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Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade
Chemical Review Committee
First meeting
Geneva, 11–18 February 2005
Item 7 (m) of the provisional agenda*

Inclusion of chemicals in Annex III of the Rotterdam Convention: Review of notifications of final regulatory actions to ban or severely restrict a chemical: Chrysotile asbestos

Chrysotile asbestos: supporting documentation from the European Community

Note by the secretariat

The secretariat has the honour to provide, in the annex to the present note, the supporting documentation received from the European Community in support of its notification of final regulatory action on chrysotile asbestos. The documentation considered by the interim Chemical Review Committee at its third session is attached in annex I. An additional paper (Opinion on risk to human health from chrysotile asbestos and organic substitutes, opinion expressed at the thirty-fifth plenary meeting of CSTEE, Brussels, 17 December 2002) is attached in annex II.

* UNEP/FAO/RC/CRC.1/1.

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Annex I

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT
Directorate C – Environment and Health
ENV.C.3 - Chemicals

Brussels, 11 -06- 2001
ENV.C.3 JF/jg D2001 430251

Mr. J Willis
Interim Secretariat for the Rotterdam Convention
UNEP Chemicals
11-13 Chemin des Anémones

CH-1219 Châtelaine, Geneva

Dear Mr. Willis,

Thank you for your letter of 1 May requesting the supporting documentation referenced in sections 2.3 and 2.4 of the European Community's recent notification of a final regulatory action in relation to asbestos.

The referenced documents are:

- Directive 1999/77/EC of 26 July 1999 (Official Journal of the European Communities L 207 of 6 August 1999, page 18) (available at http://europa.eu.int/eur-lex/en/search_lif_simple.html);
- The Opinion of the Scientific Committee on Toxicity, Ecotoxicity, and the Environment (SCTEE) of 15 September 1998 (available at http://europa.eu.int/comm/food/fs/sc/sct/out17_en.html); and
- World Health Organisation (WHO), Environmental Health Criteria, No. 203 – Chrysotile asbestos (available at http://www.who.int/dsa/justpub/add.htm).

I am enclosing a copy of the Directive, which was the latest of a series of regulatory actions in relation to asbestos. If you would like copies of the previous Directives, please let me know.

Also enclosed is a copy of the SCTEE opinion. One of the documents before the committee was a report by ERM for the European Commission on the risk posed by asbestos and substitute fibres. This contained, inter alia, a review of the risks of amphibole forms of asbestos. Relevant copy extracts from this report are also enclosed since these may be helpful to the secretariat and the interim Chemicals Review

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Committee in its future work in reviewing the notifications from both Australia and the European Community.

So far as the WHO documentation is concerned, it is assumed that this lengthy volume is readily available to all parties. I am therefore only enclosing a copy of the summary of the main findings and conclusions.

I hope that this material is sufficient. However please do not hesitate to contact me if additional information or further clarifications are required.

Yours sincerely,

Julian FOLEY

Enclosures:

Directive 1999/77/EC
SCTEEE opinion
ERM report (extracts)
WHO, EHC 203 (summary)

COMMISSION DIRECTIVE 1999/77/EC

of 26 July 1999

adapting to technical progress for the sixth time Annex I to Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (asbestos)

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations [1], as last amended by Directive 1999/43/EC of the European Parliament and of the Council [2], and in particular Article 2a thereof, introduced by Council Directive 89/678/EEC [3];

(1) Whereas the use of asbestos and products containing it can, by the release of fibres, cause asbestosis, mesothelioma and lung cancer; whereas placing on the market and use should therefore be subject to the severest possible restrictions;

(2) Whereas Council Directive 83/478/EEC [4] amending for the fifth time Directive 79/769/EEC specified that the crocidolite type of asbestos fibre and products containing it may, with three possible exceptions, no longer be placed on the market and used; whereas this same Directive established obligatory labelling provisions for all products containing asbestos fibres;

(3) Whereas Council Directive 85/610/EEC [5] amending for the seventh time Directive 76/769/EEC specified that asbestos fibres can no longer be placed on the market and used in toys, materials and preparations applied by spraying, retail products in powder form, smoking accessories, catalytic heaters, paints and varnishes;

(4) Whereas Commission Directive 91/659/EEC [6] adapting to technical progress Annex I of Directive 76/769/EEC specified that all of the amphibole type of asbestos fibres and products containing them may no longer be placed on the market and used; whereas this same directive specified that the chrysotile type of asbestos fibre and products containing it may no longer be placed on the market and used for fourteen categories of products;

(5) Whereas the Scientific Committee on Toxicity, Ecotoxicity and the Environment was consulted on the health effects of chrysotile asbestos and its substitutes;

(6) Whereas there are now available for most remaining uses of chrysotile asbestos substitutes or alternatives which are not classified as carcinogens and are regarded as less dangerous;

(7) Whereas no threshold level of exposure has yet been identified below which chrysotile asbestos does not pose carcinogenic risks;

(8) Whereas exposure of workers and other users of asbestos-containing products is extremely difficult to control and may greatly exceed current limit values on an intermittent basis and this category of exposure now poses the greatest risks for development of asbestos-related diseases;

(9) Whereas an effective way of protecting human health is to prohibit the use of chrysotile asbestos fibres and products containing them;

(10) Whereas the scientific knowledge about asbestos and its substitutes is continually developing; whereas the Commission will therefore ask the Scientific Committee on Toxicity, Ecotoxicity and the Environment to undertake a further review of any relevant new scientific data on the health risks of chrysotile asbestos and its substitutes before 1 January 2003; whereas this review will also consider other aspects of this directive, in particular the derogations, in the light of technical progress; whereas, if necessary, the Commission will propose appropriate changes to legislation;

(11) Whereas a period of adjustment is required to phase out the marketing and use of chrysotile asbestos and products containing it; whereas this period should be longer for diaphragms used for electrolysis in existing installations because the risk of exposure is extremely low and more time is necessary to develop suitable alternatives in this safety-critical application; whereas the Commission will review this derogation before 1 January 2008 after having consulted the Scientific Committee on Toxicity, Ecotoxicity and the Environment;

[1] OJ L 262, 27.9.1976, p. 24.
[2] OJ L 166, 1.7.1999, p. 87.
[3] OJ L 398, 30.12.1989, p. 24.
[4] OJ L 263, 24.9.1983, p. 33.
[5] OJ L 375, 31.12.1985, p. 1.
[6] OJ L 363, 31.12.1991, p. 36.

(12) Whereas this Directive is without prejudice to Council Directive 89/391/EEC laying down minimum requirements for the protection of workers [1], and its individual Directives within the meaning of Article 16(1) of that Directive, in particular Council Directive 90/394/EEC of 28 June 1990 on protection of workers from the risks related to exposure to carcinogens at work [2] as amended by Directive 97/42/EC [3];

(13) Whereas Council Directive 91/382/EEC [4] amending Directive 83/477/EEC on the protection of workers from the risks related to exposure to asbestos at work provides a framework of control where activities may expose workers to asbestos dust;

(14) Whereas this Directive is whithout prejudice to Commission Directive 98/12/EC [5] adapting to technical progress Council Directive 71/320/EEC on the approximation of the laws of the Member States relating to the braking devices of certain categories of motor vehicles and their trailers;

(15) Whereas the measures provided for in this Directive are in accordance with the opinion of the Committee for the adaptation to technical progress of the Directives on the removal of technical barriers to trade in dangerous substances and preparations,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Annex I to Directive 76/769/EEC is hereby adapted to technical progress as set out in the Annex hereto.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 1st January 2005 at the latest and shall immediately inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to the Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

2. Member States shall communicate to the Commission the main provisions of national law which they adopt in the field covered by this Directive.

3. From entry into force of this Directive to 1st January 2005, Member States may not allow the introduction of new applications for chrysotile asbestos on their territories.

Article 3

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Communities*.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 26 July 1999.

For the Commission

Karel VAN MIERT

Member of the Commission

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[1] OJ L 183, 29.6.1989, p. 1.
[2] OJ L 196, 26.7.1990, p. 1.
[3] OJ L 179, 8.7.1997, p. 4.
[4] OJ L 206, 29.7.1991, p. 16.
[5] OJ L 81, 18.3.1998, p. 1.

