1 fibres/millilitre.years	
Crocidolite	Best estimate about 100 deaths per 100,000 exposed. Highest arguable estimate 350; lowest 25.
Amosite	Best estimate about 15 deaths per 100,000 exposed. Highest arguable estimate 80; lowest two.
Chrysotile	Risk probably insignificant; highest arguable estimate four deaths per 100,000 exposed.
Risk summaries for cumulative exposures of 0.01 fibre/millilitre.years	
Crocidolite	Best estimate about 20 deaths per 100,000 exposed. Highest arguable estimate 100; lowest two.
Amosite	Best estimate about three deaths per 100,000 exposed. Highest arguable estimate 20; lowest insignificant.
Chrysotile	Risk probably insignificant; highest arguable estimate one death per 100,000 exposed.

Source: J.T. Hodgson and A. Darnton (2000). "The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure." *Annals of Occupational Hygiene*, vol. 44(8):565-601. (Table 11.)

Dr. Ogden referred panel members to Table 1, page four in the Andrew Darnton *WATCH* paper, which shows the estimated lifetime risk of mesothelioma per 100,000 in relation to chrysotile asbestos by the model and cumulative exposure. (This table is reproduced as Table 2 below.) For a cumulative exposure of 10 fibres per millilitre per year, Hodgson and Darnton estimate that the lifetime risk of developing mesothelioma is 25 per 100,000. The Berman and Crump estimate is 10. However, the Berman and Crump estimates fall within the range of uncertainty for the Hodgson and Darnton estimates. Dr. Ogden suggested the panelists consider the Hodgson and Darnton estimates and decide whether they need to be modified based on the Berman and Crump results.

TABLE 2:
Estimated lifetime risk of mesothelioma per 100,000 in relation to chrysotile asbestos by model (Hodgson and Darnton or Berman and Crump) *and cumulative exposure*.

	Mesothelioma		
Cumulative exposure (f/ml.yr)	HD	BC	HD/BC
10	25 (5–70)	10	2.7
1	5 (1–20)	1	4.8
0.1	1 (<1–5)	<1	8.4
0.01	<1 (<1–1)	<1	15
0.001	<1 (<1–1)	<1	18

Source: Modified from A. Darnton. *WATCH* paper. (Table 1, p. 4.)

The panelists said they felt the lifetime risk estimates at low cumulative exposures continued to pose a problem due to lack of information available at low exposure levels. Dr. Crump referred the panel members to a passage in the *WATCH* paper where Darnton indicated his preference for a linear model when estimating mesothelioma risk at low exposure levels.

From the perspective of risk assessment, the Hodgson and Darnton model is less specific and less complex than the Berman and Crump model, said Dr. Camus. The Berman and Crump model takes fibre type and length into account, and Hodgson and Darnton took one measurement per cohort, rather than doing an intra-cohort analysis. The Berman and Crump model is more specific, but predicts lower risks than the Hodgson and Darnton model. Dr. Ogden said he understood that Hodgson and Darnton had done their analysis with one point per cohort because it meant that they could use studies in which only this information was available. This meant that their risk estimations were based on more cohorts than Berman and Crump's, but it meant that intra-cohort information was not used.

"The choice is between lower risk estimates with a more specific model and high risk estimates with a coarser model," said Dr. Camus. Dr. Ogden agreed with Dr. Camus.

Note on error in exposure estimation (Agreed to following panel meeting)

Studies always state confidence limits for the risk term, but often cannot say much about the error in the estimate of exposure to which this risk is attributed. The error exists, however, and can be subdivided into two components.

Errors due to lack of air monitoring or non-representativeness of monitoring

Exposure concentrations estimated in the published epidemiological studies were mostly determined by area, rather than personal monitoring. As reported in several of these studies, area monitoring can miss short-term, high-level exposures contributed by the personal actions being performed by a worker. Moreover, certain periodic activities potentially associated with extremely high exposure (e.g., involving cleanup) were not performed during times when work areas were routinely monitored. On the other hand, monitoring was not always carried out systematically and appears in some cases to have been performed in areas were exposures were thought to be high.

It is possible that some type of respiratory protection was used by workers exposed to very high levels. The effect of this protection may not be reflected in the estimates of personal exposure. A worker may have been put into the wrong exposure group. If this happens, it can lead to an underestimate of risk at high exposures with a reverse effect at low exposures.

Published epidemiological studies differ in the frequency and time period over which sampling was conducted. With few exceptions, little or no sampling was conducted prior to the 1950s when exposure concentrations are thought generally to have been higher than those monitored more recently, due to lack of use of dust-control equipment and dust suppression procedures that were introduced only later. For many studies, therefore, early exposures had to be estimated by extrapolation from later measurements, which can induce unknown, but perhaps considerable, errors in estimates of cumulative exposure.

Studies vary in the degree to which the range of local operations associated with a particular facility were individually sampled. Exposure conditions attendant to jobs performed in association with local operations not sampled directly would then be extrapolated from measurements collected for other local operations assumed to be associated with "comparable exposures." As with extrapolations in time, these extrapolations can also induce an unknown error.

Errors from analytic methods used for evaluating air exposures

Laboratories count at different levels using optical microscopy, so that they will not agree with one another when they measure the same environment. These errors were particularly important before about 1980, when modern quality control checks became common. Also, some studies have involved conversion from particle counts to fibre counts, and the effect of this will have varied from environment to environment. Optical microscopy cannot distinguish between asbestos and non-asbestos materials and it is possible that in some particularly dusty environments, such as mining and milling, a significant amount of material counted was not asbestos.

Changes in optical microscope evaluation methods have meant that modern exposure measurements will generally be higher than old measurements in the same environment, and the difference may be several-fold. If the older measurements tend to be in higher fibre concentrations, and this effect has not been allowed for, it means that a relatively high risk can be wrongly attributed to a low exposure.

A particular sort of error arises because a range of sizes of fibres is conventionally counted by optical microscopy, but the sizes most likely to be pathogenic tend to include finer fibres, such as those thinner than 0.25µm which are not counted at all by the optical microscope method. In addition, the optical method gives equal weight to all fibres longer than 5µm, and the longer fibres in this range may be more dangerous. (This problem is investigated in the Berman and Crump studies, and Dr. Stayner is currently researching this[2].) An effect is that a given optical fibre count will correspond to more pathogenic fibres in an environment that is rich in long fibres than in one where most fibres are short. This might mean that for a given exposure by the optical microscope method there is more exposure to pathogenic fibres in textiles, so that the risk could be higher than expected from the fibre counts and the overall exposure-response relationship. In mining and milling, the risk might be less than expected. This could perhaps explain some, if not all, of the difference between potencies estimated in textile and mining operations.

Individual samples can be subject to substantial random errors, particularly when small numbers of fibres are counted. The errors at low counts are well understood. Most data points in an epidemiological study pool many samples, which will reduce the random errors.

