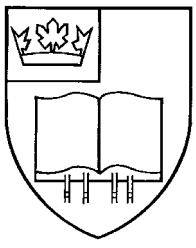
A REVIEW OF THE INSERM REPORT ON THE HEALTH EFFECTS OF EXPOSURE TO ASBESTOS

An Expert Panel Report
Prepared at the request of the

ROYAL SOCIETY OF CANADA

for
Health Canada



“studiis eodem diversis nitimur"
"different paths, one vision"

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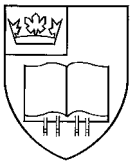

November, 1996

Ottawa, Ontario

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RSC.EPR 96-1

Expert Panel for the review of the INSERM report on the Health Effects of exposure to Asbestos

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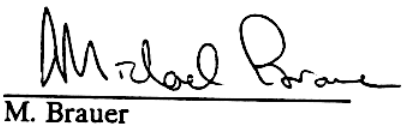
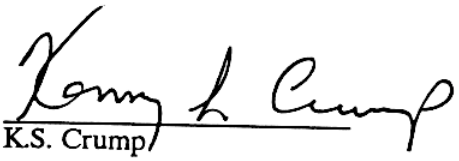
Kartini Rivers, Assistant to the Panel Chair

A REVIEW OF THE INSERM REPORT
ON THE HEALTH EFFECTS OF EXPOSURE TO ASBESTOS

Submitted by the Expert Panel on Asbestos Risk

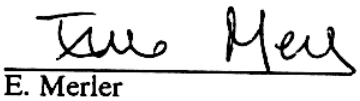


M. Brauer

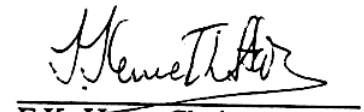


K.S. Crump

J.M.G. Davis



E. Merler



F.K. Hare, Chair

A REVIEW OF THE INSERM REPORT
ON THE HEALTH EFFECTS OF EXPOSURE TO ASBESTOS

Report of the Expert Panel on Asbestos Risk

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PREFATORY NOTE

On 17 September 1996, officials at Health Canada wrote to Dr. Robert Haynes, President of the Royal Society of Canada, requesting the Society "to convene an international expert panel to review the recent report entitled *Effects on Health of the Main Types of Exposures to Asbestos*," which had been issued in June 1996 by France's Institut National de la Santé et de la Recherche Médicale. The Society agreed to undertake this task and to do so under procedures established by its Committee on Expert Panels.

The President of the Society appointed Dr. F. Kenneth Hare to be the Chair of the Panel, a choice that was ratified by the Committee. The Committee then appointed the other panel members and also the international peer review group who commented on the panel's second draft report.

The Terms of Reference for the panel's work, as approved by the panel members during their initial meeting, are as follows:

> With reference to a report entitled "Effects on Health of the Main Types of Exposure to Asbestos", prepared by the Institut National de la Santé et de la Recherche Médicale (INSERM), France and dated June 1996, the Expert Panel on Asbestos Risk will be asked to answer the following question:
>
> Is the characterization of risks associated with exposure to asbestos in the above-mentioned report scientifically sound (i.e., supported adequately by available data)?
>
> The panel may wish to consider, in addition to any other matters that it considers important, the following aspects of the question posed above:
>
> 1. Have all critical studies relevant to assessment of health risks been included?
> 2. Are the critical studies presented in sufficient detail to justify this report's conclusions concerning characterization of risk?
> 3. Are there limitations of the critical studies which have not been presented?
> 4. Is there sufficient critical discussion of issues relevant to the risk characterization?

The panel members were asked to submit their report not later than the end of November, 1996. The Committee on Expert Panels, and the Society, are very grateful to the panel members, the panel chair, and the panel staff, as well as the peer reviewers, for taking on this very onerous task, and for the high level of professionalism and dedication all of them brought to their work.

The Committee welcomes inquiries about the procedures under which expert panel processes are conducted, which may be addressed to the Chair at the following address: School of Policy Studies, Queen's University, Kingston, Ontario K7L 3N6, tel. 613-545-6832, fax 613-545-6630, e-mail: leissw@post.queensu.ca.

William Leiss, F.R.S.C., Chair, Committee on Expert Panels, Royal Society of Canada
on behalf of the Committee members for this panel:
Professor Christopher Garrett, F.R.S.C., University of Victoria
Professor Camille Limoges, F.R.S.C., Université du Québec à Montréal
Dr. Earle Nestmann, CanTox

November 30, 1996

The President
The Royal Society of Canada

November 30, 1996

Dear Mr. President:

I have pleasure in enclosing a copy of the Report of the Expert Panel on Asbestos Risk, containing a critical review of the document *Effets sur la santé des principaux types d'exposition à l'amiante*, submitted to the Government of France by l'Institut National de la Santé et de la Recherche Médicale (INSERM). Our report contains (i) a general section covering the Panel's collective views, and (ii) an Annex made up of the four background papers written by the four Panelists. These papers express the individual views of the Panelists, slightly revised after discussion by the Panel, but still standing as personal assessments, rather than collective judgments.

The Panel's second draft report was reviewed by peer-reviewers, whose comments were then sent to all Panelists. The latters' responses influenced this submitted final report. The Panel found the peer reviews helpful and constructive. Some suggestions have been accepted, and written into the Panel's final report. But much valuable comment by the peer reviewers (who must remain anonymous) remains. This has been synthesized by the Study Director, whose overview appears in Appendix I.

As you know, this review was carried out at short notice. I could not possibly have completed the chairman's work without the prompt, willing and wise collaboration of my four colleagues — and without the aid of electronic communications. The entire Panel will also wish to congratulate Ugis Bickis, the Study Director, and my own assistant, Kartini Rivers, who attended to the production of all three drafts of the report.

I presume that you will now convey the report to Health Canada, which is anxiously awaiting receipt.

Yours sincerely,

F. Kenneth Hare
Chairman

ADVICE TO READERS

Throughout the document, the term "Panel" refers to the Royal Society's Expert Panel on Asbestos Risk. Individual members of the Panel are referred to as Panelists.

The term "report" generally refers to the INSERM document and its Summary. Page references are usually to the English translation of the Summary, except in a few indicated places.

The term "review" is used for the Expert Panel's report, to avoid confusion.

Because our Panelists and Peer Reviewers come from various backgrounds we have accepted Canadian, British or US spellings and usage without change.

A REVIEW OF THE INSERM REPORT ON THE HEALTH EFFECTS OF EXPOSURE TO ASBESTOS

Report of the Expert Panel on Asbestos Risk

I EXECUTIVE SUMMARY

This is a critical review of the report *Effets sur la santé des principaux types d'exposition à l'amiante*, submitted to the Government of France by l'Institut National de la Santé et de la Recherche Médicale (INSERM), and dated June 21st, 1996. The Expert Panel's review is based on a pre-publication copy of the INSERM report, in its original French, and on translations subsequently provided by Health Canada. The version reviewed is not quite complete, lacking Chapter 4 sections 2, 3 and 4, and certain illustrations and bibliographies.

The INSERM report consists of a detailed summary, and a lengthier document separately indexed. Chapters 1 through 4 survey what is known about the different types of asbestos and their measurement; the circumstances and levels of exposure to asbestos, notably to the French population in occupational, para-occupational and environmental settings; and the main known effects of asbestos on humans. Chapter 5 deals with experimental evidence. Chapters 6 through 10 discuss the epidemiology of asbestos-related illness from asbestosis, pleural plaques, lung cancer and mesotheliomas. Chapter 9, in particular, derives a series of risk estimates for various scenarios using a well-described model. The report discusses the rising occurrence of mesothelioma in France and other industrialized countries as a marker of asbestos-related cancers. It assumes that action is needed to reduce the burden of asbestos-related tumours in the French population.

The Panelists' experience and skills cover most of the ground treated in the INSERM report, but all the material could not be reviewed in equal detail. Because the mandate calls for critical analysis of the report, the Panelists have often expressed negative or doubtful reactions. They have not explicitly commented on many of the positive aspects of the report, but this should not hide the support they feel for

the work of their French colleagues. Their criticisms are directed only towards the report, not its authors. Where the Panelists have differed among themselves — as is normal in sound science — that fact is indicated.

In the Terms of Reference the Panel was asked:

> **Is the characterization of risks associated with exposure to asbestos in the INSERM report "Effects on Health of the Main Types of Exposure to Asbestos" scientifically sound (i.e., supported adequately by available data)?**

The Panel considers that the INSERM report represents a laudable effort carried out under what must have been difficult conditions. The integrity, competence and good intentions of its authors are obvious. The Panel extends its good wishes to them in their efforts to bring science to bear on a crucial problem in public health.

Some Panelists, though agreeing that the report is generally sound scientifically with respect to procedures, nevertheless feel that the evaluation of available data, and (more importantly) the use of these data in risk assessment, provide at best no new information, and at worst present unjustified overestimates of the risk of current exposure. One Panelist goes further, expressing disappointment with the quality of the report, and feeling that it relies too much on material from other authorities (without critical appraisal) that support INSERM's conclusions. Another Panelist takes a warmer view of the INSERM report (see p. 63).

Health Canada raised four specific questions (HC1-4 in what follows):

HC1: **Have all critical studies relevant to assessment of health risks been included?**

Some relevant papers are missing from the reference lists in the INSERM report. There is a divergence of view within the Panel about the adequacy of the coverage. Little new information is presented, and the report fails adequately to address the relevance of the available studies to the key present question: are current exposures associated with increased risk?

HC2: **Are the critical studies presented in sufficient detail to justify the report's conclusions concerning characterization of risk?**

Most Panelists feel that there are areas in which sufficient detail is indeed lacking. Some do not understand why INSERM's authors wrote as they did, for example in relation to lung cancer. In most cases, this doubt has arisen from a lack of detail in citation. A specific case in point is INSERM's estimates of asbestos-related deaths in France in 1996, which was based on an estimate from the literature specific for Great Britain without critical analysis of the methodology, or establishment that the estimate was applicable to France.

A common concern is that the INSERM report's conclusions appear to rest too much on the summary data collated in such secondary sources as the Health Effects Institute's *Asbestos in Public and Commercial Buildings* — itself a model compilation — rather than on direct consultation of original sources.

The report is not adequately directed towards indoor exposures. Most of the emphasis is placed on occupational exposures that may be of little relevance to current exposures. The report adequately presents the evidence that occupational exposure is associated with increased risk of lung cancer and of mesothelioma. What is unclear is the magnitude of risk associated with the lower current exposures.

HC3: **Are there limitations of the critical studies which have not been presented?**

The Panel finds this question hard to answer categorically. The INSERM report certainly explores such limitations in a number of cases, but panelists differed as to the effect that such exploration (or the lack of it) influenced INSERM's findings.

HC4: **Is there sufficient critical discussion of issues relevant to the risk characterization?**

The general concern here is that the risk characterization is less satisfactory because actual exposure data were not used. INSERM has clearly focused on dose-response relationships, rather than on exposure assessment, or on critical analysis of exposure data. Not only does the failure to look at realistic exposures result in less specific guidance on the actual situation in France, but the assumed exposures are likely to be much greater than those experienced by the French population. Given that imported English data were used to estimate the number of cases of lung cancer in France, the Panel feels that INSERM could equally well have used typical building exposure asbestos levels from other jurisdictions in its quantitative risk assessment. Quite generally, INSERM seems to have been more willing to import epidemiological data from other countries than to use external experience with exposure data. Moreover the Report gives too little attention to exposure assessment as a necessary component of risk assessment.

However, these are errors of omission rather than of commission, and to the extent that there is an effort to use French data wherever possible, the report is commendable. Nevertheless, the fact that it does not attempt to apply actual exposure data to the risk assessments makes the conclusions less convincing than they might otherwise have been.

The Panel agrees with INSERM's findings on the following points:

(i) all asbestos fibres are carcinogenic, regardless of their mineralogical nature;

(ii) the risk of lung cancer is higher for longer and finer fibres, though the evidence for fine fibres is not as strong as for long fibres;

(iii) the preponderance of cases of mesothelioma in males is associated with occupational exposure to asbestos;

(iv) for low dose and dose-rate exposures the linear, no-threshold model is used by all regulatory agencies that have performed quantitative risk estimates;

(v) the exposure profile data for the French population are not adequate for risk estimation, and estimates based on regulatory limits are a common approach. But it must be emphasized that the assumed exposure on which the number of deaths is predicted is hypothetical, and is higher than levels that have typically been measured in buildings containing asbestos materials;

(vi) the Panel shares in the grave reservations felt by INSERM regarding the systematic removal of sprayed asbestos finishes from buildings;

(vii) extreme vigilance is essential in strict control of occupational exposures, and the monitoring of such exposures; and

(viii) research should be done on substitutes for asbestos, whether alternative fibres, other materials, or altered technologies.

The Panel has doubts or reservations, however, about some of INSERM's assumptions or conclusions. It considers that:

(ix) the higher risk from long fibres appears to hold within a mineralogical type, but the evidence is not strong across types; a longer chrysotile fibre may not, for example, have a higher associated risk than a slightly shorter crocidolite fibre;

(x) the differences between chrysotile and amphiboles may have been underestimated by INSERM, particularly for mesothelioma;

(xi) the risk of mesothelioma from chrysotile exposure is probably overestimated by INSERM. The Panel also notes that mesothelioma risk from amosite and crocidolite, which was not estimated by INSERM, is probably higher than the estimates for chrysotile provided in the report;

(xii) the evidence for the dominant role of occupational or para-occupational exposures in mesotheliomas among females (as compared with males) is less well established;

(xiii) the linear no-threshold hypothesis for low exposure levels is not the only possible strategy in risk assessment, but evidence is not available to demonstrate that a different hypothesis is a superior predictor of risks from low exposures than the linear no-threshold hypothesis;

(xiv) the transfer of risk coefficients calculated from high exposure settings, and/or from differing techniques of measurement, involves possible errors;

(xv) the INSERM estimates of 750 deaths in France from mesothelioma and 1,200 from lung cancer in 1996 refer to deaths in 1996, but from occupational exposures at a much earlier date; they are not deaths due to exposures in 1996. Although INSERM is well aware of this, their report is not explicit enough;

(xvi) measures based on optical phase contrast microscopy should not be used in building risk assessments, as the report should indicate; direct transmission electron microscopy is the best choice for direct comparison with occupational experience;

(xvii) there is scientific validity in INSERM's call for medical surveillance, but the Panel is not sure about the value of medical monitoring to individual workers.

II THE PANEL'S COMMENTARY

The Panel has deliberately presented its substantive findings in an Executive Summary. Its review is so short that it would appear absurd to repeat the same words within a few pages. Nevertheless, a more detailed commentary is needed to convey the Panel's full opinions.

The INSERM report's assumptions, conclusions and recommendations are scattered throughout the document. Section 3 of the Summary contains many of the more important items, but others are buried in the main text. The Summary is an impressive synthesis. The main text, by contrast, urgently needs thorough scientific editing (to remove errors in units or conversion factors; and to organize the contents more consistently). We had difficulty finding our way through it.

This lack of structure led us to present our review by commenting on the INSERM conclusions, risk assessment procedures and recommendations, to which we now proceed. We have boldfaced direct quotations from the English translation of the text, and also italicized our agreement or disagreement.

1. INSERM'S Conclusions and Assumptions

INSERM, Summary, p. 65: **All asbestos fibres are carcinogenic, whatever their geological origin**. The Panel *agrees*, though the proper English adjective is "mineralogical". The forthcoming International Program on Chemical Safety (IPCS, WHO) report entitled *Environmental Health Criteria Document on Chrysotile Asbestos* confirms that chrysotile — sometimes seen as relatively safe — increases risks for asbestosis, lung cancer and mesothelioma in a dose-dependent manner; but the greater hazard presented — in particular for mesotheliomas — by other forms of asbestos (e.g., crocidolite) is indisputable.

INSERM, Summary, pp. 42-43: **The risk of mesothelioma is higher for amphibole fibres than for fibres known commercially as `chrysotile'**. Again the Panel *agrees*. But there is some feeling among Panelists that the quantitative differences between chrysotile and the amphiboles has been understressed in the INSERM report. We could not locate a discussion of the effect of fibre length as a factor in mesothelioma.

INSERM, Summary, p. 66: **The risk of lung cancer is higher for long and fine fibres**. The Panel *agrees* that longer fibres (if still in the respirable range) are more carcinogenic than shorter fibres, but as regards fibre diameter the evidence seems less conclusive. To the extent that this and other conclusions depend on quantitative extrapolation from animal data to human reaction, caution is needed. The INSERM additional clause **`whether these are amphibole fibres or fibres known commercially as chrysotile'** seems more dubious; the rule might hold <u>within</u> a fibre type but not <u>across</u> fibre type.

INSERM, Summary, pp. 42-43: **The preponderance of occupational exposure [is found] in the aetiology of almost all cases of mesothelioma in males [and further] suggesting very strongly that the aetiology of female mesothelioma is very largely due to the occupational and para-occupational exposure**. The Panel *agrees as regards males*, but *considers* that the suggestion as regards female cases is not as well supported in the literature.

INSERM, Summary, pp. 44-45: **It can therefore be confirmed absolutely that there is no argument based on an analysis of existing direct or indirect epidemiological data that supports the consideration that linear extrapolation without a threshold using data corresponding to higher levels of exposure to asbestos ... is not the most plausible, if uncertain, model. None of the data examined allows an alternative model to be proposed that would have any credibility.**

The Panel *finds the wording absurd,* and even in the original French it is unnecessarily obscure. A reasonable English précis might read "we're stuck with the linear no-threshold model". In fact this is not so, as there are other scientifically credible models that may prove to be correct; but the Panel *agrees* that regulatory agencies use the model in this form. The Panel *finds* two other more persuasive statements of similar principles in the INSERM document: `**This method is the most plausible uncertain estimate in the current state of knowledge**' (Summary, p. 53); and **the model which appears most appropriate for quantification of the excess mesothelioma mortality** (Summary, p. 50, rephrased), both of which are pragmatic. The Panel *does not agree* that this model is necessarily more appropriate than other models, and *considers* that a discussion of alternatives should have been presented by INSERM. The problem is generic in risk assessment; it also occurs in many cases of low exposures and exposure rates to other hazardous substances or radiation.

INSERM, Summary, p. 65: **The overall number of deaths attributable to exposure to asbestos in France in 1996 can be estimated at 750 deaths from mesothelioma and 1200 deaths from lung cancer, i.e. in total 1950 deaths**. The Panel *stresses* that these are "deaths in 1996", and not "deaths due to exposures in 1996". These deaths are associated with exposures in the past, and not the present levels of exposure. The report [p. 65] concludes that `**the immense majority of these deaths can indisputably be explained by circumstances of occupational or para-occupational origin**' (i.e., and not environmental or building exposures).

Although the numbers may be the best estimate available they seem uncertain to some panelists, who feel that INSERM does not present a sufficiently strong case to support their view that these values represent the lower end of possible values. Other data are available in the literature concerning increases

in the rate of asbestos-related deaths. Moreover, these figures appear to assume that all mesotheliomas are caused by asbestos.