ANNEX

In Annex I to Directive 76/769/EEC point 6 shall be replaced by the following point:

'6.1. Crocidolite, CAS No 12001-28-4 Amosite, CAS No 12172-73-5 Anthophyllite asbestos, CAS No 77536-67-5 Actinolite asbestos, CAS No 77536-66-4 Tremolite asbestos, CAS No 77536-68-6	6.1. The placing on the market and use of these fibres and of products containing these fibres added intentionally shall be prohibited
6.2. Chrysotile, CAS No 12001-29-5	6.2. The placing on the market and use of this fibre and of products containing this fibre added intentionally shall be prohibited. However, Member States may except diaphragms for existing electrolysis installations until they reach the end of their service life, or until suitable asbestos-free substitutes become available, whichever is the sooner. The Commission will review this derogation before 1 January 2008. The use of products containing asbestos fibres referred to in points 6.1 and 6.2 which were already installed and/or in service before the implementation date of Directive 1999/77/EC by the Member State concerned shall continue to be authorised until they are disposed of or reach the end of their service life. However, Member States may, for reasons of protection of health, prohibit within their territory the use of such products before they are disposed of or reach the end of their service life. Without prejudice to the application of other Community provisions on the classification, packaging and labelling of dangerous substances and preparations, the placing on the market and use of these fibres and of products containing these fibres, as authorised according to the preceeding derogations, may be permitted only if the products bear a label in accordance with the provisions of Annex II to Directive 76/769/EEC.'

Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) - Opinion on Chrysotile asbestos and candidate substitutes expressed at the 5th CSTEE plenary meeting, Brussels, 15 September 1998

1. Background

Of the options proposed by Directorate General III of the European Commission, the CSTEE chose, in the first instance, the following as the simplest for consideration:

"On the basis of the available data, do any of the following substitute fibres pose an equal or greater risk to human health than chrysotile asbestos?

- Cellulose fibres

- PVA fibres

- P-aramid fibres

Particular consideration should be given to the relative risk to para-occupational workers and other users of the asbestos-containing products in comparison to non-asbestos products"

The CSTEE acknowledged the existence of risks for fibre-exposed workers in occupations (e.g. building maintenance, construction workers) other than mining, processing and using asbestos materials. It was also aware that in some circumstances asbestos fibres in the atmosphere in the general (non-occupational) environment have reached concentrations producing damage or creating concern. Nevertheless, the CSTEE felt that its terms of reference allude, on a qualitative basis, to the inherent hazardous properties of the materials to be compared. It is obvious that for chrysotile, for its candidate substitutes, as well as for any environmental hazard, quantitative risk assessment is also determined by dose and therefore by environmental concentrations.

The CSTEE terms of reference did not include potential hazards and risks for the environment of any of the materials taken into consideration. The CSTEE understands that Chrysotile asbestos may

be replaced, in some of its uses, by non-fibrous materials, including polyvinylchloride (PVC), whose potential hazards are out of the scope of the present opinion.

All documents that were submitted to the CSTEE were examined in detail. The documents have been listed by the CSTEE Secretariat as CSTEE/97/2 Adds 1-42 and where appropriate have been quoted in the text. A recent report dealing directly to the question posed to the CSTEE was issued by the University of Leicester Institute for Environment and Health *"Chrysotile and its substitutes: a critical evaluation"* on 6 April 1998 (CSTEE 97/2 Add. 18). Thus, particular attention was given to other documents commenting, or criticising it.

The problem of whether or not there is a safe level of chrysotile exposure, raised by some documents (CSTEE 97/2 Adds. 20, 21, 22, 34, 35) submitted by the European Advisory Council of the Asbestos International Association and by Spanish scientists was considered outside the terms of reference of the Committee. Chrysotile is a proven carcinogen and there is not sufficient evidence that it acts through a non-genotoxic mechanism. Thus a cautionary approach is that there is no threshold for the carcinogenic effect of this agent. Regarding the candidate substitutes, there is neither evidence of carcinogenicity nor reliable toxicological information for identifying no effect levels, if any. Thus, a consideration of the issue of thresholds, at this point in time, would be non-productive.

References to published papers are numbered throughout the text and quoted in section 8 of the present document. Only a small number of the reviewed studies were addressed to direct comparisons between the effects of the different types of fibres to be considered by the CSTEE. No attempt has been made to verify that studies relevant to the question posed to the CSTEE have been exhaustively identified. Nevertheless, the CSTEE believes that no study that may change its conclusions (see paragraph 7) has been omitted from consideration.

2. Long-term carcinogenic effects in exposed humans

Epidemiological studies on workers exposed to chrysotile have been reviewed on several occasions. The International Agency for Research on Cancer (1) has recognised that there is sufficient evidence of carcinogenicity for all forms of asbestos (including chrysotile). A similar evaluation has been expressed in a review on chrysotile prepared by the International Programme on Chemical Safety - IPCS (2), which summarises the present knowledge in the following terms:

"The overall relative risks for lung cancer are generally not elevated in the studies of workers in asbestos, cement production and in some of the cohorts of asbestos-cement production workers. The exposure-response relationship between chrysotile and lung cancer risk appears to be 10-30 times higher in studies of textile workers than in studies of workers in mining and milling industries... The reasons for this variation in risk are not clear...

Estimation of the risk of mesothelioma is complicated ... by factors such

as the rarity of the disease, the lack of mortality rates in the populations used as reference, and problems in diagnosis and reporting. In many cases ..., crude indicators have been used, such as absolute numbers of cases and deaths ...

... the largest number of mesotheliomas has occurred in the chrysotile mining and milling sector. All the observed 38 cases (in Quebec) were pleural with the exception of one ... None occurred in workers exposed for less than 2 years. There was a clear dose-response relationship, with crude rates of mesotheliomas (cases/1000 person-years) ranging from 0.15 for those with cumulative exposure of less than 3530 million particles per cubic meter-years .. to 0.97 for those with exposures of more of more than 10590 mpcm-years ...

There is evidence that fibrous tremolite causes mesothelioma in humans. Since commercial chrysotile may contain fibrous tremolite, it has been hypothesised that the latter may contribute to the induction of mesotheliomas in some populations exposed primarily to chrysotile. The extent to which the observed excess of mesothelioma might be attributed to the fibrous tremolite content has not been resolved".

The CSTEE endorses these conclusions. Notice was taken of recent updates of the prospective mortality studies among miners in Quebec (3, 4, 5, 6) which lead the authors to stress further the "tremolite hypothesis" on the basis that: a) in miners and millers in Quebec virtually all of the risks for both mesothelioma and lung cancer have been conferred by exposure to chrysotile in the areas known to be the most heavily contaminated with tremolite and b) even at the most hazardous mines and mills only workers with long and heavy exposure seem to be at any increased risk of either lung cancer or mesothelioma.

The CSTEE does not believe that these new estimates detract from the evaluation that chrysotile is a human carcinogen. Mesotheliomas have been recently described in women living in the mining area of Quebec (7). This type of tumour has also been reported in workers extracting chrysotile in Italy (see 8 for most recent update), and China (9), as well as in studies in the asbestos-cement production, textile and friction material manufacture where commercial chrysotile but no amphiboles were used (2). It must be recognised that in practice it is not possible to know the precise composition (and extent of contamination by amphiboles, if any) of commercial chrysotile used in different settings, including those which have been investigated in epidemiological studies. Lung cancer risk estimates vary up to a factor of 1:50 between chrysotile miners and textile workers exposed to commercial chrysotile and this may well be due to different levels of exposure and/or to changes brought about by processing in the morphology of the fibres (10).

No epidemiological studies or observations in humans of long term effects of p-aramid or PVA have been reported in the scientific literature, probably because of the limited number of person-year-observation corresponding to the likely latent period of human cancer. In fact, p-aramid has been sold commercially since 1972 but the production in fibrous form started more recently (11). PVA has been

produced commercially since 1936 (12).

A recent review (13) summarises published studies on 4 cohorts of workers exposed to cellulose fibres. The underlying activities were paperwood, pulp and paper, soft paper mill and cellulose production. Excesses of cancer deaths were reported in some of the studies but no consistent target site emerges from these studies. An excess of lung cancer deaths in the study addressed to the pulp and paper industry was not standardised for smoking habits.

3. Effects other than cancer in exposed humans

The potential of chrysotile to induce non-neoplastic lung damage has been known for a long time. As summarised by the IPCS (2):

"The non-malignant diseases associated with exposure to chrysotile comprise a somewhat complex mixture of clinical and pathological syndromes not readily definable for epidemiological study. The prime concern has been asbestosis, generally implying a disease associated with diffuse interstitial pulmonary fibrosis accompanied by varying degrees of pleural involvement.