2 Subsequently published as Stayner LT, Kuempel E, Gilbert S, Hein M, Dement J, An epidemiologic study of the role of chrysotile asbestos fiber dimensions in determining respiratory disease risk in exposed workers *Occup Environ Med* Published Online First: 20 December 2007. doi:10.1136/oem.2007.035584

Effect of exposure errors upon risk estimates

Within a single study, random errors can have two types of effects: they can bias the effect towards the null, and they can make a linear exposure response appear to be sub or supralinear. Because of this, supralinear dose responses in the presence of considerable opportunity for exposure error should be viewed with caution. In general, exposure error will not make risk appear where there is none, although it will contribute to uncertainty as to the fibre exposure that leads to that risk.

An attempt was made in the Berman and Crump analysis to account for errors in exposure. The method used to estimate exposures in each epidemiological study was reviewed and a protocol was followed to estimate quantitative factors used to incorporate uncertainty in exposure into study-specific uncertainty estimates of potency factors.

Exposure-Specific Risk Estimates for Peritoneal and Pleural Mesotheliomas

Dr. Ogden invited the panelists to discuss exposure-specific risk estimates for peritoneal and pleural mesotheliomas. A study published by Boffetta *Ann Oncol.* 2007;18:985-990 concluded that exposure to asbestos was the main cause of peritoneal mesothelioma. Boffetta found that when workers were exposed only or predominantly to chrysotile asbestos, this led to a lower proportion of total deaths from peritoneal mesothelioma than when workers were exposed to amphibole or mixed type of asbestos.

The panel members had a lively discussion about the relationship between pleural and peritoneal mesothelioma, and differences in chrysotile- and amphibole-exposed populations. Dr. Bernstein suggested that a larger asbestos dose could be needed to develop peritoneal mesothelioma than would be required for pleural mesothelioma. Dr. Gibbs said Hodgson and Darnton also see a rise in peritoneal mesotheliomas at higher doses. Dr. Gibbs noted that in the Quebec study of chrysotile miners there had not been a single primary peritoneal mesothelioma among 8,000 deaths. Also, downstream peritoneal mesotheliomas were rare. Dr. Stayner agreed that the peritoneal mesothelioma in the Carolina plant could be non-chrysotile related.

Dr. Camus asked the panel to consider the following: if amphibole, but not chrysotile, caused peritoneal mesothelioma, would one not expect a different proportion of peritoneal to pleural mesothelioma in amphibole cohorts than chrysotile cohorts? The chrysotile cohorts would lack any peritoneal mesothelioma cases, whereas there would be a significant number of peritoneal mesotheliomas in the amphibole cohorts, he said.

Dr. Bernstein maintained that the difference between pleural and peritoneal mesotheliomas depended on dose. “You are talking about two biologically different compartments with

different translocation schemes," he said, but acknowledged that he had not seen any research to back up this supposition.

Dr. de Klerk said there is a strong correlation between pleural and peritoneal mesotheliomas. "The more pleural mesotheliomas you get, the more peritoneal mesotheliomas you get. I think that is all you can say from it." He asked whether it was better to consider both types together than to separate them. Dr. Crump asked why the panel had to distinguish between pleural and peritoneal mesotheliomas. Dr. Stayner also did not see the wisdom of splitting them.

Dr. Stayner asked whether pleural and peritoneal mesotheliomas might be misclassified during diagnosis and cause inequities in the number of peritoneal mesotheliomas observed in different cohorts. "Could the diagnostic practices vary between countries?" he said. Dr. Gibbs said a systematic method of diagnosing mesotheliomas has been in place in Quebec since the 1970s.

Dr. Camus said the panel should try to develop separate exposure-specific risk estimates for pleural and peritoneal mesotheliomas. "Do you expect the same mechanisms for peritoneal and pleural mesotheliomas and do the fibres travel the same path to get there?" he asked. "In the end, should we say there is a risk that is much smaller for peritoneal mesothelioma than pleural mesothelioma, or that the difference in the risk between the amphibole and the chrysotile is sharper when you look at peritoneal mesothelioma than pleural mesothelioma?"

Dr. Ogden suggested the panel revisit this question the following day.

Day 2: Epidemiological Evidence for Lung Cancer

Dr. Trevor Ogden welcomed the panel members to the second day of the meeting and informed them they would spend the morning discussing lung cancer.

Dr. Kenny Crump presented some of the calculations he had done overnight on the best estimates (MLE) for the lifetime risks of mesothelioma and lung cancer under different scenarios, and their upper and lower boundaries (see Table 3 below).

TABLE 3:
MLE estimates of lifetime risk under various exposure scenarios

- Ninety-five percent statistical upper bound on potency of chrysotile for mesothelioma is 8.2 times higher than MLE.
- Ninety-five percent statistical lower bound on potency of chrysotile for mesothelioma is zero.
- Ninety-five percent statistical upper bound on potency of chrysotile for lung cancer is 2.5 times higher than MLE.
- Ninety-five percent statistical lower bound on potency of chrysotile for lung cancer is one-third the MLE.

.

		Exposure	Age Exposure			Risk Per 100,000		
Population[a]	Fibre type	Scenario[b]	begins	ends	f/cc	Lung Cancer	Meso	Total
All	Chrysotile	Env	30	35	2	379	45	424
All	Chrysotile	Occ	30	35	2	83	10	93
All	Chrysotile	Occ	30	35	0.002	0.083	0.010	0.093
All	Chrysotile	Env	0	100	0.0005	1.2	0.2	1.4
Non-smoking males	Chrysotile	Env	0	100	0.0005	0.3	0.3	0.6
Smoking males	Chrysotile	Env	0	100	0.0005	2.8	0.1	2.9
Non-smoking females	Chrysotile	Env	0	100	0.0005	0.3	0.3	0.6
Smoking females	Chrysotile	Env	0	100	0.0005	2.5	0.2	2.8
All	Chrysotile	Occ	20	65	0.5	164	15	179
Non-smoking males	Chrysotile	Occ	20	65	0.5	42	16	57
Smoking males	Chrysotile	Occ	20	65	0.5	388	8	396
Non-smoking females	Chrysotile	Occ	20	65	0.5	47	18	66
Smoking females	Chrysotile	Occ	20	65	0.5	355	13	368
All	Amphibole	Occ	20	65	0.5	188	4257	4444

[a] *Based on US population year 2000.*
[b] *Occ (occupational) is exposure eight hours per day, 240 days per year. Env (environmental) is exposure 24 hours per day, 365 days per year.*

For example, if the occupational exposure to pure chrysotile is for eight hours a day, 240 days a year, at 0.5 fibres per millilitre, from age 20 to 65, the risk is 164 per 100,000 for lung cancer, and 15 per 100,000 for mesothelioma. For non-smoking males, it is 42 and 16 for lung cancer and mesothelioma, respectively. By comparison, a similar occupational exposure to amphibole

generates a comparable lung cancer risk (188 for amphibole versus 164 for chrysotile), but a much higher mesothelioma risk (4,257 for amphibole versus 15 for chrysotile).

Dr. Leslie Stayner commented on how useful the table is for determining the risk estimates, because the upper bounds help to identify the "most extreme possibility."