The Panel was aware of the problems involved in comparing observations of asbestos fibre concentrations using differing techniques, such as optical phase-contrast microscopy (PCM) and transmission electron microscopy (TEM). The application of risk coefficients derived from occupational experience, and using optical microscopic methods, to environmental situations involving TEM analysis, is not straightforward. Nevertheless, INSERM states, since asbestos exposures were historically assessed by optical microscopic methods, that `**the risk coefficients which have been calculated are, in all likelihood, significantly lower than the risk coefficients which might have been calculated if the measurements could have been taken using electron microscopy.**' (Summary, p. 13)

The Panel feels that INSERM does not present data that support the conclusion that **`exposure measured in "F/l" is equivalent, from the point of view of cancer risks, to exposure greater than 1,000 times this value in "f/ml"'** (p. 13 of Summary). Though INSERM's conclusion is based on the assumption that optical microscopic analysis (f/ml) results in greater than 1,000 times electron microscopy analysis (F/L) due to the inclusion of non-asbestos fibres in optical microscopic analysis, there are other differences between TEM and PCM not considered by INSERM that suggest a different conclusion: a) even if the TEM counts refer only to structures longer than five micrometres, in many environments many asbestos structures seen by TEM are too thin to be identified by PCM; b) TEM counts include complex structures (clusters and matrices) that would not be counted by PCM because they do not satisfy the dimensional requirements; and c) indirect preparation of filters for TEM analysis, which is the method prescribed in France, causes complex structures to break up into multiple structures that inflate the count. These considerations could, in fact, affect how the INSERM recommendations are implemented.

INSERM, Summary, p. 69: **It is clearly established that the highest risks of mesothelioma now involve occupations whose circumstances of exposure are characterized by their intermittent nature**. This merely states that the highest risks occur in those occupations where

intermittent exposures are very likely, and not that these risks are due to the intermittent nature of the exposure. The report presents no data to support the inference that intermittency increases risk.

The Panel discussed the issue of whether or not asbestosis was necessary for the causal attribution of a lung cancer to asbestos exposure. We *agreed* that this was still an area of active debate, and some Panelists queried INSERM's conclusion that asbestosis was not necessary for the attribution of a lung cancer to asbestos exposure.

INSERM, Summary, pp. 50 and 79: **The plausibility of a causal association with occupational exposure to asbestos in a subject presenting with lung cancer is totally independent of the tobacco consumption of the person in question [in the context of compensation]**. The Panel *agrees* that this is technically correct, but it needs to be put into context. Attributable risks are not additive; e.g. a relative risk (RR) of 2 for asbestos and RR of 10 for smoking would have a 50% risk attributable to asbestos and 90% risk attributable to smoking.

INSERM, Summary, p. 51: **the arguments supporting what is commonly called `the amphibole hypothesis' ... are clearly contradicted by the numerous epidemiological observations ...** The Panel *considers* that the phrase "are clearly contradicted", with respect to mesothelioma, is too emphatic a statement, because there are data that suggest a contrary viewpoint. The Panel was in some disagreement in this respect, however.

INSERM, Main Report, 2-282: **In the absence of specific asbestos exposure, there is a base mesothelioma incidence in every country, estimated at 1 case per million residents**. The Panel is *unclear* as to what this means, and as to the evidential basis.

2. INSERM's Quantitative Risk Assessment

By far the most ambitious conclusions and recommendations put forward by INSERM are the risk estimates proposed in section 3.1 of the Summary, and especially in the long chapter 9 of the main report. The INSERM report reviews the available data from France for occupational, para-occupational and environmental exposures. Its authors conclude that the exposure data are insufficient for quantitative assessments for lung tumours and mesothelioma as to level and gradient of risk across a range of exposure levels. Accordingly, INSERM's estimates have been based on permissible occupational and environmental levels in France. This methodology is not wrong, provided that it is clearly understood that the predicted deaths are not based on the exposure profile of the French population. The conditions of exposure are hypothetical. Similar extrapolations have been made by public groups in other jurisdictions, notably the 1984 Ontario Royal Commission.

The Panel *concluded* that it would have preferred to see risk assessments based on actual current exposures in France, but it *accepted* INSERMS' view that the data available are not of sufficient quality. It is aware of the difficulties of arriving at representative levels of exposure. In such circumstances it is acceptable to use the current regulatory limits as an index of exposure, for the purposes of risk management decisions. However, the report should have emphasized that actual exposures are in all likelihood substantially lower, and so, correspondingly, are the actual risks facing the French public.

The estimates of exposure initially presented in the report dealt exclusively with chrysotile, whereas these were summarized on p. 73 of the Summary as "asbestos"; although the ongoing use of amphiboles would not be anticipated, it should be noted that the presented risk estimates, particularly those pertaining to mesothelioma, are likely too low for amphiboles.

The Panel *believes* that the risk of mesothelioma from chrysotile exposure is likely overestimated, since it is based on a single study that involved a small amount of crocidolite in addition to chrysotile, and ignored several studies of pure chrysotile exposure, all of which indicate a smaller mesothelioma risk than calculated by INSERM. Estimates of mesothelioma risk from exposures beginning early in life assume that the observed rapidly increasing risk up to about 40 years from first exposure continues for another 30 years. This assumption is not verifiable at present, and introduces an additional element of uncertainty into estimates for exposures beginning in childhood.

The value for lung cancer is in the correct range, but the uncertainties should be pointed out, given the very wide range in the available estimates (summarised in Tables G and H of the report). It appears that the report did not take advantage of a number of studies that provide useful information on risk of lung cancer and/or mesothelioma, including several that have appeared in the literature since the HEI report was published.

The utility of risk estimates such as those provided by the INSERM report lies in the fact that they provide a clearer basis for risk measurement decisions than do qualitative evaluations of the known carcinogenic risk posed by asbestos exposure. We *agree* that the presence of risks containing uncertainty in the assessment could result in a range of options for the health authorities, depending on the availability of substitutes, economic feasibility, and several other factors. Risk estimates in fact are ultimately incorporated into social, economic, political and value judgments.

3. INSERM's Recommendations

The Panel notes that the INSERM report did not recommend that any specific action be taken, in the light of the risk estimates that it had presented, as might have been done, for example, in order to implement systematic abatement procedures. In fact, INSERM stressed its `**grave reservations**' about the possibility of systematic removals of sprayed asbestos finishes from buildings, and emphasized the information gaps that need to be addressed. The Panel *shares* in these reservations.

INSERM, Summary, p. 78, says that **extreme vigilance is essential in respect of the strict control of the conditions of exposure of people exposed occupationally to asbestos and the monitoring of their exposure**. The Panel *agrees* with this statement.

INSERM, Summary, p. 80, asserts that **The periodic publication of this material** [data on asbestos exposures associated with various buildings/activities] **in a form respecting the confidentiality of the individual measurements, but adopting greater transparency at the level of the combined statistics, is an urgent necessity ... It is also essential that studies are carried**

out on the levels of exposure of people, which would also characterize the demographics of those exposed. INSERM says (Summary, p. 78): **It also seems justified to implement medical monitoring of people exposed occupationally to asbestos throughout their active employment and beyond**.

The Panel *considers* that there is scientific validity (i.e. as a component of the research effort) for medical surveillance. For this Panel to comment on the advantages of medical monitoring to the individual worker, however, it would need more details about the suggested program(s).

INSERM, Summary, p. 83, recommends that **Appropriate research work should be carried out and developed urgently before the generalised introduction of substitute fibres.** The Panel *feels* that this concern should apply to any novel substitute materials, whether fibrous or not. Health risks associated with substitute materials and technologies need to be evaluated.

INSERM, Summary, p. 83, believes that **The production of a joint policy of studies and research on the health hazards linked to the environment in general and the working environment in particular seems now to be an absolute priority**. The Panel *agrees*, but recognizes that recommendations of this sort follow nearly all science/policy analyses!

III FINAL REMARKS

The Panel was given a series of questions by Health Canada, and was expected to answer them succinctly. They are set out in our Terms of Reference, which are presented on pp. i-ii. Our hope was that we could give consensual answers. We could always not do so.

In retrospect, the hope seems to have been foolishly optimistic. Scientists cannot achieve a consensus on contentious issues after two weeks of reading and two days of face-to-face discussion. Indeed the entire notion of consensus by argument is alien to the empirical and experimental demands of scientific thought. In science, consensus emerges; it does not arise from short-term confabulation. And it emerges most slowly when there are major uncertainties, as in the case of asbestos risks.

Nevertheless, the Panel has tried to answer the questions set out in its terms of reference, even though its conclusions have often been qualified.

The Panel's work began with the preparation of individual written submissions to their fellows. This led to a brief face-to-face meeting in Toronto, at which much common ground was discovered, but where substantial differences of opinion were apparent. These were resolved in part by a protracted exchange of views via the electronic media, and the preparation of draft reports, of which this is the final version. The Panel's work was greatly helped by the peer-review process, whose results are summarized in Appendix I. All Panelists feel, however, that more face-to-face discussions would have improved the quality of their findings. All are grateful for this chance to comment on INSERM's laudable effort.

Short Biographies of the Panel Members and Staff

Michael Brauer is Assistant Professor in the Departments of Medicine and Occupational Hygiene at the University of British Columbia. His interests are related to air pollution, particularly as regards exposure assessment, epidemiology and health effects research, indoor air quality evaluation and control, and the development of sampling methodology. He is a graduate (ScD) of Harvard University's School of Public Health, and of the University of California at Berkeley.

Kenny S. Crump is Vice-President, ICF Kaiser Engineers, Inc., K.S. Crump Group, Ruston, LA. He has had broad experience in risk assessment (especially cancer), environmental statistics, bioassay statistical design and analysis, and environmental and cancer epidemiology. He has taken part in many public health studies, including Ontario enquiries into asbestos and 2-4 D hazards, and is currently a member of the Committee on Environmental Health of the US Environmental Protection Agency. He is a graduate of Montana State University (PhD), the University of Denver, and Louisiana Tech University.

John M.G. Davis is a consultant in the pathology of occupational medicine. From 1971-90 he was head of the Pathology Branch of the Institute of Occupational Medicine in Edinburgh, and an honorary Senior Research Fellow in the Department of Pathology. He is a recognised authority on the application of experimental methods to the impact of asbestos on human health. He was a member of the Research Oversight Committee of the Health Effects Institute — Asbestos Research, and of its Asbestos Literature Review Panel. He is a graduate of Cambridge University (ScD) and a Fellow of the Royal College of Pathologists (FRCPath).

Enzo Merler holds appointments in the Environmental Cancer Epidemiology Unit of WHO's International Agency for Research on Cancer (IARC) in Lyon and in the Unit of Epidemiology, Centre for Study and Prevention of Cancer, Florence, Italy. He is highly experienced in cancer epidemiology and in occupational health. He is a Doctor of Medicine from the University of Padua, and holds a degree in epidemiology from the University of North Carolina at Chapel Hill. He has also studied at the University of Florence.

F. Kenneth Hare, the Panel Chairman, is University Professor Emeritus at the University of Toronto. Since 1977 he has chaired Royal Society Panels on transboundary air pollution (jointly with the US National Academy of Sciences), the nuclear winter, lead pollution and nuclear safety (for the Government of Ontario). He is a graduate of the Universities of London and Montréal (PhD).

Ugis Bickis, the Panel's Study Director, is Vice-President and Environmental Hygienist/ Toxicologist of Phoenix OHC, Inc. He is a Canadian and US Board accredited Hygienist. He has extensive experience in public health policy and holds several adjunct faculty appointments. He has a PhD in Pharmacology and Toxicology from Queen's University, Kingston, and also holds degrees in engineering (the University of Toronto) and zoophysiology (University of Manitoba).

Kartini Rivers, Assistant to the Chairman, is Secretary of the Technical Advisory Panel on Nuclear Safety of Ontario Hydro, and has worked with the Chairman in several of the Royal Society Panels.

APPENDIX

Summary of Peer Review Comments

N.B. The Reviewers worked on the second draft (02) of the Panel's report. Some of the comments made in this summary have already led to changes in the Panel's final report. Others refer to passages in draft 02 that were omitted from the final version.

The Panelists agree that the Peer Review comments have greatly helped in the Panel's work.

SUMMARY OF PEER REVIEW COMMENTS

Five peer reviewers were selected by the RSC Committee on Expert Panels, and were each provided with a copy of draft 2 of the report of the Expert Panel on Asbestos Risk (EPAR), as drafted by its Chair. Four Reviewers (designated A, B, C, and E) were able to respond in time for their viewpoints to be considered by the Panel. In keeping with RSC policy, the Peer Reviewers were aware of the identity of the Expert Panel, but not vice versa.

The Panel found the reviews to be insightful, useful and generally supportive of its draft report. Many comments have been specifically addressed or incorporated in this final draft of the report. Nevertheless, the overall reviews are summarized below, as they are considered to provide (in their own right) a substantive contribution toward answering the questions posed by Health Canada.

A common theme running through all the writings relating to this project is the matter of the paucity of time provided to tackle the task at hand. Three of the Reviewers chose to make this a point of discussion with respect to RSC's task; for example, one drew a parallel to the "**years** taken for corresponding reviews by WHO, ILO, IPCS, and the governments of the USA, the UK and ... of Quebec and Ontario" whereas another completed his document with "Overall, I think the Expert Panel has done a good job of evaluating the INSERM Report, considering the unreal time constraints put upon them. Whoever decided on those constraints cannot have had any idea of the complexity of the questions that had to be addressed."
The fourth Reviewer suggested, on the other hand, that the Panel's attempt to make allowances for the INSERM's report's shortcomings by invoking a shared sense of time constraint, was inappropriate, at least with respect to the conclusions of the report.

The overall viewpoints expressed by the Peer Reviewers with respect to the RSC EPAR draft report that they reviewed were:

A:
- "... agree with the general tenor of this Evaluation of the INSERM Report"
- "Overall ... good job... [etc.]"

B:
- "... a fair attempt to review positive aspects and limitations ..."
- "... share most of the conclusions of the RSC report ..."
- "... agree in particular with two important statements of the RSC report:" major limitation of INSERM report is selection of epidemiological papers used in the risk assessment and, underestimate of difference in risk between exposure to chrysotile and to amphiboles.

C:
- "... addressed its mandate, and the related questions adequately and fairly."
- "... summarizes accurately ... the structure and main conclusions of the INSERM report."

D:
- Specifically endorsed the EPAR report summation that "scientists cannot achieve a consensus on contentious issues after two weeks of reading and two days of face-to-face discussion ..." as, "a very wise paragraph which underscores the potential folly of overrapid review of extremely

voluminous and complicated scientific evidence and the potentially disastrous consequences of the hasty political decisions which result."

- where he did not completely share the EP's viewpoint, it was [generally] to the extent that an approval should have been qualified, or that a point of disagreement should have been stated more strongly.
- Having concluded, with respect to the INSERM report, that "even from a cursory examination there were many examples of misrepresentation, untrue statements and the omission of important but possibly inconvenient findings", this Reviewer feared that "the panel review is not sufficiently penetrating to provide any assurance as to the reliability and objectivity of the INSERM report".

A number of Reviewers noted that there were difficulties faced by EPAR even by virtue of the lack of structure within the INSERM report.

Reviewer C was particularly thorough, and suggested a rewriting of the draft with respect ordering, style, and manner of presentation of the INSERM conclusions. He also contributed extensively, by addendum (not included here), from his own, conceptually sophisticated, writings. Similarly, Reviewer B suggested that certain assumptions on the part of INSERM (which were termed "conclusions" in the EPAR report, for the sake of simplicity and, because the INSERM group at some point will have concluded in each case that this was, in fact, an assumption that they were going to make) should have been distinguished in the EPAR report from the conclusions of INSERM's risk assessments.

It would seem (from the reviews) that the EPAR report is a reasonable and cogent synthesis, although, like any consensual document, it may not have been sufficiently **critical** to suit individual Peer Reviewers.

The key Peer Reviewer comments not mentioned thus far are summarized below, following the outline / sequence used for draft 2 of the EPAR report, and in reference to that report.

In relation to those INSERM assumptions, conclusions and recommendations with which EPAR **concurred** one Reviewer questioned whether all asbestos fibres truly are carcinogenic: "where is the evidence that pure chrysotile, uncontaminated by fibrous tremolite, is carcinogenic for man"? The same Reviewer also would have qualified the observation that the linear, no-threshold model is used by all regulatory agencies, with the added comment: "... despite virtually all the epidemiological evidence that it does not hold for chrysotile exposure in man." With respect to INSERM's use of regulatory limits (in the absence of good exposure data) for risk estimation, and the EPAR's (draft 2 report) characterization of this as "reasonable ... provided that ...", one

Reviewer indicated that it made "some sense for occupational exposures with the proper qualifiers", but that it seemed "preposterous" for environmental exposures.

The Peer Reviewers provided more comment on EPAR's points of **disagreement** with INSERM. One Reviewer suggested that, in addition to the points that had been made, it is "wrong, misleading and fallacious" to make single point estimates of asbestos risk, given the acknowledged heterogeneity of slope

estimates for lung cancer, and the limited and imperfect data (particularly in terms of exposure assessment) for mesothelioma.

With respect to the differential risk presented by the amphiboles and chrysotile, particularly for mesothelioma, there was a remarkable degree of solidarity provided by the Reviewers, suggesting that this point should be emphasized. Only one Reviewer seemed to agree with INSERM in this respect, citing Smith, A.H. and Wright, C.C. (1996): Chrysotile asbestos is the main cause of pleural mesothelioma (Am. J. Ind. Med. 30:252-). The others, by contrast, were (largely) vehemently opposed to this concept. "The differences in risk between exposures even to commercial chrysotile and those which include important amounts of amphibole fibre ... are substantial and without exception". The same Reviewer, with respect to INSERM's work, stated "... all the studies considered in Chapter 9 included exposure to important amounts of crocidolite and none was appropriate for estimating the mesothelioma risk associated with chrysotile." Another Reviewer pointed out that INSERM's interpretation of toxicological (animal) data from different fibre types was based on an "obsolete" gravimetric measurement of instilled doses. With respect to occupational experience, he pointed out the studies that had demonstrated the significance, in terms of relative risk, of both fibre type and industrial process, and further illustrated that this is even apparent from the INSERM report itself, by examination of the SMR data (drawn from the HEI-AR report) presented in its Table C. Furthermore, INSERM's "targeting" of chrysotile was questioned, given the fact that "the exposure-effect gradient used for lung cancer was based on 10 cohorts largely exposed to amphiboles (maybe 20-40% on average), much more than the general populations of industrialized countries ... (<2%)." He felt that, since this gradient was not based on chrysotile exclusively, or even mainly, the labels on the Tables were "abusive and not founded scientifically". The third Reviewer simply singled this point out as one of two important statements of the RSC report with which he agreed in particular, namely that the INSERM report underestimates the difference in risk between chrysotile and the amphiboles.

With respect to EPAR's statement that the role of exposures in mesotheliomas in females was "less well established", one Reviewer stated that it was, instead, "completely untrue". On the other hand, another Reviewer, although agreeing with EPAR, felt that mesothelioma in women represents a small fraction of the total number of such tumors, and that different approaches are therefore "not likely to affect too much the overall risk assessment".