Studies of workers exposed to chrysotile in different sectors have broadly demonstrated exposure-response or exposure-effect relationships for chrysotile-induced asbestosis, in so far as increasing levels of exposure have produced increases in the incidence and severity of disease. However, there are difficulties in defining this relationship, due to factors such as uncertainties in diagnosis and the possibility of disease progression on cessation of exposure.... Asbestotic changes are common following prolonged exposure of 5 to 20 f/ml".

There is uncertainty and debate regarding whether the two pathological end-points of asbestosis and lung cancer are independent or whether fibrosis is a necessary pre-requisite for cancer (14). For all forms of asbestos, the associations with both end points have broadly similar dose-response relationships, similar latent periods and depend in the same way on fibre length (15).

To the knowledge of the CSTEE, no cases of lung fibrosis have been reported among workers exposed to either p-aramid, cellulose or PVA fibres. In fact, the medium and long-term effects of each of these three agents on the lung function and morphology have been investigated to a limited extent.

One study failed to demonstrate any short-term (up to one year) effect on respiratory function of exposure to p-aramid fibres and SO2 compared to a control group that may have been inadequate (16). Dermatoses may occur in workers exposed to p-aramid, at an unknown frequency (17).

As for cellulose fibres, the above mentioned study on workers in the soft paper mill production unit (13) exhibited excess mortality from chronic obstructive pulmonary disease and asthma, with no excess of

cancer deaths (which renders unlikely confounding by tobacco). Workers in this unit also exhibited a decrease in lung vital capacity and residual pulmonary volume, a finding considered by the authors to represent non specific reactions to the heavy exposure to paper dust in the mill.

4. Long-term effects in laboratory animals

In rats, chrysotile has produced mesotheliomas and lung carcinomas after inhalation and mesotheliomas after intrapleural administration. It induced mesotheliomas in hamsters following intrapleural administration and peritoneal mesotheliomas in mice following intraperitoneal injection. Results of experiments in which chrysotile was given orally to rats or hamsters have been equivocal (1). For most of these experiments, it is not known whether and to which extent the chrysotile, which was administered to animals, was contaminated with amphiboles.

The carcinogenicity of para-aramid fibrils has been tested in one adequately conducted inhalation study in rats (18). The pathology (and thus the underlying biological significance) of keratinising lung lesions found in ten rats (of an original number of 229) has been the object of a series of revisions (see review in 12) by international panels of animal pathologists. It has been concluded that these lesions are non-neoplastic and irrelevant to evaluation of cancer risks for humans. Limited data from experiments by intraperitoneal injection of p-aramid to rats did not suggest carcinogenic effects (11).

No adequate long-term carcinogenicity experiment with either cellulose fibres of PVA has been reported in the published literature (19).

5. Toxicity

Recent studies have compared the clearance of p-aramid and chrysotile fibres from rat and hamster lung after inhalation at equal target concentrations (20-22). P-aramid fibrils were clearly less biopersistent overall than chrysotile. The changes over time in the numbers of fibres remaining in the lung, and in their size distribution, suggested that in the case of p-aramid the number of shorter fibrils was increased initially by fragmentation of longer ones, and then decreased. This was confirmed in a more recent sub-chronic inhalation study with p-aramid in rats (23). The longer chrysotile fibres, on the other hand, did not fragment and were preferentially retained, presumably because they were too long to be cleared by alveolar macrophages. It is accepted that in general only longer fibres can be carcinogenic (see section 6).

In another study, high doses of p-aramid caused an increase in lung-cell proliferation, though the effect was small and had disappeared in the rat by 5 days after the end of the 2-week exposure period, and by 1 month in the hamster. At the same level of exposure, chrysotile markedly increased cell proliferation in airway, alveolar and sub-pleural tissue during 0-3 months post-exposure (24).

Available data regarding the toxicity of cellulose fibres have recently been reviewed (13). These fibres were found to be toxic to mouse macrophages in vitro, as shown by the release of lactic dehydrogenase. This was not confirmed subsequently with rat macrophages, although a high dose of cellulose did cause a transient inflammatory response in vivo (25). Cellulose fibres have been shown to be as effective as chrysotile in stimulating macrophages to release inflammogenic substances such as interleukin-1, and were more effective than asbestos in stimulating the release of prostaglandins. The interpretation of this finding is difficult. In another recent study, cellulose powder instilled into rat lung produced a persistent granulomatous response (26), but the high dose used would certainly have caused "overload" and thus inhibited normal clearance by macrophages.

Very little information is available on the pulmonary toxicity of PVA fibres in laboratory animals.

As for genotoxicity, a search of the relevant experiments in the databank of the *Istituto Superiore di Sanità*, Rome (whose exhaustivity was confirmed through a parallel search at the International Agency for Research on Cancer) produced the following summary evaluations:

Chrysotile (CAS 12001-29-5) is clastogenic and aneugenic in mammalian cells in vitro. Tests for SCE and gene mutation induction in mammalian cells are contradictory. Negative results are reported in bacterial systems and in an UDS assay. In vivo, no clastogenic effect is observed in bone marrow after ip or oral administration. The latter results should be evaluated with caution due to the lack of information on the availability of chrysotile to the target tissue.

P-aramid (CAS 24938-64-5) was inactive in gene mutation tests in bacteria in mammalian cells. No adequate evaluation of genotoxicity can be done.

No data have been found for polyvinyl alcohol (CAS 9002-89-5) and for cellulose fibres (CAS 9004-34-6).

6. Characteristics of the fibres being compared

According to the standard definition, a fibre has a length/diameter ratio of at least 3:1. Falling speed in air is proportional to the square of the diameter and directly proportional to bulk density, whereas fibre length is less significant in this context. Thus, diameter determines the length of time a fibre will remain suspended in air and air concentration. Further, the "respirable fraction" excludes almost completely mineral fibres whose diameter exceeds 3 microns and organic fibres whose diameter exceeds 7 microns. It is commonly believed that a potential carcinogenic hazard may exist with fibres longer than 8-10 *micra*, diameter smaller than 3 *micra* and a length/diameter ration greater than 3:1 (16).

After inhalation, durability of fibres is a major determinant of integrated dose. Long fibres deposited in the alveoli are cleared slowly by

macrophages. Residence time (i.e. biopersistence) is determined by the dissolving rate, which depends on the fibre chemical composition and on their ability to undergo fragmentation (a transverse break of the filament into shorter pieces which may not meet the 3:1 ratio), either by mechanical flexure within the lung tissue or by partial dissolution in the acidic environment within the macrophage. Fibrillation, instead, is the process through which respirable smaller fibres are produced and is thus an indicator of carcinogenic risk.

The following are the characteristics of the fibres considered in the present report (27):

	Length	Diameter	Fibrillation
	Micra	*micra*	
Chrysotile	> 5	< 1	+++
PVA	> 5	10-16	+/-
P-aramid	> 5	10-12	+ (need much abrasion to produce many fibrils)
Cellulose	> 5	12-40	exposure data suggest very limited fibril production

7. Conclusion

A major concern with fibres is their carcinogenic potential. There is sufficient evidence that all forms of asbestos, including chrysotile, are carcinogenic to man. No evidence of fibre-caused cancer occurrence in man is available for any of the three candidate substitutes. Admittedly, for cellulose fibres, this may reflect limitations in the design of the underlying studies, whereas the lack of epidemiological studies on PVA and p-aramid may be due to the relatively short time elapsed since the onset of industrial uses of these materials.

Lung fibrosis is a well-known consequence of chrysotile exposure, but to-date no case has been reported in workers exposed to any of the three candidate substitute fibres.

Chrysotile is an established experimental carcinogen in laboratory animals. Of the candidate substitutes, only p-aramid has been tested in adequately designed long-term inhalation experimental studies, which did not provide evidence of carcinogenicity.

Overall, acute and subacute toxicity data on the three substitute fibres are very meagre and do not allow for a proper comparison with chrysotile, with the possible exception of p-aramid, which in a series of experiments in rats was shown to cause less inflammation and cellular proliferation than chrysotile given at similar doses. In vitro, the ability of cellulose to induce certain inflammation-related changes seems greater than that of chrysotile.

Fibre characteristics, such as size, respirability, biopersistence and

fragmentability, indirectly provide elements for an overall comparison of potential effects between different types of fibres. Current knowledge on the mechanisms of long-term toxicity of fibrous materials in humans based on such characteristics is consistent with the inference that substitutes are less harmful than commercial chrysotile.