Dr. Graham Gibbs said he wondered whether making comparisons between chrysotile and amphibole caused more confusion, because each risk estimate was associated with its own uncertainty. Dr. Michel Camus reiterated the purpose of the meeting: to make a risk assessment for chrysotile to understand the risk of pure chrysotile and fibrous tremolite-contaminated chrysotile. "We thought a relative risk approach would be useful, but if you don't want to use that approach, we don't need to," he said.

Dr. Ogden introduced a work chart he had put together containing the risk estimates from the Hodgson and Darnton and the Berman and Crump studies for each fibre type (crocidolite, amosite, and chrysotile), dose (10, 1, 0.1, and 0.01 fibres/ml.yr), and cancer type (peritoneal mesothelioma, pleural mesothelioma, and lung cancer). He suggested the panel members use the chart to help them reach their decisions regarding the appropriate risk estimate to choose.

Dr. David Bernstein asked why the panel was not considering newly published studies. For example, a study by Carel *et al*. (*Occupational and Environmental Medicine*, 2007:64:501–508) examined Eastern European workers who had used chrysotile during the communist regime. The study showed no lung cancer at any dose. Dr. Stayner said several recent studies, including the Chinese study (Yano et al. (2001). *Am Jl Epid*;154-6:538-43) and results from the South Carolina study that he presented, could be included in an assessment. "Unfortunately we are looking at an old assessment," he said. However, the Carel study is a population case-control study, not a cohort study. The job information comes from subject interviews and is "prone to error," he said. "Although it is certainly surprising that it is null."

Dr. Stayner asked how the panel should proceed, knowing other recent studies are available that could change the outcome. "One study can make a big difference. If you drop the Quebec study or the NIOSH study, it totally changes the answer from the meta-analysis," he said.

The panel members revisited the inconsistencies between the data from the Quebec and South Carolina cohorts. "For lung cancer, the values we are using are about eight-fold higher than for the best estimate for Quebec, and lower for the estimate for South Carolina. That says there is a problem in estimating the risk for chrysotile," said Dr. Crump. Although the Berman and Crump analysis had hoped the differences would be reconciled with a fibre-size analysis, they were not.

Dr. Ogden offered some guidance on which studies the panel members should take into account when developing their estimates. The brief specified that the panel members would

consider reviews, not original papers. "But you still need to take into account the newer papers somehow," he said.

The conversation returned to the anomalies in the South Carolina study. Dr. Bernstein asked how much of the dust in the air sample was chrysotile. Dr. Stayner replied he thought it was virtually 100%. Dr. Ogden said nearly every possible contaminant that might explain the South Carolina situation had been considered. Dr. Fubini asked whether anyone had taken into account the "fresh surfaces" produced by textile workers. "The kind of operation textile workers do may generate surfaces that are more reactive than others," she said.

The panel members compared the similarities and differences between the South Carolina cohort and other textile cohorts.

"No matter how you slice it, the risk of lung cancer per unit dose is very similar between the different textile plants," said Dr. Stayner. He said that if amphibole has a higher potency, then the mixed exposure textile plants should have a higher risk per unit dose exposure than the South Carolina plant. "Within textiles, it appears that amphiboles and chrysotile have the same potency [for lung cancer]."

The group discussed potency estimates for amphibole and chrysotile, errors, and amphibole contamination in the Berman and Crump analysis. Dr. Ogden summarized the discussion, saying the model estimates that fibre for fibre, chrysotile is half as potent as amphibole in producing lung cancer. Dr. Crump agreed. Dr, Stayner did not. He felt that these difference could easily be explained by random variation, since there was no statistically significant difference between chrysotile and amphiboles potency for lung cancer in the Crump and Berman models. The discussion moved on to the lung cancer potency values Berman and Crump had tested under different models (referred to in the Berman and Crump paper as Table 5, and included below as Table 4) Dr. Stayner asked about the PCME Widths Model, where fibre length is equal to or greater than five microns, and fibre width is equal to or greater than 0.2 microns. For the hypothesis test that chrysotile is not potent, the p-value is 0.001; therefore the hypothesis that chrysotile is not potent must be rejected. However, the hypothesis that chrysotile and amphibole are equally potent cannot be rejected. Dr. Gibbs wondered how the results of the hypothesis test might change if the textile or the mining data were left out. Dr. Ogden asked that the table be included in the report.

TABLE 4. *Results from fitting selected exposure metrics to lung cancer and mesothelioma potency values estimated from different environments, for pure chrysotile.*
For example, the central set of four columns refers to relative potencies of fibres evaluated in the normal way, with length>5μm and width>0.2μm. The upper block of these four columns concerns lung cancer, and it can be seen from the foot of this block that the hypothesis that pure chrysotile does not cause lung cancer (H_0Rpc=0) is rejected with p=0.001. The hypothesis that chrysotile has equal potency to amphibole for lung cancer (H_0Rpc=1) cannot be rejected (p=0.51). At the foot of the lower central block, we see that the hypothesis that chrysotile has the same potency as amphiboles for mesothelioma (H_0Rpc=1) is rejected with p=0.0007, but the hypothesis that chrysotile has zero potency for mesothelioma (H_0Rpc=0) cannot be rejected (p=0.61).

Table 5: Results from Fitting Selected Exposure Metrics to Lung Cancer and Mesothelioma Potency Values Estimated from Different Environments

	Thin Model				PCME Widths Model				All Widths Model			
Length Categories:	**5 μm ≤ Length < 10 μm; Length ≥ 10 μm**				**Length ≥ 5 μm**				**5 μm ≤ L < 10 μm; L ≥ 10 μm**			
Width Categories:	**Width ≤ 0.4 μm**				**Width ≥ 0.2 μm**				**all Widths**			
Rpc Restriction:		**Rpc = 1**	**Rpc = 0**		**Rpc = 1**	**Rpc = 0**				**Rpc = 1**	**Rpc = 0**	
Rps Restriction:				**Rps = 1**	**Rps = 1**	**Rps = 1**	**Rps = 1**					**Rps = 1**
Lung Cancer (N=15)												
K_{LA} × 100	2.40	0.95	15.80	0.56	1.48	0.28	4.42	0.46	0.88	0.48	7.69	0.27
Rpc	0.26	1	0	0.34	0.38	1	0	0.48	0.42	1	0	0.46
σ	1.04	1.09	1.73	1.32	0.86	1.11	1.92	1.09	0.90	0.93	1.77	1.19
Rps	0	0	0	1	0	1	1	1	0	0	0	1
LogL	-16.55	-17.27	-20.70	-18.57	-15.45	-17.02	-21.85	-16.80	-15.50	-15.86	-21.12	-17.54
K_{LC} × 100	0.62	0.95	0	0.19	0.57	0.28	0	0.22	0.37	0.48	0	0.13
Hypothesis Tests:		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1
		p = 0.23	p = 0.004	p = 0.04		p = 0.51	p = 0.001	p = 0.1		p = 0.40	p = 0.001	p = 0.04
Mesothelioma (N=11)												
K_{MA} × 10^8	26.99	0.684	28.77	6.73	19.69	0.74	8.88	7.69	13.25	0.63	14.60	4.01
Rpc	0.0013	1	0	0.0048	0.0016	1	0	0.0033	0.0021	1	0	0.0049
σ	0.60	1.85	0.61	0.94	0.59	1.81	0.78	0.76	0.44	1.75	0.44	0.81
Rps	0	0.996	0	1	0.083	1	1	1	0	0.46	0	1
LogL	-9.32	-16.35	-9.35	-11.26	-9.76	-16.16	-10.59	-10.46	-8.89	-15.93	-8.98	-10.59
K_{MC} × 10^8	0.04	0.68	0	0.033	0.031	0.74	0	0.026	0.027	0.63	0	0.020
Hypothesis Tests:		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1		H_0:Rpc = 1	H_0:Rpc = 0	H_0:Rps = 1
		p = 0.0002	p = 0.79	p = 0.049		p = 0.0007	p = 0.61	p = 0.24		p = 0.0002	p = 0.68	p = 0.065

Source: Berman DW and Crump KS (2007). New metrics for assessing asbestos-related cancer risk that address fibre size and mineral type (submitted). In that paper it is Table 5.