INSERM's use of the linear (no-threshold) model was challenged by two Reviewers. One indicated that it was not the best alternative in terms of likelihood, that sublinear models were more consistent with occupational experience (based on cumulative exposure), and that threshold effects were certainly biologically plausible (i.e. considerations of overloading of defense mechanisms). Another

stressed that the use of the "cumulative index" of exposure is biologically dubious, and that intensity and duration should (instead) be considered separately. He further emphasized that "Several large-scale studies suggest the probability of a no-effect threshold for chrysotile at all but high levels of **intensity**." He further went on to stipulate that generally, "a major weakness of the INSERM report ... is a failure to give adequate and critical attention to two questions": the "level of risk by intensity of exposure to commercial chrysotile" and "the extent to which carcinogenicity of chrysotile in man is attributable to fibrous tremolite." It was unclear to him whether these points had been adequately considered either by INSERM, or by EPAR.

In terms of the predicted disease outcomes, one Reviewer thought that it should be pointed out that the mesothelioma incidence was likely overestimated by 1/3 due to non-asbestos mesotheliomas, and that the lung cancer estimates were very uncertain.

One Reviewer's comments suggested that the Panel's wording regarding the differential results obtained with the two analytical methods employed in air sampling (TEM and PCM) should be clarified, i.e. by stressing that PCM counts are usually lower than TEM counts and correspondingly (and contrary to INSERM's Summary), the risk coefficients are higher than they would be if measurements had been taken using electron microscopy.

With respect to EPAR's articulated "preference" to have seen risk estimates based on "actual current exposures in France", one Reviewer suggested that a more detailed discussion of air sampling methodology, and its reliability and limitations, should have been provided by EPAR, if it wished to criticize INSERM's basis for risk characterization.

Finally, the Reviewer comments with respect to EPAR's handling of the questions assigned by Health Canada, are summarized in the case of three of the four; HC2 seems not to have garnered specific comment.

HC1: Have all critical studies been included?

> One Reviewer felt that it was not worth presenting the very dissenting viewpoints of the expert panel on this question. However, this [i.e. were all critical studies included?] is also one point on which the Peer Reviewers were perhaps the most divided.
>
> Two Reviewers felt that INSERM had done a creditable job in this respect. "... the INSERM report has done a good literature review. ... The missing references might be biased but they are mostly diverging interpretations of well-known original data." The other Reviewer indicated that, although INSERM may have excluded papers that do not support INSERM's position, "... there are also omitted papers that strongly support the INSERM position."

The other two Reviewers were more cynical. One raised "the selection of the epidemiological papers used in the risk assessment" as a "major limitation" of the INSERM report, and suggested that EPAR should (further?) "assess the implications of the exclusions of som
e studies." The other found that, while "the list of references ... is long and remarkably complete ... there is much less evidence of careful and appropriate consideration of what is in these references and [instead, there are] rather strong indications of the kind of bias mentioned in [the EPAR report]".

HC3: Limitations of critical studies, not mentioned.

One Reviewer raised the issue of statistical power, and what might be related to publication bias i.e. the extent to which our knowledge is based on that information which has appeared in the literature: "... the 14 (now 16 or more) cohorts are an 'opportunistic sample' of exposure circumstances with respect to environmental exposures of the general population." ... "How much is the general population truly exposed to asbestos ... or [specifically] to amosite?" He suggested that the studies could be "weighted according to 'sampling fractions' of true environmental exposures."

Furthermore, he felt that the failure to sufficiently address whether current exposures are associated with increased risk was an important point, and should be highlighted in the Executive Summary.

HC4: Sufficient critical discussion of the issues?

It was indicated earlier that one Reviewer felt that EPAR was overly critical of INSERM, given EPAR's failure to discuss the limitations of air monitoring in more detail. On the other hand, another Reviewer stated that while the Panel had perhaps used wording appropriate for a scientific review, it had been "soft" on INSERM in terms of a risk assessment document. "For a risk assessment which leads to risk management decisions, it should be said that these risk estimates are misleading for decision makers. The assumed exposures **must** be two orders of magnitude above that of the French population, not 'may be greater' ... That is an understatement." He further agreed that it should be emphasized by EPAR that INSERM should have used actual building exposure levels from other jurisdictions.

In summary, to categorize the four peer reviews, one seemed more supportive of the INSERM document, one seemed to be critical of the EPAR document to the extent that it is not (in his opinion) sufficiently penetrating in its approach, whereas the other two were more in tune with the approach taken by RSC's EPAR, but (particularly in one case) highlighting in several different respects, or to a greater degree, various deficiencies of the INSERM report.

All Peer Reviewers provided comments that have contributed positively to the content and/or format of the final draft of the EPAR report.

ANNEX

Comments on INSERM Joint Expert Analysis on Effects on Health of the Main Types of Exposure to Asbestos

Comments by:

M. Brauer

K.S. Crump

J.M.G. Davis

E. Merler

These individual statements by Panelists were the starting point for the Panel's discussions. The authors have followed individual preferences in style of referencing. Only light copy-editing has been undertaken.

Comments by

M. Brauer

General comments on report

These general comments are presented following a review of the INSERM Joint Expert Analysis, "Effects on Health of the Main Types of Exposure to Asbestos," as well as evaluation of supplementary material from the peer-reviewed literature. These comments are presented in the form of a critical review, acknowledging that in these circumstances one expects the necessary elements to be present in the report and that it is therefore easier to be critical than it is to identify the positive aspects of the report. Finally, these comments are presented from the perspective that the primary issue of importance for risk management is the risk of low-level non-occupational exposure. My perspective is of an exposure assessment/indoor air quality expert where asbestos is an indoor air pollutant of concern. My bias prior to reviewing the INSERM report is that occupational asbestos exposure is clearly associated with lung cancer, asbestosis and mesothelioma.

Therefore, it is peculiar from the outset that the INSERM report focuses much attention on reviewing the case for historical occupational asbestos exposure associated with elevated lung cancer, asbestosis and mesothelioma risk. In this regard the report does an adequate job of explaining the relevant epidemiological studies and describing many of the continuing points of controversy - the attribution of lung cancer deaths in the absence of asbestosis, the amphibole hypothesis, the linear, no-threshold dose response curve. However, I believe the report does not address with sufficient clarity the case for a risk associated with indoor / environmental exposure or that of current levels of occupational exposure where exposures are likely to be different (not just lower) than in the historical cohorts evaluated in the epidemiological studies. The basic approach is to

1) review the levels of indoor, environmental and occupational exposures and provide a detailed review of the occupational epidemiology

2) argue that although there are no data supporting indoor / environmental exposure risks, that does not preclude the possibility that a risk exists,

3) argue that there are no data supporting an alternative dose-response model (other than a linear, no-threshold model)

4) extrapolate the occupational epidemiological data to several different hypothetical (occupational, indoor and environmental) exposure scenarios using a linear no-threshold model

There is relatively little merit in discussing point 1. The report provides a reasonable, although not exceptional review of the existing data. There is however relatively little critical assessment of the usefulness/applicability of the occupational data for assessment of non-occupational exposure risk.

Regarding point 2, it is difficult to argue with the report's conclusion that there are not adequate data to evaluate the risk on non-occupational exposure and that given this situation one cannot preclude the possibility that there is an increased risk. The report acknowledges that there are no data which argue for increased risk associated with non-occupational exposure. However, despite this, the report's approach to the issue of non-occupational exposure is somewhat biased. As the report indicates it will likely be extremely difficult, if not impossible to detect an extremely low risk associated with the low exposures. Yet, in the final analysis the report uses as base cases, exposure scenarios that are 1-2 orders of magnitude higher than currently experienced. There is nothing incorrect from a procedural standpoint of using exposure scenarios at the regulatory limits, yet there is no justification given for doing this. As this level of exposure, not to mention the assumptions regarding the duration and other temporal aspects of the exposure, is in no way representative of current exposures, the quantified risk estimates are really quite unreasonable, although technically correct.

One could debate endlessly whether a linear no-threshold model should be applied for the extrapolation. The report does little to justify the approach, other than to state that there are no alternative models that have more merit and that the linear no-threshold approach is still the standard procedure for regulatory risk assessment. This is more or less true, however, the report does fail to discuss several studies indicating the possibility of a threshold or even the argument that although there may be a mechanistic threshold it will be difficult or impossible to detect in population surveys where individual exposure assessment is not conducted. This is due to the fact that in population studies differences in individual susceptibilities may mask the presence of a threshold when in fact there is a threshold in the true biological dose-response relationship. It might have been more reasonable to at least evaluate the effect of an alternative dose-response relationship on the risk estimates.

Further, regarding the risk estimates one could argue which (occupationally-derived) dose-response slope best applies to indoor / environmental exposures. However the report has not done this and has instead deferred to previous risk assessments and simply stated that it is reasonable to use the same slopes used previously. Again, there is nothing wrong with this; however, by failing to even address the issue, this report has essentially not added anything new to our understanding of asbestos risk.

With respect to the questions posed by Health Canada, my impressions are summarized in the table below, using the matrix suggested by the panel Chair.

	Critical studies included	Presentation of studies in detail	Limitations not addressed	Critical discussion
Assessment of Exposure	X	-	X	-
Experimental Record	? unable to assess	X	X	?
Epidemiological Material	+	X -	X	-

X = adequate - = inadequate + = more than adequate

1. Have all critical studies been included / is the evidence complete?

Generally yes - with several minor exceptions, although there is more attention given to certain studies and less to others. Several examples are discussed below in the discussion of specific issues. However, even though most of the critical studies have been included, the report fails to address their relevance to the issue which should be receiving most of the current attention: Are current exposures associated with increased risk? The report argues that one will never know with certainty at these low levels. Accordingly it seems inappropriate to assess the risk of these exposures without any certainty regarding the occurrence and frequency of exposures at the base levels chosen (at 0.025 f/ml- e.g. exposure information indicates that in-building exposures are < .002 f/ml, and probably much lower in most cases). Evidence also indicates that these levels are decreasing.

2. Are the critical studies presented in sufficient detail to justify conclusions regarding risk characterization / is the evidence detailed enough?

Some studies are given more emphasis than others and in general there was not enough critical evaluation of how the historical occupational cohort studies can / cannot be adapted to the assessment of present-day indoor / environmental and occupational exposures. The procedures (risk assessment) used are reasonably sound, yet the exercise itself is not well-justified as very little exposure data of relevance is presented. Overall most of the emphasis is placed on occupational exposures that may be of little relevance to current exposures. The evidence is clear that occupational exposure is associated with increased risk of lung cancer and with mesothelioma and the report adequately supports this. What is unclear and what is the relevant question is whether the much lower (current) exposures are associated with a significantly elevated risk - the report does little to approach this topic, except to provide a cursory (and somewhat biased) review of the lack of direct evidence, then stating that the lack of direct evidence (this is often the case in environmental epidemiology) does not indicate the absence of a causal association, and then proceeding to calculate risks associated with these low exposures.

3. Are there limitations of critical studies which have not been presented / are their weaknesses in the evidence that have not been considered?

Overall there seems to be a bias towards increased asbestos risk - i.e. **at each point where the review is required to make a decision based on controversial or limited evidence, the report takes the conservative (i.e. assuming the highest risk) approach. There is nothing incorrect with this approach, in fact it has been argued that this is the standard approach for regulatory risk assessment, yet the report fails to acknowledge that the estimated risks should therefore be considered as upper limits, rather than best estimates of the true risk.** Had the report included such a qualifying statement, many of the specific assumptions which enter into the risk assessment would have been acceptable. As the report stands, however, it leaves the impression that these assumptions are either indisputable facts or the most likely interpretations of the existing data. In general, the weaknesses of individual reports and studies are considered and it is argued that these are the best data available.

4. Is there sufficient critical discussion of issues relevant to risk characterization?

No, not *critical* discussion - the report is really not critical at all, but rather a review of what has already been done by other groups, the HEI* report, for example. In fact, by relying heavily on other assessments and taking a conservative approach to the evaluation of non-occupational exposures, the report adds little to our understanding of the magnitude of asbestos risk associated with current levels of exposure and does not endeavor to seriously assess alternatives to the standard regulatory risk assessment (i.e. a conservative approach).
Several more specific issues are discussed in more detail:

Indoor / Environmental exposure risk

As the report indicates, one argument that indoor / environmental exposures are associated with mesothelioma is that there are cases of mesothelioma without identified exposure (10-30% of cases), and it is suggested that these include urban and passive exposure, plus other routes, as well as undetermined occupational exposures. The report acknowledges that essentially all cases with known exposure are occupational or para-occupational exposure. It has also been suggested, but not discussed in the report that there may be other non-occupational risks for mesothelioma, which may act independently or interactively with indoor / environmental asbestos exposure, such as radiation, chemicals, viruses, etc. There have been no epidemiological studies to test these possibilities.

The report argues that it is difficult to establish risk from environmental (near industrial sources) exposure due to confounding from occupational and para-occupational exposure in the affected communities. Case control studies indicate weak/little evidence of association.
Incorporating the notion that the study flaws do not preclude excess risk - it is concluded that risks, if any, are probably small. The recent Quebec township study (Camus, 1996) described in the INSERM report (for women due to their reduced chance of occupational exposure) - indicates little evidence for a chrysotile association with elevated pleural cancer and no association with lung cancer, although there is a possible association between tremolite and mesothelioma.

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*Health Effects Institute

The report (p 302) indicates that mesothelioma incidence in different countries is the best epidemiological marker of asbestos exposure, yet this is not really justified and it would seem that job-exposure matrices based on measurements and information on specific job titles would provide a more reliable estimate since individual level data are utilized. Mesothelioma incidence is only a marker of sufficient exposure to cause mesothelioma. If there is a mesothelioma threshold, then this is *not* a useful marker of exposure. It indicates who has been highly exposed yet does not indicate those who may have lower exposures or those with high exposures who have not developed mesothelioma. Further, assuming that there is individual variability in asbestos burden associated with equal levels of exposure and /or assuming that there is individual variability in the potential of equivalent doses of asbestos to lead to mesothelioma it becomes clear that mesothelioma incidence itself is NOT a reliable indicator of asbestos exposure.

The report also indicates that in the studies of industrial environmental exposure, the only studies which found associations with increase risks were those where the primary exposures were to amphiboles or mixed fibers (containing amphiboles).

The report suggests that, to evaluate indoor/environmental exposure, the most appropriate method (stated as "least inappropriate") is to look at the incidence of early onset mesothelioma (i.e that which may be associated with exposure during childhood. However, the early-onset mesothelioma data are not strong enough to support indoor / environmental link. These data, which suggest that early exposure does not affect the latency period for mesothelioma, also provide no evidence of parallel male and female increase in the 1990's except for Australia (where increase is much greater in men than women - indoor / environmental exposure would suggest similar increase in women and men). A parallel male and female increase in the 1990's would suggest a role for non-occupational exposure, since this would correspond to the beginning of the period when the accepted mesothelioma latency would begin to produce cases arising from the beginning of widespread asbestos use in building materials in the 1960's and 1970's. These relatively preliminary data should not be overemphasized since the report correctly argues that although there are no reliable epidemiological data regarding effects of urban and intramural environmental exposure, this still may be an extremely important issue since the latency period following most use of asbestos in buildings has not yet been reached or is just being reached.

Extrapolation of occupational epidemiology to indoor / environmental exposures

Most of the report deals with occupational exposures, with little information on how these differ from indoor / environmental exposure (intensity, duration, fiber type, friability, etc.).

Despite the report's conclusion that no epidemiological evidence supports an association, risk estimates were still calculated for these exposure scenarios, yet they may not be meaningful - given these

estimates it becomes apparent that no studies have had sufficient power to detect elevated risk. In other words, if there is excess risk associated with indoor/environmental exposure then it would have been difficult to detect it (p 386 - power calculations)

The report does not address potential occupational co-exposures - some analyses (e.g. mineral oil) have indicated no effect of co-exposure. This may have implications for lung cancer estimates - there may be additional independent or co-acting carcinogens in workplaces.

Threshold

The most recent analysis of the Quebec miners and millers cohort provides some evidence that a threshold may in fact exist for lung cancer. (JC Mcdonald, et al., Br J Ind Med 1993; 50:1073-1081 - The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-1988). The study found evidence for a threshold at 15-45 f/ml for 20 years exposure for lung cancer. Exposure assessment indicated no excess risk for exposures <15 mpcf* (approx = 52.5 f/ml). [Conversion used was 3.5 f/ml per mpcf].

The report correctly indicates that data do not support alternative dose-response models for lung cancer or mesothelioma. However the data also do not support a no threshold model to the low exposures that are currently experienced. The conservative approach chosen was to use a linear no-threshold model; however, it is important to remember that this was in fact a choice that is neither upheld nor contradicted by the epidemiological data. For example, Ilgren and Browne concluded that a review of the human and experimental literature does strongly suggest a mesothelioma threshold. This review was not in fact addressed in the INSERM report (Ilgren EB, Browne K. Reg Tox Pharmacol 1992; 13-116-132). Evidence from animal studies also supports a threshold for asbestosis and more importantly, for asbestos-associated lung cancer. It is not clear however, whether the animal model for asbestos associated lung cancer adequately represent human impacts, and in this instance with the ample available epidemiological data, it is reasonable to focus on the epidemiological data (often guided by animal studies) to evaluate risk.

Quebec township environmental studies indicate that residents who have not worked in the industries have elevated fiber burdens relative to other urban populations, yet there has been no demonstration of increased lung cancer risk. Also studies of Newhouse (friction materials), Gardner (cement), Neuberger (cement), with exposure at the 1-5 f/ml level have not found increased lung cancer risk. It has in fact, been argued that the putative threshold level is that at which asbestosis is produced.

When the Quebec environmental study (Camus, 1996) is included, as are occupational studies of maintenance workers (radiological changes seen in absence of lung cancers) it appears as though there may in fact be a threshold - - however, the report correctly indicates that it is nearly impossible to detect if risks are low.

Para-occupational exposure

Report suggests that increased risk of mesothelioma among people exposed by para-occupational or domestic routes is well established, yet this is not substantiated in the report. Only a few studies are

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*million particles per cubic foot.

mentioned; they are not critically assessed and are not presented in any level of detail allowing critical assessment. There are few or no data for lung cancer and risk of para-occupational exposure. Further, absolutely no information is presented regarding exposure levels associated with para-occupational exposure (report indicates that no data are available for DIY activities but suggests that there may be data available for other para-occupational exposure, from a spouse for example, yet these data are not presented - p. 135)

Given that para-occupational exposures appear to account for the second highest proportion of mesothelioma cases (after occupational exposure), and that para-occupational exposure will be in general lower than the corresponding occupational exposure, there is insufficient data presented regarding exactly what is the para-occupational exposure level relative to occupational (how solid are the exposure data?). One might have expected that these intermediate exposure levels could be used to help answer questions regarding intramural indoor or environmental exposure, and even that studies of para-occupational exposure could be used as a more realistic starting point for the extrapolation to lower exposures than the high level occupational exposures.