On the basis of the above, in the opinion of the CSTEE the ability of cellulose, PVA or p-aramid fibres to induce cancer or fibrosis of the lung in man is likely to be lower than that of chrysotile.

The limited amount of toxicological studies on the three candidate substitutes leaves wider margins of uncertainty in order to predict their ability to produce effects other than cancer and lung fibrosis. Nevertheless, the available data on current levels of exposure and fibre characteristics suggest that the amount of fibres of critical size and shape reaching the human pulmonary alveoli is very limited.

Thus, both for the induction of lung and pleural cancer and lung fibrosis - i.e. the end point conditions investigated to a greater extent - and for other effects, it is unlikely that either cellulose, PVA or p-aramid fibres pose an equal or greater risk than chrysotile asbestos. With regard to carcinogenesis and induction of lung fibrosis, the CSTEE has reached a consensus that the risk is likely to be lower.

The CSTEE recommends these conclusions not to be interpreted in the sense that environmental control of the workplaces where the substitute fibres are produced or used can be relaxed. Finally the CSTEE strongly recommends expansion of research in the areas of toxicology and epidemiology of the substitute fibres as well as in the technology of development of new, thicker (less respirable) fibres.

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CSTEE/97/2

Recent assessments of the hazards and risks posed by asbestos and substitute fibres, and recent regulation of fibres world-wide - Final report - November 1997 - DG III.

CSTEE/97/2 - Add. 1

A constructive commentary on :

The June 1997 draft final report prepared for the European Commission DGIII by environmental resources management, Oxford, entitled "recent assessments of the hazards and risks posed by asbestos and substitute fibres, and recent regulation of fibres world-wide" - GW Gibbs, JMG Davis, J. Dunnigan and RP Nolan - 6/9/1997.

CSTEE/97/2 - Add. 2

Answers and comments to the terms of reference regarding the document prepared by ERM for the DGIII. - Fax from Dr. Lambré (INERIS) - 5/1/1998.

CSTEE/97/2 - Add. 3

CSTEE - Chrysotile asbestos - Fax from Dr. Dybing (Folkehelsa) - 9/1/1998.

CSTEE/97/2 - Add. 4

A note on the document - dated November 1997 - "Recent assessments of the hazards and risks posed by asbestos and substitute fibres, and recent regulation of fibres world-wide", commissioned by DGIII prepared to Environmental Resources Management, Oxford (ERM)

Made by Dr. B. Terracini - 30/1/1998.

CSTEE/97/2 - Add. 5

Rapport ERM à la DG III, Référence 4259 Novembre 1997. - Fax envoyé par Prof. Dr. R. Wennig - Luxembourg, 4/2/1998.

CSTEE/97/2 - Add. 6

Observations of the EAC (European Advisory Committee of the A.I.A.) with regard to the report of 9th February 1998 of the Scientific Committee on Toxicity, Eco-toxicity and the Environment of the DG XXIV (Chrysotile).

From A.I.A. (Asbestos International Association).

CSTEE/97/2 - Add. 7

The Health Risks from Chrysotile - Discussion between British and Canadian experts, Rose Court, 30 September 1997.

Draft report from Health and Safety Executive - 12/12/1997.

CSTEE/97/2 - Add. 8

Estimation of the continuous Emission of Asbestos in the Atmosphere.

By Dr.-Ing. J. Michatz (German Association of Fibre-Cement Industries).

CSTEE/97/2 - Add. 9

Cellulosefasern zur Herstellung von Faserzement.

By K. Uebersax-Ingold, U.F. Gruber - Universität Basel, Toxikologie (1992).

CSTEE/97/2 - Add. 10

Zur Charakterisierung einiger Ersatzfaserstoffe und deren Wirkung im Tierversuch.

By K.H. Friedrichs, M. Rosenbruch, H.W. Schlipköter - Heinrich-Heine-Universität, Düsseldorf (1990).

CSTEE/97/2 - Add. 11

Working group "limitations on marketing use of dangerous substances and preparations (asbestos).

By Dr. Rolf Packroff - Federal Institute for Occupational Safety & Health - Dortmund - 10/3/1998.

CSTEE/97/2 - Add. 12

Selected synthetic organic fibres - Environmental Health Criteria 151 - First draft prepared by Dr. M.E. Meek (Ottawa).

World Health Organisation, Geneva, 1993.

CSTEE/97/2 - Add. 13

In Vivo Pulmonary Toxicity of Cellulose in Rats (1995).

Article in Journal of Applied Toxicology, Vol. 16(2), 129-135 (1996).

CSTEE/97/2 - Add. 14

Chrysotile asbestos and candidate substitutes: proposed terms of reference.

DG III/C/4 - April 1998.

CSTEE/97/2 - Add. 15

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Cancer Mortality among Man-Made Vitreous Fibre Production Workers

Keywords : man-made vitreous fibres, lung cancer, occupational diseases, mesothelioma, man-made mineral fibres, cohort study.

P. Boffetta, ...Epidemiology - May 1997, Volume 8 Number 3.

CSTEE/97/2 - Add. 16

IEH report on Natural and man-made mineral fibres : UK research priorities - Report R3 from Medical Research Council - Institute for Environment and Health (1995).

CSTEE/97/2 - Add. 17

FINAL REPORT

European Commission DGIII

Recent Assessments of the Hazards and Risks Posed by Asbestos and Substitute Fibres, and Recent Regulation of Fibres Worldwide

November 1997

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Table 3.4 sets out the main comments made in the documents submitted about the risk from amphiboles.

There is a general consensus amongst the scientific community that all types of asbestos fibres are carcinogenic [*A1 (Royal Society of Canada)*] and can cause asbestosis, lung cancer and mesothelioma.

The level of hazard is dependent on fibre type and fibre size [*K9 (Meldrum/UKHSE)*]. The difference in 'disease potential' between chrysotile and amphiboles is most clearly defined in relation to mesothelioma.

There is a general consensus that amphiboles (and crocidolite in particular) pose a much greater risk of mesothelioma than does chrysotile. Whilst few cases of mesothelioma can be attributed to chrysotile, the reverse of this is true for amphiboles [*K9 (Meldrum/UKHSE)*]. There is at least a 10-fold lower risk of mesothelioma in workers exposed to chrysotile in comparison to amphiboles [*K4 (Gibbs et al)*].

Studies suggest that amphibole asbestos may result in the development of mesothelioma at lower levels of cumulative exposure than that required for lung cancer, although no reliable exposure-response curve can be produced for asbestos-induced mesothelioma in animals or humans [*K9 (Meldrum/ UKHSE)*]. This is supported by another paper [*K23 (Bignon)*] which states that mesothelioma can develop at doses of maybe 10 to 1,000 times lower than those required for broncho-pulmonary cancer.

The greater potency of amphiboles (and particularly crocidolite) in comparison to chrysotile, particularly in relation to mesothelioma, has been explained mainly by the greater durability of amphiboles in the lung (see Section 3.3). This explanation is supported by the analysis of fibre lung burden in mesothelioma victims [*I3 (Dunnigan)*].