Notes:
Shaded cells are fixed at the values indicated.
K_{MA} Mesothelioma potency for amphiboles;
K_{LA} Lung cancer potency for amphiboles
K_{MC} Mesothelioma potency for chrysotile (= K_{MA} x Rpc)
K_{LC} Lung cancer potency for chrysotile (= K_{LA} x Rpc)
Rpc Relative potency of chrysotile compared to amphibole
Rps Relative potency of short structures (5–10 μm) compared with long (>10 μm)
σ Non-study-specific standard deviation across all exposure coefficients
LogL value of the log likelihood obtained in the fit

Dr. Stayner remarked on the paucity of fibre size information available. Fibre sizes may not be properly accounted for in the studies. He said Hodgson and Darnton could have controlled for industry type in their study to better understand chrysotile and amphibole potencies. Dr. Gibbs said he also thought fibre size was important. He referred to a study by Lash, *Occ Env Med* 1997; 54:254-263, who looked at the effect of process type on lung cancer risk. "When you take a look at his estimates for lung cancer, they come out not far from those of Hodgson and Darnton," said Dr. Gibbs.

Dr. Ogden invited Dr. Stayner to give his presentation on fibre size exposure estimates and updated mortality analysis of chrysotile asbestos textile workers.

Dr. Stayner started by showing how a meta-analysis of the potency of chrysotile and amphibole for lung cancer is strongly influenced by the Quebec and South Carolina cohorts. He referred to an analysis presented to the peer consultation workshop in San Francisco in February 2003, on the Berman and Crump meta-analysis (and summarized on p3.4 of a report circulated to the Panel: *Report on the Peer Consultation Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk*, EPA Contract No. 68-C-98-148, Work Assignment 2003-05, U.S. Environmental Protection Agency, Washington DC, May 2003). When all the epidemiological analyses were included, amphibole was three times as potent as chrysotile; when Quebec miners and millers were omitted, chrysotile was about 1.6 times as potent as amphibole; but when the South Carolina textile workers were omitted instead, amphibole appeared to be more than ten times as potent as chrysotile.

An objective of the recent studies of the South Carolina cohort was to see how fibre size (length and diameter) influenced lung cancer predictions in chrysotile textile workers (Dement et al *Occup Environ Med* Published Online First: 5 November 2007. doi:10.1136/oem.2007.033712; Stayner et al. (2007), *Occup Environ Med* Online First: 20 December 2007. doi:10.1136/oem.2007.035584). Classically, asbestos fibres that are counted are greater than five microns and have an aspect ratio of 3:1. However, toxicological data suggests that long and thin fibres may pose the greatest lung cancer risk. "We wondered whether we could explain the difference between textile workers and miners by differences in fibre dimensions," Dr. Stayner said.

Originally, the fibre count in the South Carolina cohort was carried out using PCM.

A recent paper published by Hein et al., *Occ Env Med* 2007; 64: 616-625 provided an updated mortality analysis of the South Carolina cohort through 2001. There were 198 lung cancers and three mesotheliomas; 64% of the cohort had died by 2001.

For this study TEM analysis was performed on 86 of 203 archived samples collected between 1964 and 1971. The samples were chosen using a stratified random sampling method

From the Hein study, the standardized mortality ratio for lung cancer was 1.97. Hein also did a Poisson regression using the PCM-based exposure estimates. A good fit was found with a

linear relative risk model. The slope (beta) is 0.0198. Dr. Crump remarked that in comparison, he calculated a slope of 0.021.

Dr. Stayner adjusted the original PCM-based exposures by taking a portion of the fibres from a particular size-specific length and width combination over the total number of fibres. This was repeated for each exposure area in the plant. Most of the fibres were less than five microns long, Dr. Stayner said. "It is interesting that the vast majority of stuff that people are exposed to in this plant are particles that, in the past, we have just ignored." He added that historically fibres less than 0.25 microns in width could not be detected by PCM. Dr. Stayner found that most of the fibres in the South Carolina plant were thinner than this. Toxicology studies have suggested that thin fibres may be the most hazardous, yet they have not been included in the epidemiological analysis. "None of the epidemiologic studies counted the thin fibres. You have to wonder if the heterogeneity we see is because of that," he said.

Dr. Stayner said that the model fit improved substantially when TEM methods were used and when fibres narrower than 0.25 microns were included in the analysis. There was a dramatic improvement in fit when fibres were 10 microns or longer (chi-square value >60). "They seem to be more strongly associated with predicting risk than short fibres," Dr. Stayner said. Similarly, the fit improved when fibres less than 0.3 microns in diameter were included for asbestosis (chi-square value >56).

Dr. Gibbs asked what happened when the two fractions were combined. Dr. Stayner said the pattern was very noisy and too complicated to give in the presentation, but it does appear in the paper.

Dr. Stayner concluded that TEM-based chrysotile exposure estimates produced better predictions for lung cancer, and reduced the slope. He said that this is obviously because we are counting the fibres thinner than 0.25 microns that we can't see with PCM. Exposure to thin fibres was most strongly associated with either lung cancer or asbestosis mortality. Exposure to long fibres—greater than 10 microns—was the strongest predictor of lung cancer.

In a 1980 paper, Dr. Gibbs reported the fibre size distribution observed in the Quebec mining cohort. Most were under five microns. Dr. Stayner estimated the distribution for the South Carolina cohort based on the TEM results. The South Carolina cohort had a smaller proportion of fibres shorter than five microns, and a much larger proportion of fibres in the five to 20 micron range than the Quebec study. Dr. Gibbs remarked that the results in the Quebec mills described in the paper to which Dr. Stayner referred had used a TEM method combined with light optical methods to obtain a complete size distribution. Earlier measurements using SEM could have missed some narrow fibres.