Fiber type/composition

Uncertainty of estimates (Nicholson - excess lung cancer by occupation) - may result from differences in fiber size distributions among different occupational uses of asbestos - Nicholson argues that this is more important than the amphibole hypothesis...(Dement Am J Indust Med, 1983; 4:399-419) shows that there is a much higher proportion of long fibers in textile manufacturing than in friction product or cement production. The issue of fiber length is really not addressed in the report, even though it has been suggested to be as or more important than fiber type.

International comparisons indicate the importance of amphiboles (Australia and S. Africa have had greater increases; France has lower incidence and asbestos used contains fewer amphiboles) - yet, report strongly disputes amphibole hypothesis. Although there are much data which argue against the amphibole hypothesis, it seems that one could argue that lack of exposure data on tremolite contamination of primarily chrysotile exposure combined with strong data supporting higher risk for amphiboles than chrysotile, does not refute the possibility of the amphibole hypothesis. However, from a risk management perspective this may not be important, since much of the chrysotile is contaminated with tremolite. All the geological studies reported are for tremolite, often in combination with chrysotile.

Asbestosis - asbestos attributable lung cancer

Attributable lung cancer numbers depend on the assumption that asbestosis is not necessary. For example, in the New Orleans cement-worker cohort the argument is made that asbestosis is dose related and if asbestosis is a necessary precursor to asbestos-related lung cancer, then the asbestosis dose-response relationship can be used to assess lung cancer relationship. Little asbestosis is evident for exposures below 30-40 f/ml-yrs -- evidence for threshold. Indirect analyses (ex. Barroetavena, et al., Am J Indust Med 1996; 29:183-185 “Unrecognized asbestos-induced disease”) indicate that asbestosis is not necessary for asbestos-attributable lung cancer - i.e. argument is that estimates of lung cancers attributable to asbestos are two times mesothelioma risk and this number of lung cancers greatly exceeds the number of asbestosis cases in same population.

The issue is still controversial, yet the report takes one side without really acknowledging that this is still an open issue and without discussing the magnitude of the impact of this "decision" on the risk estimate. In general, consensus, primarily based on the mechanistic arguments and NOT on the epidemiological data, indicates that there is no reason to suggest that asbestosis must be present to attribute a lung cancer to asbestos. The issue therefore is one of what assumptions are made and how conservative one wishes to be in attributing risks to asbestos exposure. On the one hand a lower limit for asbestos-attributable lung cancers are those where there is also evidence of asbestosis. The approach taken in the INSERM report is that established from occupational cohort studies where there was a significant association between lung cancer and exposure intensity and duration. Given current levels of understanding this approach seems warranted and not overly conservative in its estimate of attributable lung cancer risk.

Other

When looking within the occupational strata - it is clear that there are high relative risks for some occupations and undetectable risks for others (p. 302) which seems to implicate specific occupational (high) exposures. One could reasonably argue that even lower exposures would have no detectable risk (even though there may be a small but undetectable risk). In fact, this is what I believe the report should have addressed: applied a reasonable slope (one corresponding to the type and industrial use of fiber likely to occur in non-occupational exposures) to the current levels of exposure. If one did this, the risk estimates would be approximately 200 times lower (100 from realistic exposures, 2 from a more applicable slope), or for in-school exposures, 1.5 per million. This estimate is in agreement with those of Whysner et al (0.55/million), Hughes and Weill (2.3 - 7) using two different approaches. Even these estimates are likely to be overestimates because they are based on arithmetic average exposures, when in fact geometric mean exposures are more representative of the log-normal distribution of exposure data, and that conservative estimates regarding exposure duration and temporal pattern (constant exposure) are used. In practice the EPA considers the true risks to lie somewhere between the calculated risk estimates and zero.

The report doesn't attribute cases to low level exposure because of uncertain exposure information; instead it simply estimates number of cases per 10,000 people (i.e. it cannot determine absolute magnitude of low-level exposure-related disease since it can't determine magnitude of low-level exposure).

There are not enough actual data on exposures calculated for epidemiological studies to address this aspect of the studies.

In summary, the report is generally sound scientifically with respect to procedures, yet the critical evaluation of available data and more importantly their use in risk assessment, at best provide no new information to supplement previous reports, and at worst provide unjustified overestimates of the risk of current asbestos exposure.

Specific critique of section 1: Measurement of asbestos concentrations and exposures (1.0-1.7).

Exposure to asbestos is well documented, especially for occupational exposures. Little information on specific fiber types and on individual exposures is presented. Sufficient data is included for environmental and indoor levels. For indoor levels, mostly French data and some comparisons to other

data are presented- little data presented on current indoor levels and even on current maximum indoor levels (i.e. during abatement - which may provide an upper limit for current exposure).

More importantly, the report also lacks any serious discussion of the exposure potential associated with different asbestos sources. What is the potential for exposure in buildings with asbestos insulation relative to those with asbestos cement, etc? What are the expected lifetimes of different asbestos containing materials prior to generation of airborne asbestos fibers? Does the release of fibers occur throughout the lifetime of a material or only when it degrades? What are the factors influencing fiber release? What are the morphometric characteristics of fibers that are released from building materials? Are there specific practices which would be associated with the release of fibers with different morphometric characteristics? It seems that there would be data available to answer at least some of these questions.

Exposure information is not presented in a great deal of detail, but is adequate for a general understanding of the issues. What is lacking is a more critical discussion of the implication of exposure misclassification and the uncertainties in exposure measurements on the epidemiology - in fact, this issue is not really considered in the overall risk assessment since exposure scenarios are chosen. The relevant issue for the risk assessment is how accurate is the exposure assessment upon which the risk coefficients are based - in this regard, there is not enough data presented in the INSERM report to evaluate this - except to say that for mesothelioma these are based on only 3 cohort studies, providing 3 risk coefficients - one for “chrysotile,” one for mixed fibers and one for amosite. The rationale for only using three studies is sound (based on number of cases), except the reasons for excluding the study of Finkelstein are not adequately supported - the risk coefficient is very high and there are suggestions of problems in exposure assessment. However, other investigators have also excluded this study due to “errors in exposure assessment.”

Accordingly, for each fiber type, the corresponding risk coefficient is based upon a single study. It should also be noted that these coefficients were determined only for occupational exposure conditions. Since the report argues that the industrial processing is more important than geological origin, it seems curious that different slopes were used for different fibers, while it is assumed in the quantitative risk assessment that exposure conditions (i.e. industrial processing, similar pattern of exposure, etc.) are identical to occupational exposures for the environmental and passive indoor exposures - this is unlikely to be the case.

For lung cancer, the risk estimate which is used is simply the same that has been used by other studies (ex. HEI) - in fact, no particular rationale is given for the choice of this slope. In my opinion, given the thought that the industrial processing of the fiber is a significant parameter and that the overwhelming majority of asbestos is in cement products it would have been reasonable to also consider the slope determined for the cohort study of asbestos cement workers - i.e. 0.5%, or alternatively a slope corresponding to mining/milling of short chrysotile fibers (0.1 -0.2) , the types commonly used in buildings (in the U.S. at least). However, extremely little critical discussion is given to the validity of these slopes and the decision to use 1.0% seems entirely based on the fact that this slope was also chosen in the HEI analysis. Hughes and colleagues (Ann Occ Hyg 1994; 38(4):555-560, “Human evidence; Lung cancer mortality risk from chrysotile exposure”) argue that slope of 0.06% is more appropriate for risk assessment since four studies of chrysotile exposed workers show slopes below 0.06% (the only chrysotile slope above

this is are for textile workers and it is argued that these fibers are longer than those used in buildings and are also from the Quebec mills). Further it is argues that most fibers used in buildings are short - and therefore more similar to mining and milling fibers than they are to textile manufacturing.

In both cases of mesothelioma and lung cancer risk there is essentially no critical evaluation of the exposure assessment in the epidemiological studies. There are several comments that studies were excluded because they lacked qualitative exposure data or had too few cases (on this issue the report does not make the distinction between studies with small sample sizes and therefore inadequate statistical power, or studies which simply had too few cases), yet there is no further evaluation of these studies and their exclusion appears to be primarily based upon other assessments. Further for the few studies that were used to generate risk coefficients, they appear to have been used simply because they included some quantitative exposure measures, yet there is no critical evaluation of the quality of the exposure assessment nor is there even a disclaimer that these coefficients could included substantial error due to inaccurate exposure assessment.

The role of fine fibers and the accuracy of their measurement relative to larger fibers was not assessed. As this could significantly affect the risk estimates - it seems critical to make some assumptions, at least, about the fiber morphometry and on quantitative measurements of fiber composition, when performing the risk assessments. Most of the information on fiber type is qualitative - i.e."predominantly chrysotile," etc. There is no discussion of the physical state of fibers released from building materials vs those fibers that are present in occupational settings - differences in the fiber size distribution may affect not only the magnitudes of health impacts for a given fiber concentration (f/ml or f/L), but also the conversion factors. Use of conversions determined for occupational settings are not appropriate to apply to non-occupational settings since fiber size distributions will likely be different. An alternative approach is to base conversions on disease potential as suggested by Chesson and colleagues (Risk Analysis, 1990; 10(3):437-447).

The importance of conversion factors is acknowledged in the risk assessment, yet there is very little discussion of what INSERM views as the appropriate conversion factors for the risk scenarios and if these conversion factors have been validated (p.100). Of course the issue is not directly addressed since exposure scenarios are prescribed, yet the report does indicate that the expected deaths calculated for the base cases (exposure scenarios) could be adjusted and applied to other, real, populations. However, there is no discussion of exactly which of the "appropriate" conversion factors should be used. This omission seems to limit the applicability of the INSERM risk estimates.

Six base cases are described to characterize exposure yet this information is not used on the risk assessment. The base cases which are used are neither typical, realistic, nor representative of current exposures. There is nothing incorrect about these base case assumptions, yet they are not very helpful in understanding the risks of current exposures.

While the report acknowledges that there are no available data (for France) to determine the distribution of the French population within each of the exposure categories, this really seems to be an essential component of applied risk assessment. For example, if the risk is extremely low, yet a large proportion of the population is potentially exposed then the risk is important. If the risk is large and nobody

is exposed then the assessment is academic. While I do not know the state of French census data, U.S. and Canadian census, regulatory and even more detailed time-activity data are available which could help estimate the proportion of affected buildings and accordingly the number of individuals potentially exposed in each category.

The report states that there are significant differences in measurements depending on time and surroundings. Unfortunately these differences are not discussed in further detail, and there is in general a weak review of asbestos measurement - for example, the report does not discuss in much detail factors associated with the variability of exposure measurement (inter and intra-individual variability for personal measurements of occupational exposure) or even analytical variability, despite the fact that there are extensive data available for this purpose (i.e asbestos analytical proficiency programs - NIOSH PAT, AFRICA, etc.).

Further Notes

There are several estimates of exposure within buildings outside France. In the US, a survey in 43 federal buildings gave the range 0 to 0.2 f/ml, with a mean of 0.006. The Ontario Royal Commission report of 1984 gave as a best estimate of in-building exposure 0.001 f/ml, whereas the Health Effects Institute suggested 0.0002 f/ml. Kenny Crump suggested classroom levels of 0.0002 f/ml, and HEI 0.0005 in the same situation. Exposures (from HEI and Price) for maintenance and repair workers gave a range of 0.002 to 0.02 f/ml-year, and for other building occupants 0.00003 to 0.0005 f/ml,

The specific concern in the indoor context should be asbestos exposure associated with asbestos cement, which absorbs 85 per cent of asbestos production. What is the form and fiber distribution?

Comments by

K.S. Crump

Overall comments

I find the document reasonably complete in terms of the issues reviewed. However, in some sections much of the information presented is taken from other reviews and is not therefore an independent review of the original studies. This is unfortunate for several reasons, one of which is that some important new information not available for earlier reviews was not incorporated. In addition, there were several key points that were unsupported by the data presented, including: a common conversion between mass concentration and fiber count could be applied in all environments; indirect TEM provided counts comparable to direct TEM for fibers longer than five microns; potency factors are probably much lower than if they had been calculated based on TEM measurements; a single lung cancer potency factor is applicable to all exposure settings independent of fiber type; the mesothelioma cancer potency for chrysotile can be estimated in an unbiased manner without accounting for studies that showed low risks.

General comments on procedures for risk estimation

No independent review of the individual studies was conducted. Instead, this document summarizes potency factors for individual studies developed by Nicholson (1968) and the factors selected by various agencies to assess risk. Thus, the document relies heavily upon secondary information. It would have been helpful to have had an independent development of potency factors from various studies, particularly additional studies now available for calculating potency factors. No analysis or potency factor is presented from the new Dement and Brown (1994) followup, the latest followup of the Quebec miner cohort (McDonald *et al.*, 1993), or from the Armstrong *et al.* (1988) or de Klerk *et al.* (1989) studies of Australian crocidolite miners. The Dement and Brown (1994) study involves an additional 15 years of followup and over twice as many lung cancers as the original study, and is therefore much more definitive than the earlier study. Not developing potency factors from the Australian crocidolite miner cohort is a serious omission, since this appears to be the only cohort suitable for developing a potency factor for pure crocidolite exposures.

The potency factor for lung cancer selected by INSERM ($K_L = 0.01$) is the same as the one adopted in most other reviews. This value is roughly the middle of the range of K_L values obtained from various studies. However, since the range spanned by the individual K_L values is very large, the scientific validity of selecting a single value for all settings is questionable. It would appear more appropriate to make the choices site-specific based on the type of operation of characteristic of fiber. It is clear that no single value of K_L is appropriate for all settings, or even settings involving chrysotile exposures alone.

It appears that if INSERM had calculated a lung cancer potency factor from the Australian miner cohort, it would have weakened the argument that lung cancer potency is fiber-type independent. It appears that such a lung cancer potency would be much larger that the lung cancer potency estimated for chrysotile miners. Although tremolite is not used commercially, calculation of a lung cancer potency factor tremolite (McDonald *et al.*, 1986) could also have helped in evaluation of the hypothesis regarding a fiber-type distinction for lung cancer.

In calculating a potency factor for mesothelioma, INSERM omitted the studies of Nicholson *et al.* (1979), McDonald *et al.* (1980), Hughes *et al.* (1987) and Dement et al. (1983), citing that it is unreasonable to apply a quantitative model to studies with so few cases. However, there is no technical problem with applying the mesothelioma model to such data because the model contains only one free parameter, which can be estimated from even a single case if necessary. The number of mesotheliomas going into a calculation will be reflected in the size of the confidence intervals. Moreover, to avoid bias, studies with few cases must be included in the calculations. Each of these studies was large enough to show a clear dose response trend for lung cancer, so it is not their size that is at issue but that they observed very few mesotheliomas. These studies also involved pure chrysotile exposures (except for Hughes *et al.*, but it is possible to estimate a mesothelioma potency factor from a subcohort that was exposed only to chrysotile). If these additional studies had been used, it would be seen that, even after taking the small numbers of mesotheliomas into account through use of confidence intervals, the potency factors estimated from these studies are considerably smaller than those relied upon by INSERM. Thus the approach used by INSERM was biased towards using studies that found large numbers of mesotheliomas, and toward studies involving amphibole exposures. As a result the fiber type difference was minimized in the INSERM analysis and the mesothelioma risk from chrysotile exposure was likely overestimated. INSERM also neglected to calculate a mesothelioma potency factor for the Australian crocidolite miner population.

In summary the models and data used by INSERM to calculate risk are the same as those that have been used in numerous other studies. INSERM reviewed potency calculations made by other investigators and did not make any potency calculations of their own, nor did they develop potency estimates from a number of newer reports. INSERM applied the same summary potency factors as have been used by other reviewers ($K_L = 0.01$ and $K_M = 10^{-8}$). The unique thing about INSERM's analysis is that they customized the risk estimates to apply to a French cohort, by using French background rates of lung cancer mortality and total mortality. I checked these calculations and found them to be correct.

INSERM applied a common potency factor for lung cancer to all fiber types, despite the fact that there is more than a 100-fold difference in potencies determined from different studies. They applied a potency for mesothelioma said to apply to "essentially chrysotile exposures" although, as noted above, they ignored several studies of pure chrysotile exposure, which indicate about a five-fold lower risk. They did not estimate risks from exposure to crocidolite or amosite.

There is questionable justification for applying single potency factors for lung cancer and mesothelioma uniformly to all exposure situations. INSERM noted (I think correctly) that the risk of lung cancer (from chrysotile exposure) appears to increase as the fibers become more highly processed and likely involve a higher proportion of very long thin fibers. E.g., the highest risk is from textiles which uses

a very high grade fiber. The lowest risk is in mines, which have the lowest grade of fibers. A better approach would be to attempt to understand the fiber characteristics in various exposure situations (e.g., building exposures) and attempt to match them to the epidemiological studies. For example, it would be appropriate to estimated risks of workers in Quebec mines using data from those mines.

There was little attempt by INSERM to understand the reasons for the large differences in potencies obtained in various studies. One hypothesis, which has support from analysis of animal studies (Berman *et al.*, 1994), is that potency of a fiber is a function of its dimension and potency of a dust is not determined solely by the concentration of fibers longer than five microns. The majority of contributions to risk may be from a different size fraction (e.g., fibers longer than 20 microns), so risk appears to vary with fibers longer than 5 microns only because the concentration of fibers long than 5 microns is loosely correlated with fibers longer than 20 microns.

One very important issue that is not addressed in the risk estimates is what types of exposure data they should be based upon. Risk is estimated from exposures to various levels reported in f/ml, but different analytic methods can yield vastly different values for f/ml. For the purpose of estimating risk the measurement method must be selected to mesh as closely as possible with the method that the potency factors are based upon, which is f/ml longer than 5 microns measured by PCM in a environment involving very high asbestos exposures. This method is not suitable for use in environments, such as buildings, where exposures are much lower, since often the majority of fibers detected by PCM in such environments are not asbestos. The method that would seem to be most appropriate would be direct TEM in which only asbestos structures that would be identified by PCM are counted. A conservative approach would be to also include asbestos fibers in the count that would be too thin to be seen by PCM. Although indirect TEM has certain operational advantages over direct TEM, it involves significant disturbance of structures and produces higher counts than direct TEM. The conclusion of INSERM that indirect and direct TEM give comparable values for fibers longer than five microns is not supported by the references they cite. (This issue is critically affected by the counting rules applied, an issue that is not addressed by INSERM.) If indirect TEM is applied to assess risk, the results should be adjusted to account for the additional counts produced by the indirect procedure.