Table 3.4 *The Risk from Amphiboles - Analysis of Submissions*

Submission	Summary of Information Presented
(A1) Royal Society of Canada - A Review of the INSERM Report on the Health Effects of Exposure to Asbestos 1996	The Expert Panel agrees that all asbestos fibres are carcinogenic, regardless of mineralogic nature. However, the Panel considers that particularly with regard to mesothelioma, the differences between chrysotile and amphiboles may have been underestimated by INSERM. The risks posed by amosite and crocidolite are probably higher than those from chrysotile, although not estimated by INSERM.
(C2) INSERM - Effects on Health of the Main Types of Exposure to Asbestos	The authors note that it has been difficult to make a comparison of the *in vitro* activity of amphiboles and chrysotile, but where possible, chrysotile appears less active than crocidolite on the basis of fibre numbers. *In vivo* experiments in animals have applied different methods of exposure, and in most, asbestos fibres have been shown to cause pulmonary tumours and forms of mesothelioma. All three fibres tested (chrysotile, amosite, crocidolite) produced tumours except for samples with smaller fibres. On the basis of fibre numbers (IUC samples) the results of in-vivo experiments in animals suggest that chrysotile is less active than the other two fibre types studied, although limited results are available to confirm this.
(I1) A.Churg - Chrysotile, Tremolite and Malignant Mesothelioma in Man	Analysis of lung asbestos content indicates that induction of mesothelioma by chrysotile requires, on average, as great a lung fibre burden as induction of asbestosis by chrysotile, whereas amphibole (amosite or crocidolite) induced mesotheliomas appear at a considerably smaller lung burden.
(I3) J.Dunnigan - Linking Chrysotile Asbestos with Mesothelioma	In addition to the observations made by Churg, many other cohorts of workers have been studied by various parties, and the observations and conclusions made indicate a difference in disease potential between chrysotile and amphiboles, particularly concerning mesothelioma. Results from these studies suggest that amphiboles are mainly responsible for mesothelioma.
(I7) J.C. Wagner - The Discovery of the Association Between Blue Asbestos and Mesothelioma and the Aftermath	There is significant evidence that crocidolite is the main fibre associated with mesothelioma. The association between amosite and mesothelioma is minimal relative to crocidolite. Cases due to tremolite have occurred mainly where exposure has been to chrysotile contaminated with tremolite, whereas there is little evidence of an association with uncontaminated chrysotile. It is important to recognise those cases of non-asbestos related mesothelioma.
(I10) Differences in Pathogenic Potential Between Asbestos Fibre Types	In terms of experimental evidence, the paper notes that past studies have not been consistent with epidemiological observations indicating greater potency of amphibole fibres than chrysotile in inducing pathogenesis. More recent work using both fibre mass and fibre number units of dose have confirmed the greater pathogenicity of amphiboles. In particular, confirmation is provided by *in vitro* models and inhalation experiments by Yegles et al (1993) and McConnell et al (1994).
K4) Gibbs et al - Health Risks Associated with Chrysotile - 1993 ICOH/IPCS Workshop	It is the majority view (of the workshop participants) that, based on extensive literature, differences exist in the risk of mesothelioma associated with different types of fibre; that there was at least a 10 fold lower risk of mesothelioma in workers exposed to chrysotile in comparison to amphiboles.

Submission	Summary of Information Presented
(I11) McDonald et al - The 1891-1920 Birth Cohort of Quebec Chrysotile Miners and Millers	Of the 33 deaths from mesothelioma in the cohort to date, 28 were miners and millers and five were employees of a small asbestos products factory where commercial amphiboles had been used. These mesotheliomas were primarily of the pleura. Preliminary analysis also suggests that the risk of mesothelioma was higher in the mines and mills at Thetford Mines than at those at Asbestos. More detailed studies of these differences and of exposure-response relations for lung cancer are under way. In particular, these 33 cases are the subject of a detailed study which focuses on the possible role of fibrous tremolite and amphiboles and to exposure-response. The proportion of mortality from mesothelioma in chrysotile miners and millers only, has reached 0.4%, although this is much lower than that already found in cohort exposed to commercial amphiboles at a much earlier stage of mortality.
(K9) M. Meldrum (HSE) - Review of Fibre Toxicology	In respect to the health effects of asbestos, the main findings of this review can be summarised as follows: • that all forms of asbestos may cause asbestosis, lung cancer and mesothelioma, but that the level of hazard is dependent on fibre type (amphiboles > chrysotile) and fibre size distribution (long > short). Any useful comparisons of disease incidence for different occupational cohorts should therefore account for both fibre type and airborne size distribution; • despite the large quantity of evidence for high and prolonged exposure to chrysotile, few cases of mesothelioma can be attributed to this form of asbestos - the reverse of which is true for amphiboles. This trend can be explained by the lower degree of biopersistence seen with chrysotile asbestos. Hence, for a fixed level of exposure, amphiboles pose a greater risk for developing mesothelioma compared to chrysotile; • studies suggest that amphibole asbestos may result in the development of mesothelioma at lower levels of cumulative exposure than that required for lung cancer, although no reliable exposure-response curve can be produced for asbestos-induced mesothelioma in animals or humans.
(K23) J. Bignon - Asbestos, the True Risks and the False Problems	Mesothelioma can develop at much lower doses, maybe ten to a thousand times lower than for broncho-pulmonary cancer. There is a consensus that mesothelioma is mainly associated with exposure to amphibole asbestos or mixtures of chrysotile and amphiboles which were often used. The study carried out with Professor Valleron (INSERM U263) clearly shows that in France there are three to four times less mesothelioma compared to the number in the UK and this is correlated to an impact of amphiboles which is three times lower in tonnage.
(K25) EAC-AIA - Recent Information on Amphibole Asbestos and Chrysotile	In response to the study by Peto et al, Weill & Hughes (1995) suggested the difference in patterns of mesothelioma between US and UK incidence could be explained by the greater exposure to amphiboles in the UK in the 1970s.
(L20) D. Liddell - Health Effects of Historical Exposures to Asbestos	The risks of cancer depend not only on the degree of exposure to asbestos fibres, but on the fibre type and industrial process in which such fibres are used. The majority of disease has been caused by crocidolite (and amosite to a lesser degree).. The risk of mesothelioma following exposure to chrysotile is very low (one order of magnitude less than from amosite, and two orders less than from crocidolite).

- CANADA
- Royal Society of Canada: Expert Panel on Asbestos Risk
- November 1996
- A REVIEW OF THE INSERM REPORT ON THE HEALTH EFFECTS OF EXPOSURE TO ASBESTOS: REPORT OF THE EXPERT PANEL ON ASBESTOS RISK

Key information:

- **Nature of Document:** Scientific review of the INSERM report of June 1996 by an independent expert panel
- **Type of asbestos considered:** 'Asbestos' in general, with reference to chrysotile and amphiboles, including crocidolite and amosite (see also INSERM Report)
- **Further differentiation between fibres:** Reference is made to differences in dimensions between and within different mineralogical types of asbestos - see also INSERM Report
- **Type of scientific evidence:** A review of experimental and epidemiological data, and conclusions and recommendations as set out in the INSERM Report
- **Assertions based on:** Those findings of the INSERM Report and of the Expert Panel on Asbestos Risk

In September 1996, the Canadian Department of Health commissioned an independent review of the INSERM Report (the 'Report') by the Royal Society of Canada, which in turn selected an expert panel on asbestos risk to carry out this request. The objective was to determine whether the characterisation of risks associated with exposure to asbestos in the Report was supported adequately by available data.

The structure of this review comprises a general section covering the Panel's collective views and a separate annex containing personal assessments compiled by the four Panellists expressing their individual views. The second draft report was reviewed by peer-reviewers, whose comments have, where accepted, been written into the final report. A summary of these comments is found in an appendix to this report. The review is presented as comments on the INSERM conclusions, quantitative risk assessment procedures and recommendations. However, the substantive findings of the review are presented in an executive summary.

Overall, although recognising the Report to be of scientific basis with regard to procedures and that it represented a commendable effort, it was partly felt that the evaluation of available data and the use of such data in risk assessment provided no new information and presented unjustified overestimates of the risk of current exposure. Furthermore, it was considered that the Report placed too greater emphasis on material from other authorities that supported INSERM's conclusions - without critical evaluation.

Four specific questions concerning the INSERM Report were posed by the Department of Health to which the Panel responded:

- as to whether all critical studies relevant to assessment of health risks were included, the Panel considered there to be an omission of several relevant papers from the Report, and that the Panel had a difference in view of the

adequacy of coverage: limited new information was presented, and it failed to adequately address the relevance of available studies to the issue of whether present exposure to asbestos was associated with increased risk;

- the presentation of critical studies in sufficient detail to justify the Report's conclusions concerning the characterisation of risk was considered, by the majority, that it was indeed lacking. In particular, estimates of asbestos-related deaths in France in 1996 were based on UK estimates without critical analysis of methodology or the applicability of such estimates to France. Furthermore, there was concern that the Report relied too much on summary data collated in secondary sources, rather than on direct consultation of original literature. It was also felt that the Report placed too greater emphasis on occupational exposures that could be of little significance to current exposures, rather than addressing indoor exposure. Although the Report recognises that occupational exposure is associated with increased risk of lung cancer and mesothelioma, the magnitude of risk associated with current exposures is unclear;
- in terms of whether there are limitations of the critical studies which have not been presented, the Panel considered that such limitations are explored to some degree, but there was a difference of opinion as to whether such limited exploration influenced the findings of INSERM;
- that whether there was sufficient critical discussion of issues relevant to the risk characterisation, the Panel was concerned that such risk characterisation was less satisfactory as actual data on exposure data was not utilised. Rather, the Report focused on dose-response relationships. This failure of the Report results in less specific guidance on the actual situation in France, and that assumed exposures are likely to be far greater than those experienced in France. The Panel felt that INSERM could have used typical building exposure asbestos levels from other countries in its quantitative risk assessment. Furthermore, the Report does not sufficiently address exposure assessment as a necessary component of risk assessment. Although there is an effort to apply data from France wherever possible, the conclusions are far from convincing as it does not attempt to apply actual exposure data to the risk assessments.