TABLE 5:
Comparison of fibre length distribution, chrysotile: South Carolina textiles and Quebec mining

	Length		
	< 5 microns	**5–20 microns**	**> 20 microns**
Quebec[a]	98.73%	1.28%	0.01%
South Carolina[b]	83.67%	12.10%	4.65%

[a] Source: G.W. Gibbs and C.Y. Hwang. "Dimensions of Airborne Asbestos Fibres." In: *Biological Effects of Mineral Fibers*. J.C. Wagner, Ed. IARC Scientific Publications, Lyon, France 1980.
[b] Source: J.M. Dement, E. Kuempel, S. Gilbert, L. Stayner, M. Hein, and D. Loomis. "Development of an Airborne Fiber Size Specific Job-Exposure." *Occup Environ Med* Published Online First: 5 November 2007. doi:10.1136/oem.2007.033712

Exposure-Specific Estimates for Typical Exposure Models and Exposure-Specific Risk Estimates for Lung Cancer

Dr. Ogden asked the panel members to focus their discussion on the influence of different size fractions on the risk estimates for lung cancer. "Will that pull South Carolina into line or not?" he asked.

NIOSH's most recent evaluation of the South Carolina data using PCM generated a slope of 0.0198 f/ml.yr (Hein et al., (2007) *Occup Environ Med*.; 64(9):616-25). The TEM based estimate of the slope is lower again because of the increased number of fibers detected (Stayner et al. (2007), *Occup Environ Med* Online First: 20 December 2007. doi:10.1136/oem.2007.035584). Dr. Ogden asked if that slope could be translated into a value that represented lifetime deaths per 100,000. Dr. Stayner said he had calculated a similar estimate in the 1997 study, but had not repeated the calculation in the 2007 study. However, Berman and Crump had calculated a similar slope (0.02) using the same data, and Dr. Stayner's conclusions were comparable to those made by Berman and Crump.

Panel members discussed the differences in fibre concentrations for the Quebec chrysotile and South Carolina textile cohorts. Dr. Gibbs said a concentration of two fibres per millilitre measured by PCM would become three fibres per millilitre when based on the mining data for the Quebec chrysotile cohort. He asked how data from the South Carolina textile cohort would change under the same analysis. Using the bivariate distribution graph Dr. Stayner had presented during the morning session, the panel determined that half the fibres—the narrow

ones—would be missed. "It means that the Carolina concentrations will be increased by more than the Quebec concentration if you include the finest fibres," said Dr. Ogden.

Although a greater concentration measurement by TEM in South Carolina apparently reduces the anomaly between the two cohorts, the effect cannot be properly interpreted without TEM measurements of the Quebec concentrations also. "We won't know without actually doing it, will we? All we can do is say qualitatively that there is an expectation that this would reduce the difference between the Quebec and South Carolina risk factors, but we don't know if it is important or not," said Dr. Ogden.

Dr. Crump said it was disappointing that the corresponding data from Quebec was not available. If samples from the Quebec mining and milling cohorts could be found, researchers could do a TEM size-distribution analysis on them, as had been done for the South Carolina samples. Comparing the two would inform the debate.

Dr. Stayner said he thought Wayne Berman had some Quebec samples, but lacked the funding to analyze them, although it would be something worth doing. "It's of international importance," said Dr. Ogden. Dr. Crump confirmed that Berman had been awarded an EPA contract to collect and analyze Quebec air samples. Although the samples were collected, the contract was cancelled before they were analyzed. Dr. Stayner urged Health Canada to consider funding a study to use TEM-based methods to assess how the risk of asbestos-related diseases varies among Quebec asbestos workers. There was a general consensus in the group that this would be important.

Dr. Fubini introduced four papers to the panel for discussion as an example of the variability of clearance time and on the correctness of doses employed for *in vitro* genotoxicity studies:

- A. Searl (1997). "A Comparative Study of the Clearance of Respirable Para-Aramid, Chrysotile and Glass Fibres from Rat Lungs." *Ann Occup Hyg*, 41(2):217-233.
- A. Churg and J. L. Wright (1994). "Persistence of Natural Mineral Fibers in Human Lungs: An Overview." *Environ Health Perspect*, 102(s5):229-233.
- Y. L. Zhao, C. Q. Piao and T. K. Hei (2002). "Downregulation of *Betaig-h3* Gene is Causally Linked to Tumorigenic Phenotype in Asbestos Treated Immortalized Human Bronchial Epithelial Cells." *Oncogene*, 21:7471-7477.
- A. Xu, L. B. Smilenov, P. He, K. Masumura, T. Nohimi, Z. Yu, and T. K. Hei (2007). "New Insight into Intrachromosomal Deletions Induced by Chrysotile in the *gpt* Delta Transgenic Mutation Assay." *Environ Health Perspect*, 115(1):87-92.

Searl found chrysotile clears from the lungs in months, although long, thin fibres persist longer. Churg and Wright found chrysotile clears from the lungs in months, whereas amphibole clears in years to decades. "The few days' clearance presented by David [Bernstein] seems to be very particular to the kind of [chrysotile]," said Dr. Fubini. She said that although some of the cell-based experiments were not good and made exaggerations, they should not all be discounted.

Dr. Ogden summarized the importance of the studies Dr. Fubini had distributed to the panel as being relevant to the question of whether amphibole-free chrysotile is possibly carcinogenic. "The two bits of evidence are that according to Alison Searl, chrysotile has a half-life of months. The two papers from Columbia [Zhao and Xu] show the genotoxic activity of chrysotile," Dr. Ogden said.

Dr. Bernstein raised some objections to the papers by Searl, Zhao, and Xu. In the Searl paper, he said, NIEHS chrysotile is used. The material was ground in a "huge" grinder for three days. "It is difficult to think that the ground material used in all these studies has any representation to any real chrysotile that is used commercially," he said. The genotoxicity was produced with a one-microgram dose—about one million times human exposure, he said. He questioned whether that level of exposure is relevant. "The study has not been validated or approved by any regulatory authority as being relevant to human exposure," he said.

Dr. Camus asked if any member of the panel challenged the notion that chrysotile clears much more rapidly from the lung than amphibole, as Health Canada is trying to understand the discrepancies in the studies it has seen and trying to understand biopersistence, because it is one of the major determinants of risk. There was wide support in the panel for the belief that the vast majority of chrysotile clears within months or less. Dr. Gibbs said some chrysotile may be sequestered and clear more slowly. Chrysotile fibres have been found in the lymphatic system 90 days after exposure, said Dr. Bernstein.

The discussion turned temporarily to mesothelioma. The abovementioned study by Suzuki (Suzuki et al, *Int J Hyg Env Hlth,* 2005; 208:201-210) found large numbers of short fibres in the lungs, but no mesothelioma. "He is only telling us that chrysotile breaches the pleura, not that it causes mesothelioma in any way," said Dr. Camus. Dr. Stayner said the retention of the fibres was not consistent with the toxicology or the epidemiology. Dr. Gibbs said most of the animal data showed that fibre length was important in causing mesothelioma. Fibres less than 0.5 microns long were not associated with mesothelioma; the longer fibres—whether amphibole or something else—seem to cause mesothelioma. "If we took the argument that it was the short fibres that have a higher risk of mesothelioma, then the mining industry, which has gross exposure to short fibres, would exceed the world's record of mesothelioma, but it's not there," said Dr. Gibbs.