<u>Detailed comments</u>

(Page numbers refer to the English translation that the Review Panel worked from.)

page 6

"diameter of amphibole fibers roughly 10 times that of chrysotile fibers." The meaning and context is not clear. Does this refer to minimum diameter?

page 12

It is highly questionable whether a general equivalence between f/l and ng/m^3 is generally accepted. To see the difficulty in using a general equivalence, note that on page 6 the document indicates that amphibole fibers are 10 times thicker than chrysotile. This suggests that the relative potency of amphibole to chrysotile should be 100 times greater when measurements are in f/L than when measurements are in mg/m^3. It also says on page 6 that there are "major variations from one variety to another and, within the same variety, from one deposit to another". This strongly suggests that no single conversion exists that would be reasonably accurate in different settings, even for a single asbestos type.

page 12

The claim that "exposures measured in F/l, is equivalent, in terms of cancer risks, to exposures greater than 1000 times this value in f/ml" is a gross oversimplification, and the evaluation presented is incomplete. First, I did not see evidence presented in the report regarding the presence of non-asbestos fibers in occupational settings. Although these are surely present to some extent, it is not clear that they would be present in significant quantities. In addition there are a number of factors that would suggest that it could well go the other way. 1) Even if the TEM counts refer only to structures longer than five microns, in many environments many asbestos structures seen by TEM are too thin to be identified by PCM. 2) In some environments (e.g., building settings) the majority of structures counted by TEM are complex structures (clusters and matrices) that would not be counted by PCM because they do not satisfy the dimensional requirements. 3) Indirect preparation of filters for TEM analysis, which is the method prescribed in France, causes a complex structures to breakup into multiple structures which inflates the count.

page 16, Figure 1

The way the data are presented in this Figure (lines indicating ranges with no measures of central tendency) is not very informative. The reader needs to know whether the upper limits are maximum level, 90th percentiles or what. Measures of central tendency are also needed. It appears (based on Figure 2 page 12 in the report) that a large body of data on building exposures were ignored by INSERM. (See comment below re. page 123.)

page 19

The summary exposure values given on this page were originally measured in ng/m^3 and then converted to f/l. It would be more appropriate to continue report the results in ng/m^3, since, as noted above, no universal conversion is likely to be appropriate.

page 27

It should be pointed out that the animal studies generally suffer from inadequate characterization of exposure. In addition, exposures characterized by mass are inadequate for making comparisons regarding relative potency of various fibers, since different formulations of asbestos can have extremely different fiber concentrations on a per mass basis.

page 28

The notion that a threshold would exist because the latency would exceed the lifespan is totally fallacious. Although the fact that a threshold exists for an individual when his latency exceeds his lifespan is a tautology, a population threshold will not occur just because the average threshold exceeds the lifespan. It is easy to construct models consistent with observed dependence of latency upon dose in which the average latency is over 1000 years, yet risk of regulatory concern remains. Looked at another way, the average latency for total human cancer already exceeds the human lifespan since fewer than 50% of humans die of cancer. Nevertheless, cancer remains a serious concern.

page 31

Since asbestos fibers are ubiquitous, everyone is "exposed". "Exposure" needs to be given a precise meaning in this section.

pages 88-103

This section does not contain any discussion of counting rules. This is a serious omission. In many exposure settings the majority of structures seen are complex structures rather than simple fibers. Many of these structures would not be counted by PCM. How these are handled in the counting rules (whether not counted, counted as a single fiber, or whether components are counted) can have a large impact upon the estimated concentrations.

page 94

The emphasis upon TEM for measuring ambient levels is well said and quite important.

page 95

The conversion value given by Doll and Peto for converting from particles to fibers must be put in proper context. They were considering impinger data, I believe. Further, there is no reason to accept this value as a universal constant. As noted earlier, the value varies between operations and even within operations. One should choose the best value for the data under consideration rather than selecting a single value as a universal constant.

page 97

Comparing PCM with TEM, without providing additional information on the TEM method (whether direct or indirect, on the category of structures being included in the TEM counts)

is not helpful. It is not possible to interpret this information without further details. Likewise the description of comparisons of TEM and SEM are not interpretable without additional information (e.g., were direct or indirect methods used; what sizes of structures are being considered; since comparisons of TEM and SEM are certainly size dependent; were the differences explainable by the known differences in resolution of TEM and SEM or were other unidentified factors present?).

page 98, last paragraph on relation of indirect TEM to direct TEM

This is a very important issue, given that France has adopted an indirect TEM method. The conclusions of this paragraph do not appear to be supported by the references cited (Chatfield 1983, 1985; Sebastien *et al.*, 1984, Chesson *et al.*, 1990, Kauffer *et al.*, 1996).

The Sebastien *et al.* study was of outdoor samples, not indoor. It did not conclude that there was no difference between the two methods when ultrasound was less than 10 minutes and only fibers longer than 5 microns were considered. No filter was analyzed both by direct and by indirect with ultrasound less than ten minutes. The only comparisons based on the same samples were between direct and indirect with two hours of ultrasound. Combining results from four filters, the indirect method found 163 f/L longer than 5 microns, whereas the direct method found only 7 f/L longer than 5 microns (Sebastien *et al.*, Table VII). This large difference apparently cannot be accounted for by the difference in time of ultrasound. The size distribution of structures longer than 5 microns found by direct and indirect was also substantially different. Thus, the Sebastien *et al.* paper appears to indicate far higher asbestos concentrations when measured by indirect than by direct, even when considering fibers longer than five microns.

Chesson *et al.* (1990) do not refer to indirect analyses. However, a different Chesson *et al.* (1990b) [EPA 560/5-89-004] does compare samples prepared by direct and indirect, so perhaps the reference is incorrect. Chesson *et al.* (1990b) report finding only one asbestos structure longer than 5 microns by the direct method in all the samples they analyzed. They concluded as follows: "TEM analyses of air samples using indirect transfer methods tends to provide estimates of airborne asbestos concentration that are higher than those we obtained using direct transfer methods. This conclusion is consistent with the general opinion and implies that airborne asbestos levels estimated by one method are not directly comparable to those estimated by the other. ... There is no single factor that can be applied to convert measurements made using an indirect transfer method with measurements made using a direct transfer method." Chesson *et al.* also review other studies of indirect and direct TEM in reaching these conclusions. Chesson *et al.* neither indicate that direct and indirect TEM provide comparable results for fibers longer than 5 micron, nor provide any evidence in support of such a conclusion.

The only reference to indirect preparation in Chatfield (1983) appears to be a brief description of the method, ending with the statement, "The validity of this preparation technique is, of course, contingent on a successful demonstration that the ultrasound treatment used does not significantly change the fibre dimensions or concentrations reported." I haven't seen Chatfield (1985).

Although I haven't been able to obtain the Kauffer *et al.* study, the conclusion cited from it contradicts the idea that indirect and direct give the same results for fibres longer than five microns.

In summary, I have found no support in the cited papers for the notion that direct and indirect give comparable results, even for fibers longer than 5 microns.

I find the high correlation reported between mass and f/ml very surprising and strongly doubt that this would be true in general, since a single thick fiber can outweigh hundreds of thin fibers. I have not been able to obtain a copy of the Bignon *et al*. (1990) reference, but in light of the other data I have seen on this issue, it is highly questionable as to whether this correlation would hold up in other situations. This correlation equation predicts that 1800 ng/m^3 is equivalent to 1f/ml. On page 320 INSERM reports that three review groups recommended that 40,000, 30,000 and 25,000 ng/m^3, respectively, be considered equivalent to 1 f/ml. The great disparity in these values confirms that no single conversion factor is appropriate for all situations.

page 105

The discussion of determining whether a person has been exposed is rather meaningless without further definition of what is meant by "exposed." In its most literal meaning, most persons are "exposed" to asbestos everyday, since asbestos is ubiquitous in ambient air.

page 124, Figure 2

This figure is taken from the HEI* report. The HEI report presented two sets of data, one termed "non-litigation" and the other termed "litigation". INSERM reported only the data labeled "non-litigation". The "litigation" data were not referred to by INSERM, although the these data were just as extensive, and appeared to employ just as good QA, as the "non-litigation" data. INSERM erred by not discussing these data.

page 282, last paragraph

Presumably the "base rate" refers to mesotheliomas not caused by asbestos exposure. It is not clear how this base rate can be considered to be firmly established if, as noted two pages later, the percentage of cases with no known asbestos exposure ranges from 3% to 94%. Moreover, if this rate is firmly known, then the subsequent work to estimate the number of mesotheliomas caused by asbestos is not needed, since one only needs to subtract from the total the number predicted by this base rate.

page 289, bottom of page

I find the argument presented based on Table 4 difficult to swallow. It appears that there are five countries where the data tend to support the hypothesis and three countries, including the U.S., where the data do not. The observation that "Overall, the differences between men and women are less significant in the same country than between countries" is not obvious. Even if this argument is accepted, it does not imply the major conclusion of this section (in bold) that "the very great majority of cases of mesothelioma in women ... can be attributed to occupational exposure". Even if the vast majority of mesotheliomas in women were caused by asbestos, I don't see why one would expect to see a common yearly percentage increase in men and women. What evidence is there that the observed increases in women are not adding to a base of non-asbestos-related tumors?

pages 293 - 296

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*Health Effects Institue

Using data on the incidence of mesothelioma before age 45 to assess the effect of building exposures is fraught with uncertainty. Since there are so few cases, efforts should be made to review the exposure history of cases. Some occupationally-related cases probably occur in persons below the age of 45. Another source of information that should be applied is predictions of the numbers of such cases expected based on mesothelioma risk models and estimates of building exposures.

page 301, estimate of the number of cancer deaths attributable to asbestos exposure in France

This estimate is inadequately documented. The estimate of the number of lung cancers is calculated from an estimate of the percentage of lung tumors attributable to asbestos in England. INSERM did not critically examine the basis for this estimate. No systematic attempt is made to compare the English and French situations, to determine whether the estimate is appropriate for France. The estimate of the number of mesotheliomas caused by asbestos exposure is an estimate of the total number of mesotheliomas that would occur in France, with the implicit assumption that all mesotheliomas are caused by asbestos. There is absolutely no justification for the comment (in bold) that the estimate is certainly a lower limit. First, INSERM cannot claim to have made a conservative estimate of the number of lung tumors without critically evaluating the methodology underlying the estimate developed for the British population. Second, although they claim here that the mesothelioma incidence is likely under-evaluated, they claim on page 298, next to last paragraph, that the estimates of the number of mesothelioma deaths were adjusted for under- or over-estimation. Thirdly, the the assumption that all mesotheliomas are caused by asbestos is highly likely to be anti-conservative.

page 314, next to last paragraph

Infrequency of mesothelioma should make it easier to link with asbestos, not more difficult.

page 319

Conversion factors between MMPCF and f/ml are probably crude at best, and likely differ among industries and applications.

page 320, top of page

This section should specify what type of electron microscopy is being referred to. There is considerable difference in the resolving power of TEM and SEM. Presumably this comparison refers to f>5μ as measured by indirect TEM. If so, the conclusion is not warranted for a number of reasons: 1) There is no evidence presented in the report (so far as I could tell) indicating that significant numbers of non-asbestos fibers were present in these occupational setting involving very high asbestos exposures. 2) Even if the TEM counts refer only to structures longer than five microns, in many environments a substantial fraction of the asbestos structures seen by TEM are too thin to be identified by PCM. 2) In some environments the majority of structures counted by TEM are complex structures (clusters and matrices) that would not be counted by PCM because they do not satisfy the dimensional requirements. 3) Indirect preparation of filters for TEM analysis, which is the method prescribed in France, causes a complex structures to breakup into multiple structures which inflates the count. Therefore, contrary to the conclusion reached by

INSERM, exposures measured by TEM would very possibly have been higher that would be obtained by PCM.

page 320, second paragraph

This paragraph seems to imply that f/ml PCM measurements are comparable across environments. This assumption is unwarranted, and is particularly inappropriate for making risk estimates in buildings with ACM since the vast majority of structures counted by PCM typically are not asbestos.

page 320, third paragraph

As noted earlier conversions between f/ml and ng/m^3 appear to be highly variable across environments. Further concentrations measured in ng/m^3 are extremely sensitive to the presence of large asbestos fibers, since a single large asbestos structure can overwhelm the presence of thousands of thin fibers in a measurement reported in ng/m^3. This correlation equation presented by INSERM on page 100 predicts that 1800 ng/m^3 is equivalent to 1f/ml. On page 320 INSERM reports three review groups recommended that 40,000, 30,000 and 25,000 ng/m^3, respectively, be considered equivalent to 1 f/ml. The great disparity in these values confirms that no single conversion factor is appropriate for all situations.

page 322

It is not clear why this review by Esmen is reported here since exposures in various environments were reviewed earlier in the report. Some of the data presented are very difficult to interpret. For example, a single number is presented for chrysotile in schools, with no indication of the circumstances of the measurements, measuring technique, whether this is an average value and if so, what type of average, and no indication of the number of samples upon which is was based.

page 326 - 327

No mention is made of the relative risks of mesothelioma posed by different fiber types -- a serious omission.

page 329 last paragraph

The basis of comparison is not provided. Are relative risks being compared, or are they comparing potency factors that are normalized for exposure? I assume it is the latter. This conclusion appears valid within a fiber type, i.e. chrysotile, but not across fiber types. The potency factor for chrysotile miners is less than that of any other group, whereas it appears that a potency factor for crocidolite miners would be higher than the potency factor for most chrysotile exposure situations.

page 330 first full paragraph

The meaning is obscure. To have a valid comparison, adjustment for exposure differences must be made, but this was not done in the referenced Table C. Also, the number of excess cases is an inappropriate basis for comparison, since this depends upon the size of the cohort, and there are very large differences in cohort size among the studies presented. Relative risk is a more appropriate basis of comparison. Also, this Table ignores studies of pure crocidolite. As a result of these inadequacies, I think it would be unreasonable to draw any conclusions from Table C.

page 331, 2nd paragraph

The claim that the dose response relationship is remarkably close to a linear relationship should not be over-interpreted. Actually, the misclassification of exposure that invariably occurs in epidemiological studies would tend to make even a threshold response appear to be linear. Further, these studies do not examine the shape of the dose-response curve in the range of environmental exposures.

page 335

The potency factor for lung cancer selected by INSERM (K_L = 0.01) is the same as the one adopted in most other reviews. This value is roughly the middle of the range of K_L value obtained from various studies. However, since range spanned by the individual K_L values is very large, the scientific validity of selecting a single value for all settings is questionable. It would appear more appropriate to make the choices site-specific based on the type of operation of characteristic of fiber. It is clear that no single value of K_L is appropriate for all settings, or even settings involving chrysotile exposures alone. Moreover, the data do appear to indicate a fiber type distinction, since the potency factor for pure amosite exposure is higher than the chrysotile potency factors. I think a fiber type distinction would become even more apparent if INSERM had developed potency factors for tremolite and crocidolite exposure.

page 340

The review of lung cancer potency factors presented in Table E is now ten years out of date. It needs to be updated incorporating newer studies that have since become available.

page 341, last paragraph

The statement that this model "satisfactorily describes the risks of death from lung cancer observed in the approximately fifteen cohorts ..." is clearly not true. The document has previously pointed out the very wide range of risks (actually potencies) observed in these studies. It is clear that no single model can "satisfactorily describe" these risks. One principal reason for the wide range of potency values is likely to be that lung cancer risk is not a simple function of the concentration of f>5µm. That is, different dusts with different fiber size distributions can have the same concentration of f>5µm and yet pose very different risks. The uncertainties inherent in the use of a universal model for lung cancer is not adequately discussed in the document.

page 345, second paragraph

This claim, although true, is somewhat misleading in that it fails to address perhaps a more important issue -- that is, whether the probability that a lung cancer is "attributable" to asbestos is an adequate basis for determining whether an award is justified or the level of an award. For heavy smokers, for example, it may be possible to conclude that it is almost certain that the cancer would not have occurred had the person not smoked, even after taking into account his asbestos exposure. It seems reasonable to take that information into account, i.e., consideration of the risk attributable to asbestos exposure vis-à-vis risk attributable to other known risk factors (such as smoking) could

be a more reasonable basis for determining eligibility for an award or level of award than consideration of risk attributable to asbestos alone.

page 347, fourth paragraph

To the contrary, studying a subcohort does not necessarily reduce the statistical significance of associations.

page 351

It is very important to know whether Wilkinson controlled for smoking.

page 351

Last sentence should add "except insofar as it may indicate lower exposure".

page 354

Same comment as for page 345.

pages 360-364

There is a bias present in the analysis of fiber type differences for mesothelioma which tends to overestimate the potency of chrysotile. In calculating a potency factor for mesothelioma, INSERM omitted the studies of Nicholson *et al.* (1979), McDonald *et al.* (1980), Hughes *et al.* (1987) and Dement *et al.* (1983), citing that it is unreasonable to apply a quantitative model to studies with so few cases. However, there is no technical problem with applying the mesothelioma model to such data because the model contains only one free parameter, which can be estimated from even a single case if necessary. The number of mesotheliomas going into a calculation will be reflected in the size of the confidence intervals. Moreover, to avoid bias, studies with few cases must be included in the calculations. Each of these studies was large enough to show a clear dose response trend for lung cancer, so it is not their size that is at issue but that they observed very few mesotheliomas. These studies also involved pure chrysotile exposures (except for Hughes *et al.*, but is possible to estimate a mesothelioma potency factor from a subcohort that was exposed only to chrysotile). If these additional studies had been used, it would be seen that, even after taking the small numbers of mesotheliomas into account through use of confidence intervals, the potency factors estimated from these studies are considerably smaller than those relied upon by INSERM. Thus the approach used by INSERM was biased towards using studies that found large numbers of mesotheliomas, and toward studies involving amphibole exposures. As a result the fiber type difference was minimized in the INSERM analysis and the mesothelioma risk from chrysotile exposure was likely overestimated.

INSERM also neglected to calculate a mesothelioma potency factor for the Australian cohort exposed to crocidolite.

page 363, last paragraph

I think that Rochdale exposures may have been 5% crocidolite rather than the 2% indicated by INSERM. More importantly, this analysis omits several studies of pure chrysotile exposures that

show a considerably smaller potency than the Rochdale study. This analysis also fails to calculate a potency factor for crocidolite.

page 364

Another characteristic of the exposure settings is that followup of the cohorts has been limited to, at most, about 45 years following first exposure. Therefore, the shape of the time-risk curve is unknown more than 45 years into the future.

page 364, last paragraph

Whether "the excess risk is permanent" is an imprecise term whose meaning is unclear. If this refers to an ever increasing risk from a given finite increment of exposure, then both the Seidman data and the Selikoff data "challenge the hypothesis that the excess risk is permanent." The Seidman (1984) study strongly suggests a drop-off in mesothelioma risk more than 40 years following end of exposure. This is also suggested in the Selikoff (1979) study. If this dropoff is real, it would make risks from exposures very early in life considerably less risky than would be predicted by the current model. This issue could possibly be resolved by further followup of the Seidman cohort.

page 365, next to last paragraph

Certainly is would be imprudent to draw any conclusions that are not supported by the data. However, those conclusions that can be made should be, with any relevant uncertainties or caveats also expressed.

page 372

These discussions omit the studies of the Australian cohort exposed to pure crocidolite. When this cohort is taken into account there is stronger evidence of a fiber type effect in addition to an effect of operation.

page 374, last paragraph

The comparison of percent of deaths from mesothelioma in the two cohorts with same followup time does not adjust for exposures in the two cohort and therefore is not reliable.

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Comments by

J.M.G. Davis

Chapter 5 - Current data on the mechanisms of fibrosis and tumour production.