The Panel is in agreement with the following findings of the INSERM Report:

- that all asbestos fibres are carcinogenic, regardless of mineralogical nature;
- that longer and finer fibres pose greater risks of lung cancer, although there is greater evidence of risk for longer fibres;
- that the predominance of cases of mesothelioma in the male population is associated with occupational exposure to asbestos;
- that all regulatory agencies that have carried out quantitative risk estimates, have used the linear, no-threshold model for low dose and dose-rate exposures;
- that the exposure profile data for the French population is not sufficient for risk estimation, and estimates based on regulatory limits is the common approach. Although it should be emphasised that the assumed exposure on which the number of deaths is predicted is hypothetical and is higher than levels typically measured in buildings containing asbestos materials;
- that there are great reservations concerning the systematic removal of sprayed asbestos finishes from buildings;

- that considerable caution is essential in the strict control of occupational exposures, and the monitoring of such exposures;
- that research should be carried out on asbestos substitutes based on alternative fibres, materials or technologies.

However, the Panel considers that:

- the higher risk from long fibres appears to be true within a mineralogical type, but that evidence is weak across types. For example, a longer chrysotile fibre may not pose a greater associated risk than a slightly shorter crocidolite fibre;
- particularly with regard to mesothelioma, the differences between chrysotile and amphiboles may have been underestimated by INSERM;
- INSERM has probably overestimated the risk of mesothelioma from chrysotile exposure, and that the risks posed by amosite and crocidolite are probably higher than those from chrysotile, although not estimated by INSERM;
- compared with males, the evidence for the dominant role of occupational or para-occupational exposure in causing mesothelioma in females is less well established;
- in terms of risk assessment strategies, the linear, no-threshold model for low exposure is not the only possibility for predicting risks from low exposure, but evidence to demonstrate that a different hypothesis is more applicable is unavailable;
- errors may be involved in the transfer of risk coefficients calculated from high exposure settings, and/or from differing techniques of measurement;
- estimates of deaths from mesotheliomas and lung cancer in France refers to deaths in 1996, but from occupational exposures at a much earlier date - they are not deaths due to exposures in 1996. The Report is not explicit enough in this statement;
- as the report should indicate, measures based on optical phase contrast microscopy should not be used in developing risk assessments - direct transmission electron microscopy is the optimum choice for direct comparison with occupational experience;
- although there is scientific basis for INSERM's call for medical monitoring, it is uncertain how the value of such surveillance would be to individual workers.

Further Comments

No new data on exposure to asbestos or on mortality/morbidity from asbestos exposure is presented.

- FRANCE
- INSERM
- June 1996
- EFFECTS ON HEALTH OF THE MAIN TYPES OF EXPOSURE TO ASBESTOS

Key information:

- **Nature of document:** A scientific review/assessment of the hazards to human health of the main types of asbestos, taking into account previous work undertaken by other governmental expert analysis groups
- **Type of asbestos considered:** Amphibole and chrysotile asbestos
- **Further differentiation between fibres:** Differentiation is made between length and diameter of fibres, and reference is also made to 'commercial' chrysotile
- **Type of scientific evidence:** Both in vitro and in vivo experimental studies, together with epidemiological evidence
- **Assertions based on:** Available evidence from epidemiological and experimental studies

At the request of the Labour Relations Service and the French Health Directorate, this report has been prepared by a group of experts set up by INSERM in an attempt to assess the hazards to human health of the main types of asbestos, taking into account previous work undertaken by other governmental expert analysis groups in the United States, Canada and Britain.

The report is divided into three sections:

1) background summary of essential information relating to asbestos;

2) health hazards associated with exposure to asbestos, including a summary of scientific data from both experiments and epidemiological studies:
   - methodological problems posed by individual assessment of cases of exposure to asbestos;
   - what is known of the risks of cancer (mainly mesothelioma) in various circumstances of exposure to asbestos;
   - description of the development with time, the incidence of mesothelioma in industrial nations;
   - quantification of lung cancer and mesothelioma risks associated with occupational exposure to asbestos;
   - estimate of the risks of lung cancer and mesothelioma associated with low-level exposure.

3) the main consequences relating to the known health hazards of exposure, on the management of such risks, and recommendations.

The authors emphasise that in preparation of this report, they have not considered the risks associated with substitute fibres or the technical feasibility of replacing asbestos. Furthermore, that the management of the risks associated with exposure to asbestos was not within their competence, and the report does therefore not provide an opinion on:

- the relevance of exposure values as provided by regulation;

- the possibility of banning asbestos or systematically removing asbestos from buildings;
- the need to modify the procedures for providing compensation for diseases caused by exposure to asbestos.

It is noted that only the risks of lung cancer and mesothelioma are considered.

The report considers both *in vitro* and *in vivo* experimental studies that have been carried out using IUC-prepared amphibole and chrysotile fibres. With regard to *in vitro* studies, most research has focused on crocidolite and chrysotile. In these studies, both fibres caused no or few gene mutations, whereas they did lead to chromosomal mutations and heterozygote losses. Other results included chromosomal abnormalities in the short term. Based on these results, the authors suggest that cells exposed to asbestos fibres develop both structural and numerical aberrations corresponding well with cytogenic abnormalities seen in mesothelioma. Furthermore, that research carried out with asbestos fibres demonstrated that cells undergo phenotypic alterations associated with the transformation, also supporting the possibility of asbestos being a complete carcinogen. The authors note that it has been difficult to make a comparison of the *in vitro* activity of amphiboles and chrysotile, but where possible, chrysotile appears less active than crocidolite on the basis of fibre numbers. Furthermore, the authors state that it is difficult to extrapolate from fibre concentration used in such experiments to those experienced through human exposure.

In vivo experiments in animals have applied different methods of exposure, and in most, asbestos fibres have been shown to cause pulmonary tumours and forms of mesothelioma. All three fibres tested (chrysotile, amosite, crocidolite) produced tumours except for samples with smaller fibres, hence demonstrating that long fibres are more carcinogenic than short. The importance of dimension has also been demonstrated through intrapleural and intraperitoneal injections, and on the basis of fibre numbers (IUC samples) the results suggest that chrysotile is less active than the other two fibre types studied, although limited results are available to confirm this.

The authors indicate that few experimental studies have investigated the role of exposure at low doses over prolonged periods, and effects from large doses over short periods, hence all results must be viewed with care.

Results from both *in vitro* and *in vivo* experiments are, however, in agreement. In particular, a given fibre type can result in a different response depending on the proportion of long fibres in a sample, amongst other factors. *In vivo* animal experiments showed that for both inhalation or innoculation, a carcinogenic potential exists for both chrysotile and amphiboles, and in man the difference in potential for causing mesothelioma is explained by a lesser degree of durability or bio-persistence of chrysotile compared to amphiboles. Hence, experimental studies have shown the durability of chrysotile to be lower than that of amphiboles, but that a quantitative relationship between durability and tumorigenic capacity in animals has not yet been established.

In terms of epidemiological evidence, the authors of the report discuss the difficulties of assessing individual instances of exposure to asbestos, and

highlight the unknown and potentially large proportion of instances of 'hidden' exposure that could be the cause of some cases of mesothelioma.

In terms of the risk of mesothelioma associated with occupational exposure to asbestos, all types of epidemiological study suggest all types of asbestos, including chrysotile, are able to cause mesothelioma. However, it should be noted that present levels of occupational exposure are likely to be lower than past levels, but as these occupations employ large numbers of people, this would explain the high number of reported cases of mesothelioma. This is particularly so, as a number of high-risk occupations are cited which are not considered 'at-risk' and are subject to reduced monitoring and protection.

The existence of increased risk of mesothelioma among people exposed in para-occupational and domestic circumstances is well-established. However, it is impossible to know whether the high incidences observed can be attributed to early exposure or to significant cumulative exposure or both. The predominance of mesothelioma in males can be attributable to different conditions of exposure depending on the sexes. It is noted that the majority of studies in this area have been on exposure to tremolite, and studies on exposures related to the natural environment do not allow the role of chrysotile to be excluded in relation to pleural mesothelioma.