Dr. Ogden asked the panel members to direct their attention to a matrix he had developed. He suggested panel members enter their best risk estimates for each cell (fibre concentration, fibre type, disease type), using the Berman and Crump and the Hodgson and Darnton estimates and ranges as a guide. Dr. Crump confirmed that the numbers he and Berman had devised for chrysotile are "intended to apply to pure chrysotile." Dr. Ogden reminded the panelists that the Hodgson and Darnton risk estimates for chrysotile are for the fibres as they presented in the cohorts; "there was no adjustment for contamination by tremolite," he said.

Dr. Stayner expressed doubt about the exercise. He asked why a risk estimate should be produced for pure chrysotile—a "hypothetical fibre" that is never found in the real world. He said that for lung cancer, he would have to give two risk estimates: one for the textile industry and the other for the mining and milling industry, because of the heterogeneity he had seen in the meta-analyses of the epidemiologic studies.

Dr. Ogden said it would be fine to take that approach, as long as panel members gave a reason for providing two numbers. Dr. Camus explained that Health Canada was interested in a risk estimate for pure chrysotile, because it would help them develop risk estimates for amphibole-contaminated chrysotile.

The heterogeneity of the lung cancer risk in the textile and mining industries also posed problems for other panel members. Dr. Crump said he, too, would be likely to enter two numbers rather than take those he and Berman had calculated in their analyses. He asked if they should consider smokers and non-smokers separately. Dr. Camus said that for this exercise, the panel members should only provide risk estimates for non-smokers.

Dr. Stayner said the conversation revealed "how complex this issue of quantifying risk is, and that to do this in a two-day meeting … is a hazardous exercise." He added he was uncomfortable with a probabilistic exercise—how much riskier amphibole is for peritoneal mesothelioma than chrysotile, for example. Dr. Crump agreed, but said time was not the only challenge they were facing; they also lacked the data to make good estimates for each scenario.

Dr. Ogden decided the panel should come up with a "narrative conclusion" to state that the Berman and Crump and the Hodgson and Darnton studies represent the situation, but two data anomalies—the Quebec chrysotile and the South Carolina textile results—cannot be explained. The narrative could be added to the probability plots Dr. Camus had also requested.

Continuation of Dose Response Estimation; Indication of the Degree of Confidence of the Individual Panelists' Estimates; Synthesis of Main Areas of Agreement and Disagreement

Dr. Ogden summarized the panel's discussion with regard to typical exposure models and exposure-specific risk estimates. "My feeling … is that we weren't happy to deal in the detail that I'd hoped," he said, requesting that the panel instead "come up with some sort of narrative statement." He proposed the following statement as a starting point:

> *We believe that the general approach of the Berman and Crump analysis gives a fair range of estimates of risk for mesothelioma and lung cancer in the light of present knowledge, subject to the following further comments:*

> 1) The risks in chrysotile textile manufacturing at Charleston were higher than those predicted by this and other models. Further research may elucidate the reason for this.
>
> 2) The risks in chrysotile mining and milling are less than those predicted by this and other models. Further research may elucidate the reason for this.

Dr. Ogden said he believed the panelists would align themselves with this, but might add further points on an individual basis. "For example, if you believe in the fast clearance of chrysotile, you may want to add 'I believe that chrysotile presents little or no risk at low concentrations…' or 'I believe that risks calculated by Hodgson and Darnton should be taken into account….'"

Before discussion on this statement commenced, Dr. Ogden told participants that while the objective of the panel is to offer Health Canada some numbers to use, with this approach Health Canada could take the Berman and Crump calculations and the individual statements from participants to create its own risk estimates.

Dr. Stayner said he was satisfied with the first part of the statement, but troubled by the range of estimates of risks: "Because of the heterogeneity, coming up with a single estimate of risk is really glossing over an important aspect of the data," he said. He added that he was unsure whether the estimates were useful at that point, due to their tendency to smooth or average results from different studies that are currently unexplained. He said a more reasonable approach to risk assessment for Health Canada might be to "use your own data" for estimating risk for Quebec workforces, and possibly environmental exposures.

Dr. Camus said he felt the Quebec cohort was "not sufficiently generalizable" to do this, due to the risk that something was missed in the Quebec studies or that distribution was different. He suggested that all available data be used, but that the estimate of risk be qualified with a statement such as "values can be as high as or as low as […]. Then it is for the regulators to apply this based on confidence intervals, knowing that one is due to chrysotile textile and others [are due to] chrysotile mining."

Dr. Ogden added that ultimately the panel is making a scientific statement, and "how Health Canada applies this is their own concern."

Dr. Stayner said he believed that the Berman and Crump analysis provided a reasonable starting point. He said, however, that some serious limitations must be considered; he added that the limitations should be clearly stated and the model would need to be updated periodically. "I think it is a good framework and approach, but because of heterogeneity, we are not providing clear answers," he said.

Dr. Camus asked participants if they felt this type of approach was more informative than that taken by Hodgson and Darnton, or if the two models were equivalent. "I think we need to

narrow it down," said Dr. Gibbs, who also asked for clarification that the discussion was currently focusing only on chrysotile. He said he did not agree that the panel was "lumping" crocidolite and amosite, but did agree with what Dr. Stayner had said. "If the heterogeneity seems to show we can't lump them together, I don't think we should lump them together," Dr. Gibbs added. In his opinion, the available data showed clearly that crocidolite poses a considerably greater mesothelioma risk than does amosite.

Dr. Camus said the problem is that pure chrysotile does not exist; there is also an unknown proportion of amphiboles. Dr. Stayner suggested that because estimates for amphibole exist, perhaps those could be presented; however, Dr. Ogden said participants did not really need to come up with statistics, provided that Health Canada was given a means of calculating them, and he appreciated Dr. Stayner's statement that this was a "reasonable starting point."

"At the end of the day, the model is only as good as the data that goes into it," said Dr. Camus. He added that although the framework of the Berman and Crump model is sufficient, their data taking into account fibre size is too poor to be of great assistance: it has problems with regard to both fibre size characterization and fibre heterogeneity. Instead, Dr. Camus proposed taking risk estimates from the Quebec and Carolina cohorts and "recognizing that the truth may be somewhere between the two," until more information on fibre size distributions is available.

Dr. Stayner said he felt the Berman and Crump model is a reasonable approach, as it considers size and uses raw data. However, the problem is that available data is inadequate with regard to estimating the effects of variability in fibre sizes.

Dr. Crump said he had put together a table of potency factors and confidence intervals. "If a person knew how to interpret that along with risk estimates," he said, "then there would be a way to evaluate the uncertainty." He said if this approach was appealing, participants could use the estimates he had provided in the morning (Table 6) as a starting point and incorporate other potency factors to make their own decisions. He added he did feel the environmental exposures in Quebec are more important to Quebec than those from South Carolina.

Participants agreed to look at Dr. Crump's table. Dr. Ogden revisited the working statement based on the discussions so far:

> *We believe that the approaches of Berman and Crump and Hodgson and Darnton are reasonable for estimating risk for mesothelioma and lung cancer in the light of present knowledge, subject to the following serious reservations. Application of the models to particular environments must take into account (1) and (2) in particular:*
>
> > 1) The risks in chrysotile textile manufacturing at Charleston were higher than those predicted by these and other models. Further research may elucidate the reason for this.