This chapter gives a very variable impression section by section. It was probably written by an expert on cellular studies because the coverage of this type of work is extensive and I believe quite correct. In contrast the *in vivo* studies are dealt with very superficially in three tables and just a few pages of script. Certainly no attempt has been made to produce comprehensive coverage of the literature, for example only studies of asbestos carcinogenicity in rats, guinea pigs and mice are mentioned, although data is actually available for several other species the most relevant being baboons and monkeys. Having said this, however, the studies included are for the most part the best ones to illustrate the major points that have a bearing on asbestos hazard. The main failing of the chapter is that while I think all of the relevant aspects of asbestos bioeffects are at least mentioned some of them are not put in to the correct context of how they might affect the development of asbestos related disease and particularly the risk factor of developing tumours.

I propose to make comments on the report on a page by page basis and then to produce a section of how I feel the drawing together of facts and how they relate to the human situation has been inadequate.

Chapter 5

Page 192 Rats, mice, hamsters, rabbits, gerbils, monkeys and baboons should have been mentioned.

Page 199 No mention is made of the study by Hesterberg et al. (1991) in which a large proportion of hamsters treated with refractory ceramic fibre (RCF) by inhalation developed mesotheliomas. While this is not strictly asbestos, RCF is mentioned in comparisons in other places in this script.

Page 201 A recent publication by Berman et al. (1995) re-emphasising the importance of very long fibres (> 20 microns in length) in asbestos carcinogenicity could have usefully been mentioned for added emphasis.

Page 204 In discussing reference 49 the French original is ambiguous and the translation more so. The inhalation period was 6 hours per day for five days and biopersistance was measured at different time points during the succeeding months.

Page 216 There is no actual evidence that very short fibres (1-3 microns) have any carcinogenic effects at all consequently the last statement in the first paragraph is much too strong.

Page 217 Is this statement regarding the Dement study strictly true? As I recall it this cohort showed a high excess of lung cancer and very few mesotheliomas.

Page 219 The authors of the INSERM report seem to have no idea how to deal with the Wagner paper. In fact the data in table 6 shows that 3 months exposure at a massive 10 mg/m^3 is enough to cause pulmonary tumours to develop while after one day exposure tumour numbers are similar to controls. The Davis paper had severe limitations which were made clear in the original script but not in the INSERM report. For practical reasons is was not possible to obtain a better differential between "peak" and "even" exposure than 5:1. At these levels there was no difference in tumour production probably because the doses are still massive. In consequence these results have no bearing on the human situation where peaks are often 100-1000 times the level of constant exposure.

Page 221 (Table 7) - There is an error in the French original as well as in the translation. The second group of studies should both be amosite at both 50 mg and 10 mg.

Page 221 Conclusions - So much data has been presented in chapter 5 that I feel a mere 22 lines of conclusions is extremely disappointing. There should have been a better attempt to demonstrate how the available data might help to better understand human risk and indeed to show how experimental study results often explain human findings. Sometimes experimental results that appear anomalous actually help in understanding asbestos bioeffects when they are put together with data from other fields. One particular omission in this section is that while the mechanisms by which asbestos produces fibrosis are well discussed *the important connection between fibrosis and tumour production is completely omitted*. It is mentioned in the human studies section but animal data is of particular importance. Most of the long term asbestos studies reported have data on pulmonary fibrosis which is not mentioned in the INSERM report and Davis and Cowie (1990) summarised these figures from 18 different experiments discussing its relevance to the human situation. The statements made in this section regarding biopersistance are extremely one sided. Low durability of chrysotile is by far the most likely explanation for the acknowledged fact that chrysotile produces fewer mesotheliomas than the amphiboles in humans where development time is 30-40 years. In experimental studies Pott has demonstrated that low durability fibres produced either fewer or no peritoneal mesotheliomas when injected into rats as compared to asbestos. I have data on some man made mineral fibre types that confirms this although this information is as yet unpublished

<u>General comments on conclusions that ought to have been drawn from data presented in chapter 5 of the INSERM report</u>

Data from experimental studies on the genetic changes caused in cells by asbestos is limited and mainly from *in vitro* experiments. The only consistent positive finding is that asbestos fibres can disrupt the mitotic apparatus during cell division causing chromosome deletions. What is uncertain is whether the resulting daughter cells are carcinogenic or even viable in the *in vivo* situation where they would be

subjected to examination by the immune response. The fact that for practical purposes most studies are undertaken *in vitro* is of importance in considering the findings because many cell types *in vitro* take up asbestos fibres when they do so rarely *in vivo*. In living tissues macrophages take up fibres with avidity but macrophages are end cells with little power of division and do not appear to produce tumours. Compared to macrophages the likelihood of asbestos fibres being taken up by other cell types is lower by orders of magnitude. The second most frequent cell in the lung in which asbestos fibres can be found is the interstitial fibroblast, related to asbestosis certainly but not pulmonary tumours as far as can be determined. Asbestos fibres can be found in both type 1 and type 2 pneumocytes which do give rise to lung cancers but the finding is comparatively rare and consequently the chances of fibres producing tumours by direct methods would appear to be small.

As chapter 5 well illustrates macrophages containing asbestos fibres secrete a large number of factors that may generally be grouped into two classes either toxic materials such as reactive oxygen intermediates (ROI) or growth factors. ROI has been shown to damage DNA and growth factors stimulate cell proliferation.

From these findings a theory of asbestos carcinogenesis has developed which while it cannot yet be proven does at least bind together the known facts. This theory is supported by a number of workers who have published copiously in the asbestos experimental literature as described by Browne (1986). According to this theory asbestos fibres are not directly carcinogenic themselves but they cause the secretion of materials such as ROI which damage DNA and cytokines which cause the proliferation of cells leading to populations of altered and potentially carcinogenic cells. As a modification to this theory is the possibility that causing cell proliferation is the only primary result of asbestos exposure with the large populations of dividing cells having an increased likelihood of spontaneous mutations to the neoplastic state. Regardless of which is correct the implications of the indirect action of asbestos fibre is that ROI and growth factors are known to require quite large concentrations to affect tissues and that with growth factors at least these concentrations need to be maintained to produce a continuing effect. Thus to produce tumours the asbestos dose in the lung must be quite considerable and the fibres must persist for quite long periods. This is where the relationship between fibrosis and tumour production is important. As chapter 5 reports quite clearly the same types of macrophage derived growth factors are involved in fibrosis as well as the causation of cell proliferation in general. Although not mentioned at all in this report animal experimental studies clearly show that pulmonary fibrosis and asbestos related pulmonary carcinogenesis are quantitatively related whether or not they are cause and effect as some authorities claim. Human studies clearly show that in populations of asbestos workers an increased incidence of lung cancer is very largely limited to those with clinical asbestosis and may be completely limited to those with pulmonary fibrosis detectable at autopsy. *This subject of whether or not a lung cancer can be attributed to asbestos exposure when no asbestosis is present is still hotly debated* but the argument tends to be limited to asbestosis as recognised by chest radiographs and radiography is a relatively crude technique. Certainly quite significant areas of fibrosis can be present in lung tissue even when they are too small to be seen by X-rays. It is unlikely that the fibrosis *per se* is causally related to tumour production merely that both result from the same general type of tissue damage caused by the same necessarily relatively high dose of asbestos fibres. If there has been insufficient damage to produce pulmonary fibrosis then the chances of tumour production caused by similar mechanisms are correspondingly remote. The clear

association between levels of fibrosis and pulmonary cancer in animal experiments strongly suggests an effective threshold dose (Ilgren & Browne 1991).

It is important to consider the relationship between the pathogenicity of the different asbestos types both in animals and humans and fibre biopersistance. Chapter 5 lists findings from animal experiments correctly but does not draw attention to where the data is unexpected and to the implications that can be drawn from this. Human studies show that apart from textile operations there is evidence that chrysotile exposure is less likely to produce lung cancer than amphibole exposure. This trend is much more marked with mesotheliomas where relatively few have occurred in the Quebec chrysotile mines and where none at all have been properly verified for the Zimbabwe chrysotile mines. In spite of this animal studies show that in general at equal doses chrysotile produces as many lung cancers as amphibole dusts in inhalation experiments and even more surprisingly chrysotile produces as many mesotheliomas when injected into animals as do the amphibole asbestos types. The explanation of these findings is that the innate harmful potential of all the asbestos types is similar and a secondary factor is associated with the lower chrysotile potency found in humans. This factor is biopersistance. Both studies of human lung dust content and animal experiments have shown that chrysotile is removed from lung tissue much faster than amphiboles. In rats the removal appears 10 times faster. The fact that chrysotile is still active in animal studies is due to the experimental protocols used. In inhalation studies massive doses of chrysotile are administered either for the full animal lifespan or at least for one year (50% of a lifespan). In these circumstances even with the rapid removal of chrysotile the dose still remaining the lungs can be much above that required to cause disease. In intracavity injection studies the lung clearance mechanisms are by-passed and although some solubility of chrysotile appears possible in these circumstances the biopersistance of chrysotile versus the amphiboles is much less different than in the lung. In humans only the most massive exposure levels approach the animal figures (2000 fibre years) and at lower doses the removal of chrysotile has a much better chance to keep retained dust levels below the disease threshold. Biopersistance is likely to be at its most relevant in relation to mesotheliomas. Fibres have first to be deposited in the lung and then transported to the pleura or peritoneum before they can begin to initiate the carcinogenic process. This means an added chance that fibres of low biopersistance will never reach critical sites at all. In humans there is the suggestion that mesotheliomas resulting from “chrysotile” exposure are actually caused by tremolite present as a contaminant. Tremolite fibres are amphiboles that certainly have a high potency regarding mesothelioma production and are retained in lung tissue far more readily that chrysotile. Whether tremolite is responsible for all “chrysotile” mesotheliomas is still uncertain but suggested evidence comes from the lack of mesotheliomas in the chrysotile mines of Zimbabwe were tremolite is supposedly absent.

General Comments on the INSERM Report

This report is in general poorly constructed and uncoordinated. I believe this has been due to an attempt to produce it in a timescale that was very much too short. I fear that the report of our expert panel to The Royal Society of Canada will suffer from exactly the same problems and will be of poorer quality than the committee members would wish. The INSERM report is similar to one produced in 1991 by the Health Effects Institute in the USA which also attempted to evaluate the risks associated with asbestos exposure. The INSERM report is a comprehensive document that certainly includes and

correctly reports most of the relevant publications in a number of fields. In many places it is a good and accurate compendium of the known facts. Although at some points where critical arguments are presented it is noticeable that papers presenting an alternative point of view are omitted. The INSERM report like the HEI found two critical problems. Risk can only be calculated with any accuracy if the exposure levels in good epidemiological studies are also accurate and if the correct model relating risk to dose is adopted. There are serious difficulties in both these points. Techniques for accurate evaluation of asbestos exposure were not perfected until the 1960's yet much of the exposure that caused reported disease was before this date. Attempts to produce extrapolated and corrective figures for exposure may be the best that can be obtained but the probability is that they are widely inaccurate. This is particularly likely because during the period in question industry was struggling to reduce dust levels and *the reported figures were often the most optimistic ones and far below the worst case situations*. If indeed the true figures for asbestos exposure in the past are under-estimated it follows that present day risk calculations are over-estimates. The second problem concerns the dose response model adopted. In all aspects of toxicology other than carcinogenicity a standard Sigmoid curve is accepted for dose response estimates even though the data for the lower doses is often as poor as with the cancer studies. Workers in the cancer field have tended to adopt a straight line dose response which implies no safe threshold because they feel that it is at least possible for 1 molecule of carcinogen or 1 fibre to cause the transformation of a single cell and because the adequate examination of carcinogenic effects at low doses is an extremely time consuming and expensive operation. The INSERM report is at fault because in adopting the no threshold model it does not even discuss the vast amount of data that was in favour of a threshold that was well summarised by Browne (1986) and Ilgren & Browne (1991). The no threshold model is most unlikely to be true because in the unlikely event that one fibre could produce a single cancer cell the chances of this one cell being able to multiply and produce a clinical tumour are remote. This is because of the extremely effective series of protective measures that the body has for the precise purpose of stopping this eventuality. These defences, loosely described as the immune response, are extremely effective. Tumours only develop if the immune response can be overwhelmed or confused until it is too late an event which is only likely to happen where multiple cell transformations are occurring in an area of actively proliferating tissue. The causation and maintenance of such areas of cell proliferation require a significant dose of any carcinogen and the lowest dose capable of producing and maintaining this change is the effective threshold. The problem in undertaking a balanced debate on the subject is that while the straight line response is theoretically unlikely the available data do not allow an alternative response curve to be predicted with any greater precision. The INSERM report does in fact point out in some places that there are uncertainties in the straight line response but then presents risk calculations with an unjustified confidence in their accuracy. These figures in fact present the worse case scenario and the report should make this clear.

There are a number of other significant debates concerning asbestos related disease at different points in the report and these may be commented on in the order in which they appear. Firstly, the relationship between pulmonary fibrosis and lung cancer is discussed in several places in the INSERM report (pages 154, 164, 227, 345 *et seq.*) but I feel that incorrect conclusions are drawn from the most studies since evidence for asbestosis (fibrosis) is obtained only by chest radiograph. There is now good evidence that this relatively crude technique demonstrates only what can be considered from the pathological point of view to be relatively advanced asbestosis. The most important paper in this field is that by Kipen *et al*. (1987). In this publication all of 138 cases of lung cancer in insulation workers

had asbestosis demonstrated histologically although in 18% of cases this was not visible on X-ray. This level of insensitivity in the radiographic detection of asbestosis is confirmed in a case control study by Wilkinson *et al*. (1995). The 100% association between asbestosis and lung cancer detected by Kipen *et al*. is extremely strong evidence in support of the suggestion that asbestos has to be present in lung tissues in doses sufficiently high to produce fibrosis before lung cancer will develop. Discussions in the INSERM report accept the threshold concept for fibrosis without accepting that this also implies a threshold for tumour production.

Discussion occurs in several parts of the INSERM report about the likelihood that environmental exposures to asbestos may cause mesotheliomas. Here a number of doubtful suggestions are made and conflicting evidence, often not quoted at all, is not given full weight. It is claimed that the only known agent associated with mesothelioma development is asbestos and that the 25-30% of cases with no occupational exposure are still due to asbestos (page 282). There is no mention of the paper by Ilgren and Wagner (1991) which reports that a number of agents other than asbestos have caused mesotheliomas. The INSERM report does accept that at present there is no direct evidence that environmental exposures can cause mesotheliomas (page 304) but the implications of a straight line dose response would be that such tumours would occur.

The INSERM report documents and discusses the relationship between smoking and lung cancer in asbestos workers. This association is well known and the report agrees that the combined effect is probable multiplicative. In spite of this the incredible suggestion is made on page 345 that smoking need not be taken into account in attributing a cause or relationship between asbestos and lung cancer. I feel that the error that has been made here is to consider that a tumour is either attributable to asbestos or not in an all or none relationship. This ignores the facts. If five excess cancers of the lung occur in a population of non smoking asbestos workers and five excess cases of cancer occur in a non asbestos exposed population of smokers the combined effect in smoking asbestos workers, using the multiplicative model, would be 25 excess cancers. Of these 15 would never have occurred without smoking and so are not in any way attributable to asbestos alone. These 15 cases may be considered partially attributable to asbestos and partially attributable to smoking in a proportion related to the actual exposure levels of both. In cases of compensation it is most important to consider these exposure levels. In a worker heavily exposed to asbestos who smoked but little the asbestos effect is the major one but in lightly exposed heavy smokers asbestos will have contributed little to the tumour development. In these circumstances the suggestion that smoking need not be taken into account in compensation cases seems incredible.

In assessing the potential of chrysotile fibres to produce mesotheliomas attention in the past has been drawn to the possibly major effect of tremolite present as a contaminant. Because chrysotile fibres are removed rapidly from lung tissue and amphibole fibres (tremolite) are not there are many reports of cases of “chrysotile” mesotheliomas where at autopsy the vast majority of fibres remaining in the lung are tremolite. In these circumstances it is logical to assume that tremolite might be a major factor in any tumours that occur and in the case of mesotheliomas it may be the only factor involved. This proposition has proved difficult to substantiate. The problem of the “amphibole” hypothesis is discussed in the INSERM report on pages 368-373 with most of the mentioned publications being presented as evidence against the “amphibole” hypothesis. However, the way much of the data is

presented fails to understand one point about mesothelioma development. This is that while there is evidence of a dose response relationship to levels of asbestos exposure the response is much less clear cut than with lung cancer. With mesotheliomas all that may be required is that the threshold exposure to asbestos must be exceeded and that subsequent tumour development may depend on individual factors such as the speed of fibre transport etc. In these circumstances the fact that mixed exposures of chrysotile and amphibole seem to produce as many mesotheliomas as pure amphibole exposure is not evidence that chrysotile is involved at all. As long as sufficient amphibole is accumulated in the tissues whether this amphibole is crocidolite or tremolite present as a chrysotile contaminant is unimportant. A number of papers have examined the tremolite effect in the development of mesotheliomas in the Quebec chrysotile mines and some publications quoted in the INSERM report have concluded that there is no association with tremolite exposure. The number of cases from the Thetford Mines area where tremolite is high seems comparable to the numbers from Asbestos where the tremolite is much lower. Common failings in these papers is that no account is taken of the fact that in Asbestos a small factory facility used commercial amphibole fibres and that no lung dust figures are available for comparison. A most important recent publication by McDonald and McDonald (1995) is not mentioned in the INSERM report. This publication reports that it was noticed that all reported cases of mesothelioma from the Thetford Mines area of Quebec came from five out of the fifteen mines operating. Lung dust figures from controls without mesotheliomas showed that the tremolite content of those that had worked in the five critical mines had four times the amount of tremolite than those from the remaining ten. To some extent of course the amphibole hypothesis in relation to mesothelioma production is academic. In mesothelioma cases resulting from pure “chrysotile” exposure it does not matter to the asbestos industry whether the active agent is chrysotile itself or the contaminant tremolite. The importance of the tremolite findings to the “amphibole” hypothesis is that they support the contention in mixed exposures that the effects of a few percent of amphibole fibre are likely to outweigh a much higher exposure to chrysotile. One important piece of information that supports the amphibole hypothesis of mesothelioma production is the complete or almost complete absence of mesotheliomas in the Zimbabwe asbestos mines where tremolite is supposed to be absent. The Cullen (1991) paper quoted by the INSERM report is of extremely poor quality and the two mesothelioma cases reported cannot be accepted as adequately certified. Even if they were the result of chrysotile exposure this trivial figure of two contrasts with the hundreds reported from similar mines producing crocidolite and argues that the true relative potency of crocidolite is much more than the 2-4 times quoted in the INSERM report.

In conclusion my opinion of the INSERM report is that a most commendable attempt has been made to consider all aspects of the interaction of asbestos fibres with tissues. I feel however that it ends up presenting an unjustifiably pessimistic assessment of the risks of asbestos exposure particularly at low levels because of placing undue value on doubtful figures for dust exposure and the use of a dose response model that is incompatible with the latest information on mechanisms as disease production. It is noticeable that where critical arguments are presented important publications presenting an alternative view are sometimes omitted.

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Comments by

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These notes are intended to present : a) the context in which the INSERM Report has been presented; b) additional contributions on the health risks on asbestos exposure published or in press and of interest; c) comments on some sections of the INSERM Report, namely the use of asbestos in France, the occurrence of mesothelioma (mortality and incidence), and the estimation of risks associated with asbestos exposure.