The authors continue by stating that the possibility of increased incidence or comparatively high death rates for forms of cancer attributable to asbestos in the geographical area concerned, due to para-occupational and occupational circumstances, can be expected. Therefore, it is difficult to confirm the existence of an industrial source of pollution by asbestos and any excessive incidence of cancer. However, if a population was subject to increased monitoring or a larger population subject to the same exposure, such an excess may then exist. Furthermore, various studies indicate the possibility of a risk of cancer (pleural mesothelioma) associated with exposure to industrial sources of asbestos. The authors note the difficulties of interpreting all studies analysed, and state finally that none of the studies provide an exposure-effect quantitative judgement.

In terms of exposure in buildings containing asbestos and in the urban environment, the authors report that there are practically no direct epidemiological data that can provide an answer to the question of possible risk. In particular, no epidemiological studies on urban exposure has ever been published to the authors' knowledge. When analysing the little data that does exist on exposure, it should be considered that at the current time, no direct and substantial epidemiological evidence is available allowing a decision to be made as to the health effects associated with passive-urban and intramural environmental exposure. However, this does not allow for such a risk to be ignored.

Analysis of the development of the incidence of mesothelioma in the male population of industrialised countries demonstrates a real pandemic. The development in the female population is seen to be parallel to that in males, suggesting the aetiology of female mesothelioma is largely due to occupational and para-occupational exposure. However, the predominance of such exposures means that it is very difficult to identify a possible

environmental component of intramural/urban origin. Furthermore, the authors consider that the increased incidence of early mesothelioma is not an argument for or against an effect of passive intramural/urban environmental exposure. Overall, the authors conclude that analyses confirm the important role of exposure to asbestos of occupational/para-occupational origin in both sexes, although this does not exclude the possibility of a role for passive intramural and urban environmental exposure. They report that only the implementation of long-term monitoring on a large scale of the incidence of mesothelioma together with systematic and thorough research on the circumstances of exposure to asbestos - especially in early cases would be likely to allow the assessment of a possible role of passive exposure of intramural/urban environmental origin. The authors therefore confirm there is no argument based on analysis of available epidemiological evidence (direct or indirect) 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 for an alternative credible model to be proposed.

In France, the authors report that the incidence of mesothelioma is currently relatively low compared to most other industrialised nations.

In terms of the quantification of the risks of lung cancer and mesothelioma associated with occupational exposure to asbestos, epidemiological observations from 47 cohorts exposed occupationally to asbestos show that occupational exposure to all varieties of asbestos is causally associated with an increase in the risk of lung cancer and mesothelioma - this increase becoming more marked as cumulative exposure increases for cancer, and higher, longer and older the exposure is for mesothelioma. For mesothelioma, it is also more marked in cases of partial/total exposure to amphiboles. The exposure to asbestos and tobacco consumption are shown to have a joint multiplying effect on the value of the relative risk of lung cancer.

The authors consider that arguments in support of the 'amphibole hypothesis' are clearly contradicted by the large amount of epidemiological data on the risks of lung cancer and mesothelioma associated with instances of exposure to asbestos, Furthermore, that the risks of mesothelioma are higher for exposure to amphiboles or to mixtures of amphiboles and chrysotile than for exposure to commercial chrysotile alone.

With regard to an estimate of the risks of lung cancer and mesothelioma at low levels of exposure (1 f/ml), the authors of the report state that there is no method allowing the direct and certain quantification of the risks of lung cancer and mesothelioma in human populations exposed to this level or below. The only approach is extrapolation, although this does not provide scientific certainty but represents an aid to reflection on the subject of controlling risks.

The main conclusions presented in the report are as follows:

- for the year 1996, an estimated total number of deaths attributable to exposure to asbestos if given as 1,950 for France. Of this total number of deaths, 750 are from mesothelioma, of which the incidence is constantly

increasing, and 1,200 from lung cancer. The clear majority of these deaths can be attributed to occupational or para-occupational exposure;

These estimates of deaths caused by exposure to asbestos at low or moderate levels (1f/ml) are, however, based on some firm evidence as well as some uncertainty. In particular, it is now known that:

- all asbestos fibres are carcinogenic;
- with early, high, and prolonged exposure the 'whole-life' risks of lung cancer and mesothelioma are much greater;
- the risk of lung cancer is higher where exposure has been to long and fine fibres - either amphiboles *or* 'chrysotile' (commercial);
- the risk of mesothelioma is greater for exposures to amphibole compared to 'chrysotile' fibres.

However, the main uncertainties concerning the given estimation of lung cancer and mesothelioma risk at low to moderate exposure to asbestos are:

- the precise form of the dose-risk relationship for exposure below or equal to 1 f/ml, and on this basis, the Group has adopted the principle of extrapolation, although uncertain, to low doses of the risk models established for cohorts exposed occupationally; and
- past or present exposures to asbestos within the French population, in particular, the exact location of the exposed population and the numbers involved. On this basis the estimates given are for hypothetical populations which would be placed in certain circumstances of exposure to asbestos, and according to age at start of exposure and duration (years).

Furthermore, the estimates given by the authors are based on the theory of constant exposure, and so do not provide for an estimate of cumulative 'whole-life' or 'whole-career' exposure in populations exposed intermittently. It is acknowledged by the authors of this report, that the greatest risks of mesothelioma are in those occupations where exposures are characteristically intermittent.

On this basis, the 'expected' number of deaths (disregarding any exposure to asbestos) in an average population of 10,000 in France, assessed from time of birth, or the age of 20 years, to the age of 80 are given as:

- for the male population, 529 deaths due to lung cancer, and 0.5-1 from mesothelioma; and
- for the female population, 70 and 0.6-1.1 deaths respectively.

The estimated number of 1,950 deaths caused by exposure to asbestos (lung cancer and mesothelioma) are additional to the 'expected' number of deaths given above.

The authors provide an overall summary of the 'whole-life' estimated risks of cancer due to 'constant' exposure to asbestos in various circumstances. These estimates are mean values from cohorts with varying conditions of exposure, and are therefore subject to a degree of variation. It would also be

appropriate to reduce the following estimates on the basis that they relate to uninterrupted exposures to the limited doses specified below:

- 30 additional deaths in a population of 10,000 males subject to constant occupational exposure (0.1 f/ml) from 20-65 years of age (1920 hours);
- 6 additional deaths in a population of 10,000 people comprising equal numbers of both sexes subject to constant passive exposure (0.025 f/ml) throughout the period of active employment (1920) from 20-65 yrs of age;
- 3 additional deaths in a school population of 10,000 people comprising equal numbers of both sexes subject to constant passive exposure (0.025 f/ml) throughout school-life from 5-20 years of age (900 hrs);
- 9 additional deaths in a population of 10,000 people subject to constant passive exposure (0.025 f/ml) throughout both school-life and active employment from the age of 5-65 years of age.

In relation to the management of the risks associated with asbestos, the authors make some specific points:

- in relation to an asbestos ban, any carcinogen must be removed whenever technically feasible under European law, but that any ban on asbestos must take into consideration the selection of substitute fibres for which the Group has limited information to carry out an assessment of the possibility of replacing asbestos with substitute fibres which are free of any risk;
- with regard to the carcinogenicity of 'chrysotile' (commercial), the main points highlighted by the authors are that mortality from lung cancer is as high as for those populations subject to combined exposure or exposure to amphiboles alone, whereas exposure to 'chrysotile' is also the cause of a definite increase in mortality from mesothelioma;
- the estimation of the health hazards ('whole-life') provided by the authors represent 'individual' risks, and it is essential to have information on the 'collective' risk based on number, level, duration and age of a population - for which information needs to be collected;
- the risk estimates provided for both lung cancer and mesothelioma corresponding to the current reference values under French regulations, provide an estimate of the maximum risk only where it is feasible to comply and ensure compliance with current MACs throughout France under all circumstances;
- a distinction must be made between the estimation and assessment of risk, in respect of the management of health hazards;
- the Group expresses some concern over the possibility of systematic removal of asbestos, particularly with regard to actual conditions under which this may be carried out;
- that particular vigilance is necessary with respect to the strict control of conditions of occupational exposure, as no identifiable lower limit of risk currently exists.