2) The risks in chrysotile mining and milling are less than those predicted by these models. Further research may elucidate the reason for this.

Dr. Ogden suggested that he personally does not agree with putting crocidolite and amosite together. Dr. Gibbs agreed. He noted that South African mines showed differences in mesothelioma risks between amosite and crocidolite and that there might even be regional differences for crocidolite between the Cape and Transvaal.

Dr. Gibbs also said he felt Berman and Crump's linear approach to making lung cancer estimates was probably better than the non-linear approach used by Hodgson and Darnton. "As you go down in scale, they start to deviate drastically," he said. Dr. Crump agreed but asked, "How can we say that the linear model is better at low dose but at the same time [recommend] the Hodgson and Darnton model? How could we resolve that?" Dr. Ogden suggested simply adding a statement to say, "We are inclined to favour the linear approach of Berman and Crump over the non-linear approach of Hodgson and Darnton."

Dr. de Klerk said that points one and two in the working statement relate only to lung cancer. Dr. Gibbs said the qualifying statements should be clearly separated under the headings of chrysotile and lung cancer, and chrysotile and mesothelioma, for the sake of clarity—even if it led to repetition.

Dr. Crump said that because Quebec is at the top of the confidence intervals and Charleston is at the bottom, effectively the working statement acknowledges the risk is being under-predicted in Charleston and over-predicted in Quebec. Dr. Stayner said the models need to be updated with more data, such as the recent Chinese and Eastern European studies. Dr. Bernstein expressed concern about "putting all the studies together," as all are based on different models.

Dr. Camus cautioned participants against their "university and research biases," adding, "People have been studying this stuff for 50 years and debating models for 25 years. We already have an existing EPA model that is being challenged by Berman and Crump and Hodgson and Darnton." He emphasized that the recommendations made by participants today must reflect what they "know and believe *today*," and said that not all the data is quantitative. Participants should try to "integrate these things with your human brain and experience" and conclude whether it is reasonable. He added, "If you cannot take a position on that, then not a single risk assessment exists."

Dr. Stayner replied that he felt further research was needed, but he also acknowledged that data exists to update the model, such as that from his own research and from the Chinese and Eastern European studies. "What [Dr. Crump] did was up to date 10 years ago," he said. However, he was not recommending waiting for research to make decisions, he said. Dr. Stayner said he also supported offering a range of estimates for different scenarios. "I think that is where we are at this point," he said. "The best we can do is to say that there is a range of estimates."

Dr. Camus said that was perfectly acceptable; however, he noted this would imply all previous risk assessments were wrong because they "lumped" all studies together. "This recommendation would have a paradigmatic revolution note to it," he said.

Dr. Gibbs said he was concerned about what conclusions could be drawn regarding longer fibres. He said the science appears to indicate differences between processes and between fibres, but why this is so is still unclear. He expressed reluctance at being in a position of making policy decisions.

Dr. Crump said he had liked some aspects of the "numbers" presented in the morning, as they laid out the differences regarding environmental and occupation exposure, and the impact of smoking. He added that he also appreciated the linearity and asked if it was possible to provide the numbers from earlier in the day, but also offer some adjustment factors for different populations. When prompted by Dr. Camus to be more specific, Dr. Crump suggested a statement such as, "We favour the approach of Berman and Crump because 1) of its linear form, 2) it included smoking, 3) it used actual data that was available, 4) it is an attempt to incorporate fibre size into analysis—unsuccessful, but noble."

There was a brief discussion around the table as participants sought to clarify Dr. Crump's suggestion, and as the table was put on the projector so Dr. Crump could explain his proposal.

Dr. Crump told participants he was proposing a table similar to the one they were viewing, without the first three lines of the table, with a separate table of KL and KM values added. He suggested including text to explain how the tables were generated and to deal with the issue of heterogeneity, as well as instructions for using the tables. Dr. Crump's explanation was followed by considerable simultaneous conversation among participants.

Dr. Stayner said he was concerned that participants were "getting back into estimating numbers." He offered an alternative to Dr. Crump's proposal, which incorporated similar tables based on the South Carolina and Quebec miners and millers and another table based on Hodgson and Darnton. "Then let Health Canada decide," he said, adding, "I think we are treading on risk assessment policy here."

Various participants sought clarification between the two proposals, as they essentially seemed to be different executions of the same concept. In summary, Dr. Ogden said Dr. Crump was proposing a table to which adjustment factors could be applied to allow for different populations. These factors would be based on those needed to generate the Quebec and South Carolina population tables. This would essentially be the same as generating multiple tables, which Dr. Stayner proposed. Dr. Crump said he had also suggested including confidence intervals in the tables.

Dr. Ogden summarized his observations: participants generally seemed to favour presenting the Charleston and Quebec estimates separately in some form, and recommending that Health Canada employ population-specific risk estimates.

Dr. Stayner said he was still "bothered" by the adjustment factors and preferred to generate tables with confidence intervals. Dr. Gibbs suggested a solution might be to do both, to provide the table and multipliers and use the Quebec and South Carolina cohorts as examples. Dr. Camus said that for this meeting, it was "sufficient to say that the data will be converted to tables in coming days."

The discussion turned to determining what type of risk estimates should be applied to specific situations. Dr. Camus asked what would happen if a building were to be demolished: how would generalizations be made beyond the environments that have already been studied? Dr. Ogden replied, "I don't think we can give that, because there [are] an infinite number of environments or cohorts that you'd be interested in." Dr. Camus suggested formalizing a statement to the effect that there was insufficient data to offer risk estimates to apply to demolition.

Dr. Stayner offered the example of California for applying risk estimates; California has natural deposits of chrysotile. He asked which model would be most appropriate for its situation: the textile model, or, if they made use of shorter fibres, the Quebec results.

Dr. Crump presented a potency factor table to participants (see Table 6 below). He said it could be used to give the lower and upper bounds for chrysotile, amphibole, Quebec, and South Carolina. Users could be told how to factor in other scenarios.

TABLE 6:
Potency Factor Table

Potency factors	KL MLE	95% LB	95% UB	KM MLE	95% LB	95% UB
Chrysotile (BC)	0.0022	0.00075	0.0056	2.60E-10	0	2.10E-09
Amphibole (BC)	0.0046			7.70E-08		
Quebec (BC)	0.00029	0.000085	0.00091	1.60E-10	4.40E-11	5.60E-10
South Carolina (BC)	0.021	0.0081	0.051	2.50E-09	2.30E-10	1.20E-08

Dr. Ogden said he "sensed a general favouring of his kind of approach," but he was a bit "thrown" by Dr. Camus' question about applying the estimates to particular situations. "I would have hoped that the confidence limits would incorporate all the other ranges of

environments that Berman and Crump looked at, except for South Carolina and Quebec," he said. Dr. Camus responded that ultimately, they might need to rely on their own judgment; Dr. Bernstein agreed, saying there is no "turnkey solution."