1. Context

The INSERM Report should be read having in mind the context in which it was requested.

France has been a large producer of asbestos-based products and a large consumer of raw asbestos.

In relation also to the decreasing or abandoned use of asbestos in several European countries, France was, in the last few years the third importer of asbestos worldwide. As in other European countries, asbestos started to be used industrially at the beginning of the century, but its use greatly increased in the early fifties. In France the peak of imported raw asbestos was reached in 1976 (144,000 tons). The import of crocidolite was highest in 1974 (5,500 tons) and stopped in 1988, whereas amosite was imported until 1991 (2,800 tons in 1973) (*data in INSERM Report*). In 1977 the European Community published a report on the use of asbestos and asbestos products in its member states. In that year the consumption of chrysotile was similar in Italy, France, United Kingdom and Federal Republic of Germany (varying from 130,600 tons in Italy to 173,300 tons in Germany, and 150.000 tons in France). By fibre type, whereas United Kingdom stood out in the use of amosite, in France the use of amosite and crocidolite was of the same order of magnitude as in other European countries (*EEC Document 344/77*).

Since the sixties, and increasingly after a fire in an high school which impressed the public opinion, public and private buildings in France have been extensively insulated with sprayed asbestos. The large use of metal as a construction material in buildings was another reason for the extensive use of sprayed asbestos in schools, research facilities, prisons, hospitals and metro stations. The largest public buildings ever insulated with asbestos are located in France. However, in these buildings the amount of asbestos used and the types of asbestos fibres used are unknown. Only a few data are available on the pollution occurring in these buildings and the deterioration of the asbestos insulation.

The first regulation of asbestos exposure for the industrial setting was introduced in France in the late seventies (Decret 17/8/ 1977: daily permissible mean concentration 2 fibres/ml) without differentiating by asbestos fibre. The regulation was introduced after two years of work of an

interministry commission. The distinction by fibre type was subsequently established in 1987 and 1992, when, following the European Directive of 1983, permissible levels in workplaces were reduced (Decret 27/3/ 1987 and 6/7/ 1992, daily permissible mean concentration 600 fibres/l for chrysotile and 300 fibres/l for all other asbestos fibres). The present limit, introduced in 1996, for 8 hours at workplaces is 0.3 f/ml for chrysotile and 0.1 f/ml for amphibole fibres.

In the European Union (EU), to which France belongs, asbestos use in the industrial settings was the object of a first Directive, for which unanimity among member states was at that time required. The Directive introduced different standards by fibre type, considering crocidolite to be more dangerous than other fibres, a policy subsequently enlarged by the ban on crocidolite in some applications and the restriction of the use of any type of asbestos fibre in some products (introduced in the French legislation with the Decret 28/4/ 1988). The ECE Directive 3/12/ 1991 was introduced in the French legislation by the Decret 26/7/ 1994 permitting only the use of chrysotile for certain products.

Insulation of buildings with sprayed asbestos (more that 1%) was banned in France in 1978 (Decret 20/3/ 1978). In 1996 (Decret 7/2/ 1996) a limit for the presence of asbestos fibres inside buildings (compulsory intervention at 25 f/l, alarm at 5 f/l but level permitted) was introduced. The permissible levels inside buidings in France are thus higher than the limits established in other European countries (such as Germany and Switzerland, alarm at 1 f/l).

Several countries of EU decided on more restrictive regulations of asbestos than those approved by the EU Parliament. Germany and the United Kindgdom banned the spraying of asbestos in 1970. Denmark, Sweden, Finland, the Netherlands, Italy and Germany have imposed a general ban of all type of asbestos use and asbestos products, inclusive of their commercialisation. In addition more restrictive permissible levels at workplaces have been defined in some European countries or asbestos has been banned (Switzerland, Norway).

As far as the EU legislation is concerned, a Directive approved in 1991 by the European Parliament, and subsequently introduced among member states, regulates the presence of carcinogenic substances at work. The Directive holds for all agents or industrial processes classified as carcinogenic; for some agents, regulated by specific Directives, as is the case of asbestos, exposure limits remained in place. The carcinogenic substances should be replaced whenever possible. Employers must justify their use to the health authorities of the country. When a carcinogenic substance is allowed to be used, the maximum level of prevention must be assured (in terms of use of technology, closed systems, environmental protections, personal devices, information to workers, labelling of products, hygiene measurements, nominal registration of workers employed, medical surveillance during and after employment, and treatment of wastes).

In France the system of compensation for occupational diseases goes back to the twenties. Asbestosis became a defined and compensable disease in 1957 (but could have been eligible for compensation under the definition of pneumoconiosis from 1946). Mesotheliomas of any site have been recognized as occupational diseases since 1976. Lung cancer without asbestosis in asbestos workers became a recognized occupational disease only recently (1996), after publication of the

INSERM report. However, the number of mesotheliomas covered by compensation has always been very modest (a few dozen until 1988; 77 in 1993, last year of available data) (1993 data, *INSERM Report*).

In spite of the important production and use of asbestos products, epidemiological research on the risks associated with asbestos and the collection of environmental data on exposure to asbestos has remained sporadic in France.

A group composed of experts on asbestos inclusive of representatives from social groups and the asbestos industry, supported economically by the asbestos industry, was created in 1982 (Comité Permanent Amiante). This group has been influential in all legislative decisions taken in recent years.

The INSERM Report was produced by a group of French scientists at the request in September 1995 of the Ministry of Public Health.

The need of a report was triggered by several issues: the increasing number of requests for compensation due to asbestos-related diseases due to occupational exposure; the request for court trials in asbestos-related diseases considered to have originated from environmental exposures, primarily in buildings insulated with asbestos; and an increasing anxiety about the possible health effects due to the deterioration of sprayed insulation in buildings. In addition, a large debate in the press originated in France due to a publication from the UK on mortality due to primary pleural tumours and projections of mesothelioma expected to occur in the next few decades (*Peto et al., 1995*). The debate included a critical evaluation of the occurrence of this disease in France, recognizing that the number of deaths due to primary pleural tumours previously stated in the documents produced by the above mentioned group were lower than the true value.

2. General remarks

In few nations worldwide have reports on asbestos been produced by public or governmental authorities: the few available reports have been prepared in UK, USA, and in the province of Ontario,Canada.

The INSERM Report is of outstanding quality, accuracy and extensiveness. In the French tradition of health reports, the INSERM Report on asbestos is again outstanding.

2.1. Structure of the Report

The INSERM report is composed of a summary report and a document structured in 12 sections, each dealing with a specific question. The summary report was released first, whereas the document is still a draft, not available for the public. All the material will eventually be published.

As a general picture each paragraph of the document presents the study question in a comprehensive manner; clearly indicates the scientific uncertainties; quotes the available relevant scientific literature and expresses the point of view of the group of scientists.

Two parts are dealt with in more depth: (1) the part dealing with a presentation of data on the incidence and mortality from primary pleural tumours and lung tumours in France (pp. 276-343), and (2) the section dealing with the estimates of cancer risks due to the exposure to asbestos (pp. 309-344 and 379-398).

The section on incidence and mortality for primary pleural tumours and lung tumours is related to the mandate requested by the Ministry of Public Health. The section on risk estimates is an effort to provide data to the French health authorities for regulation.

The scientists do not attempt to indicate which regulation(s) should be pursued by the health authorities, rather restricting themselves to a detailed presentation of the implications of each choice.

2.2. Completeness of the Report

The report presents an overview of all the aspects dealing with the carcinogenicity of asbestos. Some parts of the report specifically address the French situation, such as the use of asbestos in France, and an evaluation of the mortality or incidence of asbestos-related tumours. The document does not address the question of the availability and the hazards posed by agents used to replace asbestos: it is, however, known that the French Ministry of Health, as done for the Report on asbestos, asked the INSERM to produce a Report dealing specifically with this question.

Because of the limited amount of research (but stating clearly that the term `limited' does not imply any general judgement about its quality) done in France on asbestos health effects and the limited collection of exposure data both in the industrial setting and in different environments, an extensive use of data gathered in other nations and published in the scientific literature constitute the basis for the Report.

It should be noted that after the report was published new scientific contributions have been published or are in press on some of the issues discussed by the INSERM report. Because of the relevance of some of them, they are summarized below.

3. Additional references of high relevance published or in press after the INSERM Report

3.1. The IPCS document on chrysotile asbestos

(International Programme on Chemical Safety, WHO, Geneva. Environmental Health Criteria Document on Chrysotile Asbestos) (in press).

Within the framework of the International Programme of Chemical Safety (IPCS), co-sponsored by the World Health Organisation (WHO), International Labour Office (ILO), and the United Nations, a group of 17 international experts from 10 countries was appointed to evaluate health

risks involved in the industrial production and utilization of chrysotile. The group met in the summer of 1996 and more than 140 IPCS contact points -collaborating centres, institutions and individuals both in dveloped and developing countries - were involved in the preparation of the evaluation of chrysotile.

The IPCS document is different from the INSERM Report because it deals with a review of the scientific literature on health risks due to chrysotile exposures only and includes conclusions and recommendations for public health protection.

Following a presentation of the available data and evidence, the IPCS document stated among the conslusions:

"Exposure to chrysotile asbestos poses increased risks for asbestosis, lung cancer and mesothelioma in a dose-dependent manner. No threshold has been identified for carcinogenic risks.
Where safer substitute materials are available for chrysotile, they should be considered for use. Some asbestos containing products pose particular concern and chrysotile use in those circumstances is not recommended. These include friable products with high exposure potential. Construction materials are of particular concern for several reasons. The construction industry work force is large and measures to control asbestos are difficult to institute. In-place building materials may also pose risk control to those doing alterations, maintenance and demolition. Minerals in place have the potential to deteriorate and create exposures.
Control measures, including engineering controls and work practices, should be used in circumstances where occupational exposure to chrysotile can occur. Data from industries where control technology have been applied have demonstrated the feasibility of controlling exposure to levels below 0.5 fibres/cc. Personal protective equipment can further reduce individual exposures where engineering controls and work practices prove insufficient.
Asbestos and cigarette smoking have been shown to interact to greatly increase the risk of lung cancer. Those who have been exposed to asbestos can substantially reduce their lung cancer risk by avoiding smoking."

The conclusions are important with regards to the INSERM report because we should, at this state of the art, concentrate on the parts of the INSERM report which goes beyond the IPCS document, namely the risks due to environmental exposures and quantitative risk assessment on asbestos fibres.

3.2. IARC Scientific Publication No 140. Mechanisms of fibre carcinogenesis

Kane AB, Boffetta P, Saracci R, Wilbourn JD (eds). Mechanisms of fibre carcinogenesis. IARC Scientific Publication n. 140, IARC, Lyon (in press)

In January 1996, a group of experts convened at the International Agency for Research on Cancer (IARC), Lyon, France to discuss the mechanism of fibre carcinogenesis. The volume includes a Consensus Document summarizing " *the strength, weaknesses and gaps in the present knowledge on fibre characterization, genotoxicity, cell proliferation and activation, and animal studies. The second part of the report provides answers to specific questions on the relevance of mechanistic data from in-vitro and in-vivo assays in the assessment of the carcinogenic risks of fibres to*

humans. Finally, the relevance of mechanistic data in the evaluation of fibre carcinogenicity is discussed".

The Consensus Document stated:

" At present, there is insufficient understanding of how the physical and chemical proporties of fibres contribute to mechanisms of fibre-induced carcinogenesis to make reliable predictions of the carcinogens potential of fibres based solely on these types of data..."
" In addition to dimension and durability, there may be other aspects of the physical and chemical properties of fibres that can provide information on potential fibre toxicity in-vivo. These were considered to include the following: the presence of iron or other transition metals on fibres, the ability of a fibre to accumulate iron, the ability of fibres to gererate free radicals, the ability of a fibre to interact with and alter biologically relevant molecules (e.g. DNA, lipids, proteins), and the ability of fibres to cause lysis of erythrocytes/liposomes..."
"Experimental studies with fibres showing significant numbers of lung tumours have always shown high levels of pulmonary fibrosis. This does not necessarily indicate a cause-effect relationship since both processes may be a response to high fibre dose... Fibre-induced chronic inflammation leads to fibrosis. There are no data on direct links between inflammation and carcinogenesis. However, one widely held theory is that, in areas of chronic inflammation, substances such as ROS and cytokines are produced that may be involved in tumour production"
"The exact mechanism leading to the development of cancer after exposure to asbestos fibres is poorly understood. Most lung cancer in humans exposed to asbestos occurs in cigarette smokers; however, an excess of lung cancer also occurs in a small percentage of people exposed to asbestos fibres alone. It is not known whether the same mechanism is responsible for the development of these tumours in smokers and nonsmokers exposed to asbestos. While fibres can produce both lung cancer and mesothelioma, different patterns of molecular alterations have been identified in human lung cancers associated with asbestos exposure and cigarette smoking in comparison with diffuse malignant mesothelioma. Therefore, it is possible that different cellular and molecular mechanisms are involved in the development of these two tumour sites...".

The IARC document makes clear that the gaps in our knowledge impair the use of simplified theories on the mechanisms of fibre carcinogenesis.

3.3. The Health and Safety Executive (HSE) report on cancer risks on asbestos workers after the 1969 regulation on permissible levels on asbestos at workplaces in UK

S. Hutchings, Jones J, Hodgson J. Asbestos-related diseases. In: F. Drever (ed). Occupational Health. Decennial Supplement. HSE, London, 1996 pp 127-152

The importance of the report lies in the following aspects.

The UK was the first nation worldwide, that extensively used asbestos, to cease the importation of crocidolite in 1969. The UK implemented a standard for occupational exposures (in 1969) specifically intended to limit the cancer risk (0.2 f/ml for crocidolite and amosite; 0.5 f/ml for chrysotile). In addition, asbestos spraying in buildings was prohibited in 1969.

A program covering England, Wales and Scotland has been implemented in census workplaces subject to the 1969 regulation and workers in these factories. Hygiene measurements have been carried out in the factories. Workers exposed to asbestos in the factories subject to the new standard or who started work thereafter were enumerated and have been examined every two years, as long as they remained in that employment. Examinations consist of collection of exposure history, smoking habit, and chest X-rays. All workers have been included in a cohort mortality study.

A national cancer registry covers the UK. In addition, since 1968 all newly diagnosed cases of mesothelioma and all death certificates mentioning mesothelioma have been compulsorarily reported to a National Registry of Mesothelioma.

The results of the follow-up for 1971-1991 and of the surveillance system on mesothelioma (1968-91) have now been published as a chapter of the decennial Supplement on Occupational Health.

The report also presents an analysis of the mesothelioma deaths occurring in the general population of the UK, inclusive of an analysis by age-and birth-cohort.

A section of the whole cohort of the workers included in the above described program, fullfilling some predefined criteria and composed of 57,402 subjects, was followed up for mortality (1971-1991), counting the person-years at risk from the medical examination. Expected deaths have been computed on the basis of age, sex, period, and area rates. Mesothelioma and asbestosis deaths have been represented as a percentage of excess deaths from all causes. In total 5,327 deaths have been identified (183 mesotheliomas deaths). A lag of 10 years from first recorded exposure was introduced in computing SMRs for workers recorded as being first exposed after 1969.

The HSE report shows that:

— the working force subject to the asbestos regulation is the source of a small fraction of the national occurrence of mesothelioma deaths (some 200 recorded mesothelioma cases whereas about 10,000 deaths due to mesothelioma were recorded in the same period). This implies that exposures to asbestos occurring outside the workplaces and workforce subject to the 1969 asbestos regulation explains the majority of the deaths in UK from primary pleural tumours;

— a relevant number of deaths due to mesothelioma (21 deaths, 1.28% excess deaths) is observed among the workforce which entered the factories after the 1969 regulation. However, a larger number of deaths due to mesothelioma is observed among subjects at work before the 1969 regulation (162 deaths, 4.61% excess deaths), suggesting that the reduction in exposure to asbestos following the new regulation has been effective in decreasing but not capable of avoiding mortality due to mesothelioma;

— deaths from lung tumours follow the same pattern as mesothelioma deaths: among workers first exposed 1970 or later, the SMR is 123.5 (95% CI 106.7-142.1, based on 194 lung cancer deaths), and among workers first exposed prior to 1970, the SMR is 141.3 (95% CI 129.7-153.7, based on 555 lung cancer deaths). The mortality from all malignant neoplasms is also statistically increased among both groups;

— a relevant decrease in asbestosis deaths has been achieved through the new standard (among workers first exposed prior to 1970: 85 deaths, excess deaths 2.42%; 5 deaths among workers first exposed after 1970, excess deaths 0.30%);

— overall, the occurrence of lung tumours appears strongly related to the smoking habit of workers, as stated at the last health examination: among smokers, SMR 288.8, (95% CI 191.8-325.8, based on 601 lung cancer deaths); among non-smokers, SMR 10.3, 95% CI 4.1-21, based on 17 lung cancer deaths); among ex-smokers, SMR 67.7, (95% CI 56-81, based on 118 lung cancer deaths). It should be noted that overall the proportion of current smokers observed in the cohort is higher than the national level (54% versus 42 %).

In conclusion, the new UK asbestos standard introduced in 1969 (more than twenty years ago) reducing the permissible exposure to asbestos at workplaces, and followed by a ban in the import of crocidolite, does not appear to have been capable of avoiding deaths due to mesothelioma and of avoiding a statistically significant excess in mortality from all cancer and lung cancer among subjects who entered workplaces after the new regulation.

The epidemic of mesotheliomas occurring in UK among workers is explained mainly by sources of asbestos exposure outside the factories and the workforce fullfilling the criteria of the new asbestos regulation.

4. On the consumption of raw asbestos in France and the mortality due to primary pleural tumours

In section 8 of the INSERM Document "Development of mesothelioma incidence in different countries" is stated that " *the likely reason (of the relatively low incidence of male mesothelioma in France) is that France used less asbestos at a later date than other countries, and that asbestos used undoubtedly contained fewer amphibole fibres*" . This opinion seems to underestimate the French situation, with regard to the European scenario.

In fact, the French consumption of raw asbestos fibres from 1940 to 1973 has been higher than in Italy and similar to the one in the Federal Republic of Germany (**Fig. 1**)[*].

[*]Source of data: Denmark: Andersson M. et al. Brit J Cancer 51:699, 1985; France: Avril J. In: Shapiro H.A. (ed) Pneumoconiosis. Oxford University Press, 1970; FRD; Woltowitz H.J. Am J ind Med 2:71, 1981; Italy: Gaffuri E. et al. Med Lav 82:155, 1991; Netherlands: Hurdorf L. Am J ind Med 20:547, 1991; UK: Advisory Committee on Asbestos, Vol 2, HMSO, London 1979.

As stated, the INSERM report presents original data on both the incidence of mesothelioma and the mortality for primary pleural tumours occurring in France. The data presented partially cover the preexisting gaps in knowledge, but work is still needed in this field.

A point which deserves discussion is that "*current mesothelioma incidence in men in France, according to estimates, is relatively low compared to most industrialized countries"* (pp 300-301).