Participants discussed the need to include a general statement with the recommendations, to say that Health Canada will have to take into account the individual characteristics of each situation when it applies the model, and the need for caveats and qualifiers for specific situations like asbestos cement destruction.

Dr. Bernstein noted that studies of asbestos cement production exist. Dr. Gibbs agreed, but said the studies were inconsistent, possibly because plants had often used amphiboles as well as chrysotile. The reason that the Hughes *et al.* study data was useful was that she was able to separate workers who worked in the "chrysotile only" plant. This was not the case for the Ontario study, where exposures had included considerable quantities of amphibole fibre. Dr. Crump said he did not recall well enough, so he was concerned about including information of that nature.

Dr. Ogden asked if all participants were satisfied with a statement to the effect that "Health Canada will have to take into account the nature of environment."

Dr. Crump said the model does not distinguish between short and longer fibres. Dr. Gibbs objected to the use of "amphibole" in the table, as it in fact refers to a mixture of amphibole and chrysotile. Dr. Crump suggested qualifying the table to that effect.

Dr. Ogden asked participants how they should deal with different amphiboles. Dr. Crump said that when they wrote the article, they had not found any difference between them, which was why they had combined the data; he said he did not think it was critical to break them out. He expressed his uncertainty that satisfactory figures for tremolite in fact exist. The references to "tremolite" in vermiculite studies were mentioned as a possible source of data.

Dr. Bernstein said there is a difference: an inhalation study by Davis described tremolite as "the most potent fibre he'd ever seen." He added that no real data exists for crocidolite, and that amosite fibres have produced mesothelioma in hamster models. Dr. Fubini added that tremolite is "certainly different in terms of composition"; she said, however, she has seen no evidence of environmental danger in tremolite.

Dr. Gibbs said he would not argue against Dr. Crump's figure, but he also had serious concerns about combining the amphiboles. "The risks associated with crocidolite are very real," he said. The risks associated with amosite are less well defined and variable. "I worry that the figure in the table underestimates the risk of crocidolite." Dr. Ogden added that Hodgson and Darnton have risk summaries for chrysotile, amosite, and crocidolite.

Dr. Stayner asked whether it was necessary to provide numbers to Health Canada, as the panelists were suggesting a very general approach. He suggested that rather than publicly

presenting Health Canada with the table, they should present an approach, such as the models the participants had discussed at the meeting. Dr. Camus agreed, but added that risk estimates were also required.

Dr. Stayner said he felt the estimates should be updated with current data. Dr. Camus said Dr. Stayner could make a strong recommendation that the model should be continually updated with new data.

The working statement was revised to read as follows:

> *We believe that the approaches of Berman and Dr. Crump and Hodgson and Darnton are reasonable for estimating risk for mesothelioma and lung cancer in the light of present knowledge, subject to the following serious reservations. Application of the models to particular environments must take into account (1) and (2) in particular.*
>
> 1) The lung cancer risks in chrysotile textile manufacturing at Charleston were higher than those predicted by these and other models. Further research may elucidate the reason for this.
>
> 2) The risks in chrysotile mining and milling are less than those predicted by these models. Further research may elucidate the reason for this.
>
> 3) We are inclined to favour the linear approach of Berman and Crump.
>
> 4) New data is likely to require updating of the models.

Next, Greg Paoli presented the results of the relative risk elicitation exercise participants had completed before the meeting. The exercise had required participants to attempt their own estimation of exposure-specific risks for chrysotile for lung cancer, peritoneal mesothelioma, and pleural mesothelioma. The results were projected for the participants to see.

Participants first looked at the range of opinion on lung cancer relative risk. Five participants had taken part in the exercise, and Mr. Paoli said there was a considerable range of opinion among them.

Participant P1 indicated that a fair amount of weight should be given to relative risks of greater than 1.0, whereas "P2 was convinced that numbers greater than 50 were appropriate," said Mr. Paoli. P3 recorded some possibility that chrysotile is worse than amphibole; in other words, a relative risk of less than 1.0, but the bulk of the weighting was between 1.0 and 20. P4 indicated there was strong evidence around 1.0, with some accommodation for numbers greater than one. Finally, P5 indicated "broad uncertainty."

Dr. Camus said this showed there is some significant heterogeneity among the participants, adding that the differences of opinion on lung cancer may be irreconcilable. He said it would be "unfair" to come up with an average, but he requested that participants still make some

statement to give Health Canada. "It would be nice if we could say something like there is no more than a 10% chance that amphiboles are more dangerous than chrysotile in lung cancer. We really need an idea so we can take into account if we need to be more careful with amphibole or chrysotile," he said.

Participants looked next at the results for peritoneal mesothelioma. Mr. Paoli said that relative to lung cancer, these results could be called consensus, but only in a relative sense. He added that pleural mesothelioma also had more consistent results. Only four participants had taken part in the exercise for the mesotheliomas.

Dr. Ogden suggested that based on this information, participants were at least 80% certain that amphiboles are at least 30 times more dangerous than chrysotile. Mr Paoli concurred, saying four out of the four participants who scored had given at least 80% of weight greater than 30-fold. Dr. Stayner said he had not given much thought to the differences between pleural mesothelioma and peritoneal mesothelioma before the meeting, so he had not participated. He also expressed concern about the small size of the group. "I think it is an interesting exercise, but I don't think I'd publish that," Dr. Stayner said.

Dr. Camus said the participants had given Health Canada guidance on chrysotile. He added that Health Canada would also need clarification about whether the panelists' opinion was based on pure chrysotile or commercial chrysotile.

Dr. Gibbs said Health Canada should ask if chrysotile could be produced without amphibole and ascertain the probability it would cause mesothelioma risk. Dr. Ogden added that Hodgson and Darnton had taken a different approach and defined the lower bound as insignificant, not zero.

Dr. Camus asked if any of the participants wanted to add a statement to the effect that even though the confidence interval may include the value of zero, they exclude the possibility that chrysotile does not cause mesothelioma. The question is pertinent because some geologists at McGill University in Montreal believe that pure chrysotile could be mined by avoiding the tremolite veins. "We have one data point," said Dr. Stayner, adding he did not think that was sufficient. . Dr. Ogden said he did not think participants could reach an agreement at this time, but "we could only say that four panelists voted on this and they all put figures of at least 80% certainty that the relative risk was more than a factor of 30." "

Conclusion, Thanks, Homework Directives, Deadlines

Before adjourning the meeting, Dr. Camus reminded participants of their post-meeting "homework," which consisted of answering the 14 questions sent to them in the panel work outline before the meeting. He acknowledged that most of the questions had been addressed in the past few days, and asked participants to answer the questions based on the meeting. He added that the participants should be honest in their responses. "If you don't know the answers, tell us you don't know," he said.

Dr. Camus added he would send the participants a revised list of questions based on those in the panel work outline, and he would ask for their probability distributions again and send them the summary of the distributions discussed that afternoon.

The meeting was concluded. Dr. Ogden thanked Dr. Camus for inviting the participants to Montreal, and Dr. Camus thanked the participants for their contributions.