The lowest age-standardized rate x 100.000 (standard: world population) of the six French cancer registries covering the period 1983-87 included in the the Volume of Cancer Incidence in Five Continents (*DM Parkin, CS Muir, SL Whelan, YT Gao, J Ferlay, J Powell (eds). Cancer incidence in five continents. Vol VI. IARC Scientific Publication n. 120, Lyon, IARC, 1992*) is recorded in Tarn (0.3± 0.1), the highest in Bas Rhin (1.6± 0.3) (among females 0.2±0.1 and 0.1± 0.1, respectively). These values largerly overlap with incidence rates among most industrialised countries of Europe and North America. However, the highest incidence rates of mesothelioma are not recorded in France, but in Italy (Italy, Trieste; 4.7±1.0 among males) and Australia (Western Australia; 2.9± 0.3 among males).

A contribution to the understanding of the situation in France with regard to the mortality of primary pleural tumours can be derived from an analysis of mortality rates by calendar periods and age groups using the WHO mortality and population data, restricted to the use of the 8 and 9 International Classification of Diseases for primary pleural tumours among males (Fig. 2) (unpublished data). The data suggest that mortality rates among age groups (from 40-45 to 75-80) in Italy, France and Germany express overall the same pattern, with the oldest age groups having the highest rates and increasing trends over time periods. The oldest age group (age 75-80) and the age groups of 60-65 and 55-60 in France compared to both Italy and Germany express increased rates of mortality, expecially in more recent periods, thus suggesting a worse situation in France than in the other countries considered **(Fig.2**).

In my opinion, therefore, the French situation on both the consumption of asbestos and the incidence and mortality of mesothelioma as presented in the INSERM Report is questionable.

With regards to the occurrence of mesothelioma among females, it should be noted that the results of mesothelioma cancer registries suggest an higher percentage of unknown exposure circumstances among female than among male cases. It is less clear, therefore, from the life histories, which proportion of pleural mesothelioma among females is attributable to asbestos exposure (occupational, para-occupational or environmental) and thus potentially avoidable.

5.1. On the association between para-occupational and environmental exposure to asbestos and the risk of mesothelioma and lifetime risk estimates of mesothelioma

Epidemiological data on the association between para-occupational and environmental exposure to asbestos and the risk of mesothelioma are growing.

It seems worthwhile to quote the relative risk of mortality due to primary pleural tumours (SMR 792, 95% CI 215.9-2028.8) (incidence within the cohort as pleural mesothelioma deaths per 1,000 deaths: 19.1) among the wives of workers of an asbestos-cement factory in Italy (the study is extensively quoted in the INSERM Document, but the risk estimate is not) *(Magnani C et al. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. Br J Ind Med 50: 779-784, 1993*). The para-occupational exposure to a mixture of fibres (crocidolite and chrysotile) explained the deaths due to mesothelioma among the wives of workers.

From 1979 to 1994, 34 cases of mesothelioma have been detected among women and subjects exposed when children because of living in the village of Wittenoom Gorge, Western Australia and visitors to the mine of crocidolite at Wittenoom Gorge exposed to crocidolite because of environmental exposures. A strong increasing trend in the proportion of environmental mesotheliomas is observed during the time period. Airborne exposures in the town have been collected and the list of residents reconstructed.

The authors estimated an upper lifetime risk of developing a mesothelioma from 64 to 57 deaths (based on different assumptions) per million persons for a child aged 6 years and an upper lifetime risk of developing a mesothelioma from 23 to 20 deaths for an adult 21 years exposed for 10 years to 0.001 f/cc. The model assumes linearity (*Rogers A et al. Occupational and environmental mesotheliomas due to crocidolite mining activities in Wittenoom, Western Australia. Scand J Work Environ Health 21: 259-264, 1995*) (the study is not quoted in the INSERM Document; the article was published in August 1995, and became available in the following month, so that it is possible that the results were not available when the INSERM Report was prepared).

It is worth noting that these estimates are based on observed cases and observed levels of environmental exposures, so that the estimates are based on a range of exposure data very far from those estimated in occupational cohorts.

The risk of developing a mesothelioma presented in Rogers et al. is not dissimilar to the excess risk estimated in the INSERM Document in the quantitative risk assessment, based on exposure estimates and observed cases in occupational cohorts (Table N, males, age at first exposure 5, duration of exposure 10 years, excess lifetime risk of mesothelioma 4.7 x 10.000 at 0.025 f/ml; Table M age at first exposure 20, duration of exposure 10 years, excess lifetime risk of mesothelioma 1,9 x 10.000 at 0.025 f/ml). The correspondence between the two estimates is the following: 18.8 excess lifetime cases of mesothelioma for children in INSERM versus 64-57 in Rogers et al.; 7.6 excess lifetime cases of mesothelioma for adults in INSERM versus 23-20 in Rogers et al.

In conclusion, the INSERM quantitative estimates appear to be validated by the occurrence of mesothelioma deaths in Wittenoom due to environmental exposures, considering that crocidolite appears likely to be three of four times more potent than chrysotile in causing mesothelioma in humans (*Smith AH, Wright CC. Chrysotile asbestos is the main cause of pleural mesothelioma. Am J Ind Med 30: 252-266, 1996).*

5.2. Estimation of risks associated with asbestos exposure

The INSERM Report (pp 329 and following) discussed quantitative elements on asbestos exposure and mesothelioma and lung cancer mortality.

The authors correctly remember that "*two quantitative elements must be taken into consideration before the differences in the excess lung cancer risk observed in the different cohorts can be interpreted in any way: the statistical precision of the risk estimates calculated in the different studies and the value of the cumulative exposure levels in the different cohorts*" (p. 333).

Consideration of these two elements is the basis for the selection criteria applied by individual scientists or groups of experts to the available studies to be used for estimation of risks.

In the selection criteria for the studies with cumulative exposure levels, the INSERM scientists adopted a conservative approach, in line with previous group of experts: in particular the study of Finkelstein among workers in asbestos cement, a study detecting the highest slope in lung cancer deaths for each additional unit of cumulative exposure, was excluded as affected by *"systematic errors in exposure assessment"* (p. 336). It seems relevant to consider that the HEI-AR report - the most recent and important report on estimation of risks of asbestos exposure - states (pp 6-25) that the study on Quebec chrysotile miners and millers (Mc Donald, 1980), detecting the lowest dose-response slope, is also questionable in the measurements of asbestos exposure, because "*conversion of particle to fibre counts was based on inconsistent measurements at relatively low levels*" so that " *the conclusion that exposure in chrysotile mining is 20 to 100 times less dangerous than in chrysotile textile production at the same measured fibre level is extremely insecure*". The study was, instead, included by the INSERM report validates the INSERM quantitative estimates of risk, thus obtaining overall a conservative estimate of the cancer risk.

As far as pleural mesothelioma tumors are concerned, the selection criteria of inclusion for the available cohort studies, in addition to those used for lung cancer, includes the criteria of at least twenty years of latency and more than 10 cases observed. Whereas the criterion of latency seems biologically solid, the criterion of at least 10 observed cases is questionable. In addition, the studies on miners and millers of crocidolite at Wittenoom Gorge, Australia, are excluded even if based on 94 deaths due to primary pleural tumours in the latest presentation (*Armstrong et al. Br J Ind med 45: 5-13, 1988; De Klerk N, Armstrong BK. The epidemiology of asbestos and mesothelioma. in: Henderson DW et al. (eds) Malignant mesothelioma. Hemisphere Publ Corp, New York, 1994, pp223-250).*

The exclusion is parallel to the HEI-AR report; it produces overall a more conservative quantitative estimation, considering the high value of the slope. However, as a consequence of these exclusions, the estimates of the INSERM Document for mesothelioma rely on a very limited set of data.

The INSERM report stresses that "*the magnitude of the uncertainties associated with the different estimates of K thus call for extreme caution in interpreting the differences between*

studies. For instance, Hughes et al (1986) recommend that the model selected be independent of the geological origin of the fibres (chrysotile or mixed fibres), while McDonald et al (1985) feel that the same model can probably be applied to all occupational exposure situations.

The same position has been adopted by 6 groups of experts established by public authorities to assess the risk of cancer associated with asbestos exposure (HEI-AR, 1991)...

A K value of +1.0% has been adopted as an estimator or as the geometric mean of an uncertainty interval by four of these groups of experts, three of them in the United States (the Environmental Protection Agency in 1986, the National Research Council in 1984 and the Health Effects Institute - Asbestos Research in 1985) and one in Great Britain (the Health and Safety Commisiion in 1985). One group of expert, the Ontario Royal Commisiion in Canada, proposed a lower geometric mean (+0.29%) and a large uncertainty interval (+0.02% to +4.2%). Finally, one group, the Consumer product Safety Commission in the United States, has adopted a higher value (+2%).

In view of all these observations, it seems reasonable to adopt a single value of +1% for the risk coefficient K, regardless of the geological origin of the fibres".

The methods and the choice of the INSERM scientists are reasonable. The computations are correct.

The INSERM Report could have underestimated the number of deaths due to asbestos exposure. In fact, in addition to causing human lung and pleural mesothelial tumours, exposure to asbestos also causes peritoneal mesothelioma in humans (and it possibly increases the risk of cancer at other sites, larynx, renal, colon and rectum). Deaths from peritoneal mesothelioma are not considered, quoted or counted in the INSERM report, which resulted in a possible underestimation of the causes of deaths attributable to asbestos that are potentially preventable.

The INSERM Document extensively quoted the available data in France capable of characterizing the exposure profile for environmental, para-occupational and occupational exposures to asbestos. The available data are considered insufficient for use in quantitative estimates for lung tumors and mesothelioma for level and gradient of risk across a range of exposure levels.

The INSERM Document thus presents estimates of risks for the occupational and environmental permissible levels in France.

This methodology is not wrong, in spite of its shortcomings, as long as it is clearly understood that the predicted cases of deaths are not based on the exposure profile of the French population. The condition of exposure are hypothetical.

It should be noted that the same approach and assumptions of the INSERM Document in calculating the likely lifetime risk from non-occupational exposures have been use by other government or public authorities, including the Ontario Royal Commission, for the same level of exposures possibly encountered in buildings and the same age groups.

The estimates of lung and mesothelioma deaths for the French situation presented in the INSERM Report for different intensity of exposure, duration and age at first exposure are derived from the above model. As the Report clearly states the estimates are derived from exposures occurred in industrial settings and applied, with several intrinsic limitations, to exposures of a different order of magnitude.

The INSERM Document sufficiently stresses the limitations and measurements errors in both exposure and response variates of the available data and the consequent uncertainties in risk estimates.

For this part, in conclusion, the INSERM Report faces the intrinsic problems of quantitative risk assessment. “Quantitative risk assessment may be an effective tool for policy decision-making on potential health risks, depending on the appropriateness of the model and the completeness of the scientific database” *(Hardy TS, Weill H. Crystalline silica: risks and policy. Environ Health Perspect 103: 152-155, 1995).*

The model used in the INSERM Document is the one considered most appropriate by individual scientists and groups of experts, whereas the set of data used are simply, with all their limitations, the scientific literature published on the cancer risks of asbestos.

The positive aspect of the useful exercise of the INSERM Document lies in the fact that it provide a clearer basis for risk management decision than qualitative evaluations of the carcinogenic risk posed by asbestos exposure.

If after a century from the industrial use of asbestos we still lack proper data to produce consensual quantitative risk assessments, in the presence of cancer risks clearly demonstrated for asbestos exposures, the uncertainties in quantitative risk assessments could results in options for the health authorities, which depend from the availability of substitutes, the economical feasibility and several other factors. Risk estimates in fact are ultimately incorporated into social, economic, political and value judgments.

We should, however, avoid using the uncertainties in quantitative risk assessment to disclaim the value of public health actions.

Fig 1

CONSUMPTION OF RAW ASBESTOS

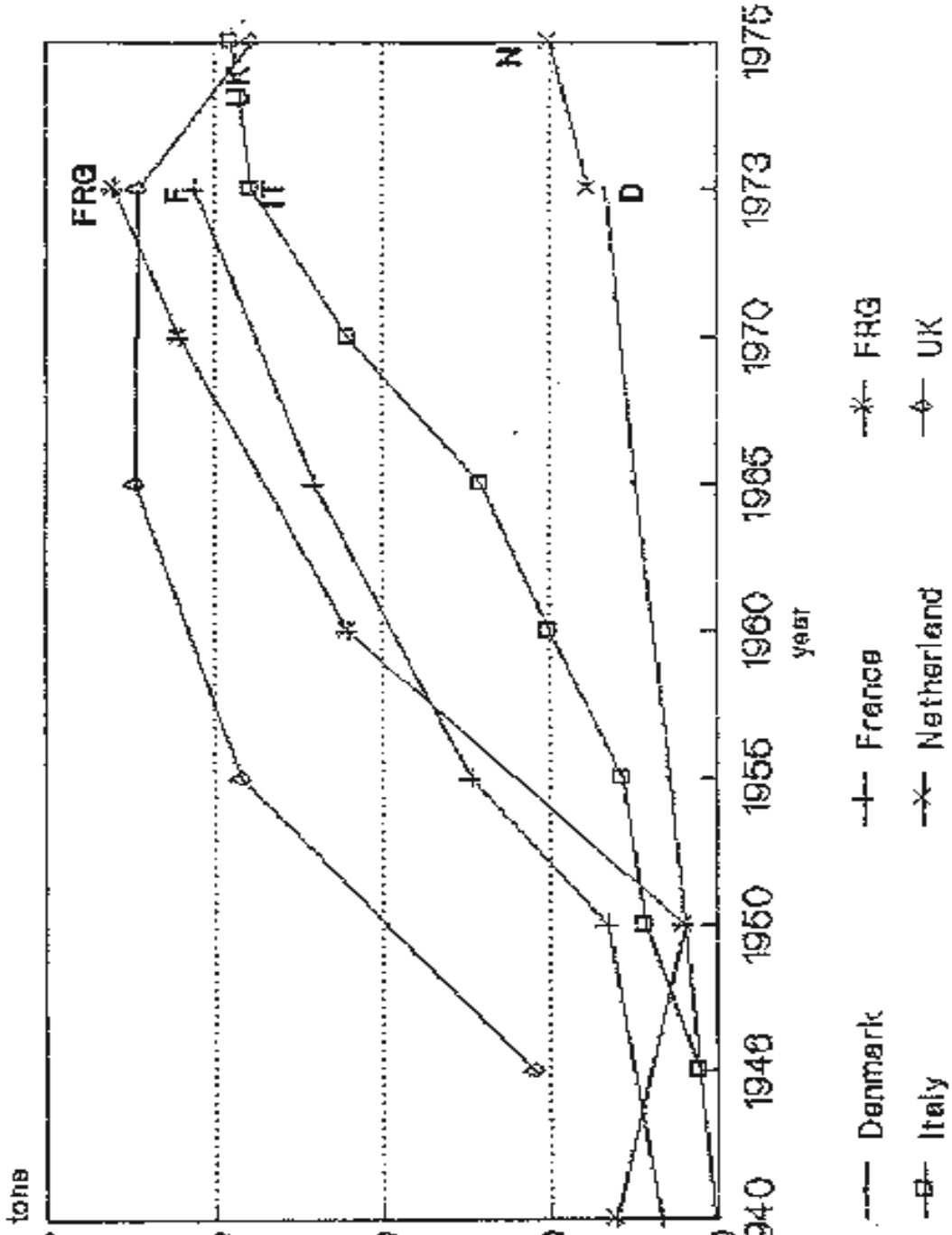
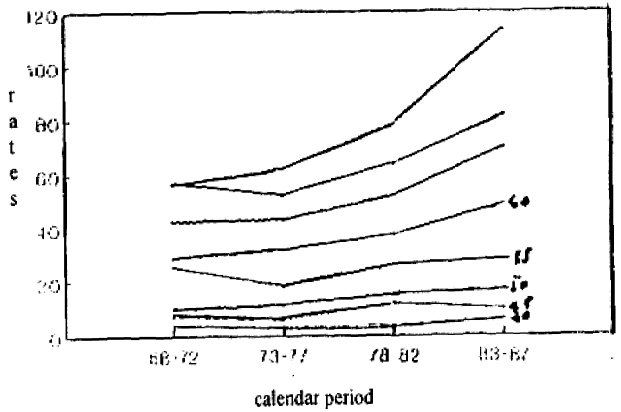


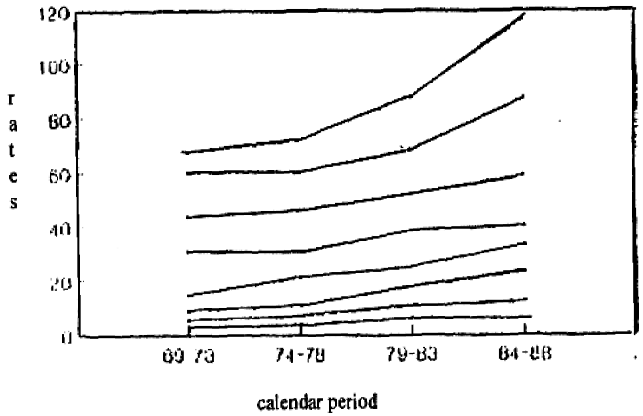
Fig. 2

Pleural Tumour Rates in Italy
by calender periods and age groups



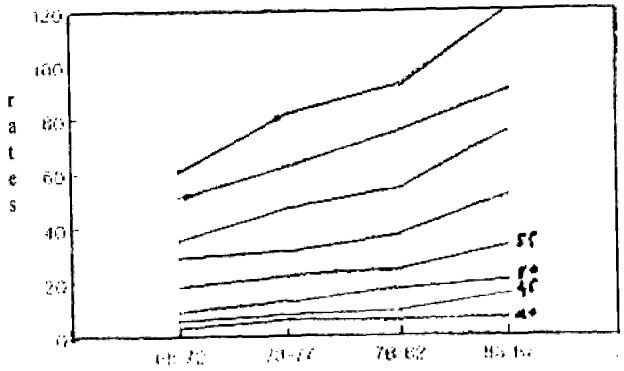
age groups : 40 45, ... 75-80

Pleural Tumour Rates in F.R. of Germany
by calender periods and age groups



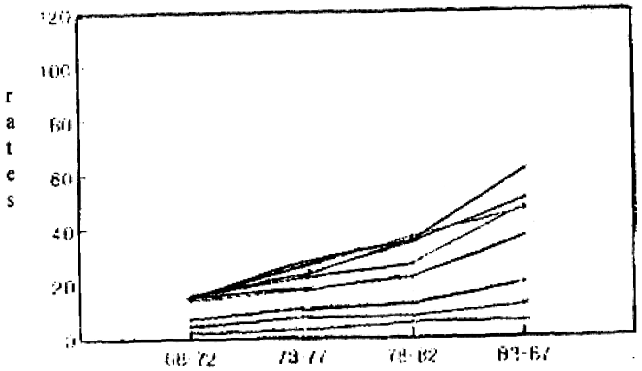
age groups : 40 45, ... 75-80

Pleural Tumour Rates in France
by calender periods and age groups



age groups : 40 45, ... 75-80

Pleural Tumour Rates in United Kingdom
by calender periods and age groups



age groups : 40 45, ... 75-80

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