The a key recommendations made by the report are:

- to collect available material on exposure to asbestos encountered in various occupational sectors, public and private buildings;
- to carry out studies on the levels of occupational, passive intramural and urban exposure of people;

- the essential monitoring of the development of health hazards associated with asbestos, particularly in terms of the incidence of mesothelioma, as this provides a specific indication of the risks of lung cancer, as well as the monitoring of earlier non-cancerous respiratory effects;
- the need for research on the risk associated with the different circumstances of exposure (past or present) to asbestos, involving experimental and methodological research;
- urgent research on substitute fibres, prior to the generalised introduction of such fibres.

- SPAIN
- Churg. A
- March 1988
- CHRYSOTILE, TREMOLITE AND MALIGNANT MESOTHELIOMA IN MAN: A REVIEW (in CHEST, 1988, 93(3):621-628)

Key information:

- Nature of **document:** Scientific review of research and data
- **Type of asbestos considered:** Chrysotile asbestos
- **Further differentiation between fibres:** Some differentiation between 'pure' and 'commercial' chrysotile
- **Type of scientific evidence:** Review of epidemiological data on the incidence of mesothelioma caused by chrysotile contaminated with tremolite.
- **Assertions based on:** Findings of several epidemiological studies (see below)

This report is a review of the available evidence on chrysotile asbestos as to whether it causes mesothelioma in man.

Recent overviews of epidemiological investigations on the role of chrysotile in mesothelioma production have been published, and this review attempts to assess the problem from a slightly different angle and examine three areas:

- using all evidence and particularly using data on fibers found in lung, whether there are properly documented cases of chrysotile-induced mesothelioma in man, and if so, with what type of exposure they are associated;
- the levels of exposure/lung burden of fibres associated with chrysotile-induced mesothelioma in man; and
- the importance of tremolite in this process.

Review of the literature suggests that only 53 acceptable cases of chrysotile-induced mesothelioma have ever been reported, and of these, 41 cases have occurred in individuals exposed to chrysotile mine dust, all of it naturally contaminated with tremolite. Ten cases have occurred in secondary industry workers, but these cases are highly suspected to be related to amphibole contamination ('occult exposure' to amosite or crocidolite)). Analysis of lung asbestos content indicates that induction of mesothelioma by chrysotile requires, on average, a great a lung fibre burden as induction of asbestosis by chrysotile, whereas amphibole (amosite or crocidolite)-induced mesotheliomas appear at a considerably smaller lung burden. The data, although limited, is consistent with the hypothesis that tremolite is the actual causative agent of chrysotile-induced mesothelioma. The low incidence of mesothelioma in secondary chrysotile users may reflect the small amount of tremolite left in the product. These observations indicate that although chrysotile asbestos can produce mesothelioma in man, the total number of cases is very low and the required dose is very high. Data is consistent with the thinking that mesotheliomas seen in chrysotile miners and some secondary industry workers are produced by tremolite contained in chrysotile ore, but that the short length and low aspect ration of the tremolite make its carcinogenic potential very low. Despite these 'indirect' findings, the

potential for chrysotile to act as a mesothelioma-inducing agent is still possible.

In this report, Churg makes reference to data from reported cases of chrysotile-induced mesothelioma in man as provided by 16 studies; to reported cases of tremolite-induced mesothelioma in man as provided by 3 studies; and tremolite:chrysotile ratios in various occupational groups as provided by 5 studies.

- SPAIN
- Dunnigan, J
- 1988
- LINKING CHRYSOTILE ASBESTOS WITH MESOTHELIOMA (in American Journal of Industrial Medicine, 1998, 14:205-209)

Key information:

- **Nature of document:** Scientific review of research and data
- **Type of asbestos considered:** Chrysotile in particular, with reference to amphiboles
- **Further differentiation between fibres:** Reference is made to both 'pure' and 'commercial' chrysotile
- **Type of scientific evidence:** Review of epidemiological data against any link between chrysotile and mesothelioma
- **Assertions based on:** Findings of several epidemiological studies on (these are detailed below)

This report is in response to the questions over causality of asbestos-related mesothelioma, for example, as highlighted in a recent publication of Mealy's Litigation Report (1987) which reported the outcome of a litigation involving a shipyard worker where it was decided that chrysotile was the cause of the subject's mesothelioma despite the knowledge of exposure to both chrysotile and amphiboles. The objective of this review is to present evidence of the overwhelming consensus as to the different potentials of the different asbestos fibre types in inducing mesothelioma.

Observations made by Churg on fiber lung burden in long-term chrysotile miners and millers raised the possibility that the amphibole component of the chrysotile ore is important in the development of mesothelioma - similar to that induced by mixtures of chrysotile and commercial amphiboles, although recent work by Churg has indicated that the relative lack of tremolite may account for the near absence of mesotheliomas in those experienced to chrysotile in the textile and friction products industries.

Many other cohorts of workers have been studied by various parties, and the observations and conclusions made indicate a difference in disease potential between chrysotile and amphiboles, particularly concerning mesothelioma:

- Weiss (1977);
- McDonald and Fry (1982);
- Dement et al (1982);
- Newhouse et al (1982);
- Berry and Newhouse (1983);
- Thomas et al (1982);
- Acheson et al (1982).

Results from these epidemiological studies suggest that amphiboles are mainly responsible for mesothelioma, whereas chrysotile has little or no mesothelioma-producing potential.

In terms of lung burden by fibre type and disease, current methods for identifying, quantifying and measuring fibers in tissue have shown a predominance of amphibole fibres in the lungs of cases of mesothelioma when compared to age-matched control cases. This is based on the work of various parties including:

- Wagner et al (1982);
- Wagner et al (1986);
- Jones et al (1980);
- McDonald, (1980);
- McDonald, 1985);

Data presented by Churg (1985) on mineralogic content in mesothelioma cases was also in agreement with results presented by these studies, who found that pulmonary content of chrysotile asbestos was within the range of the general population, whereas values of commercial forms of amphibole asbestos were far in excess of those levels seen in the general population.

Results of tissue burden analysis are accepted as a key factor in identifying those fibre types that have the longest durability (residence time) in lung tissue, and which fibre types are most likely to be related to disease. It should be noted that it has been observed that chrysotile ores are sometimes contaiminated with tremolite, but it does not follow that all such ores from all sources contain tremolite.

In conclusion, decisions concerning the cause of mesothelioma must be based on the best available evidence, including tissue burden mineral analysis, or the present concensus that amphiboles are mainly responsible for mesothelioma, whereas chrysotile has little or no mesothelioma-producing potential.

- SPAIN
- Wagner, J.C.
- 1991
- TTHE DISCOVERY OF THE ASSOCIATION BETWEEN BLUE ASBESTOS AND MESOTHELIOMAS AND THE AFTERMATH (in British Journal of Industrial Medicine (1991) 48:399-403)

Key information:

- **Nature of document:** Scientific review of research undertaken by the author, presenting the background to the discovery of the association of between pathogenesis and asbestos fibres, in particular, 'blue' asbestos or crocidolite carried out between 1956-1990
- **Type of asbestos considered:** Crocidolite, chrysotile and amosite as the three major types of asbestos produced in South Africa
- **Further differentiation between fibres:** No differentiation is made with regard length of fibres, although there is some consideration of 'commercial' types of asbestos
- **Type of scientific evidence:** Findings presented are based on findings of earlier experimental and epidemiological studies, presented in 1972, together with updated information available from the author in 1990
- **Assertions based on the findings of:** See above

This paper presents the background to the discovery of the association between 'blue' asbestos and mesotheliomas in the north western region of the Cape Province in South Africa, and the development of further experimental and epidemiological research up to 1990.

The discovery in 1956 of the first case of diffuse malignant mesothelioma of the pleura together with the presence of asbestos in lung tissue is described. The further discovery of more cases associated with the western region where blue asbestos (crocidolite) was produced from a series of mines extending along the range of the Asbestos mountains prompted further investigations which confirmed the association between blue asbestos and relevant environmental, occupational and para-occupational exposure is also described by the author. Further work investigated the possibility of an association with other types of asbestos, including chrysotile and amosite, which also produced some epidemiological evidence of non-asbestos related mesothelioma due to lack of any form of exposure.

Further studies continued on occupational exposure and with animal experiments, warranting an international investigation which led to the establishment of an ad-hoc committee that presented its advisory findings in 1972 in the form of questions and answers on the topic of health and asbestos. This information was updated by the author in 1990, and his conclusions are presented as follows:

- All major commercial types of asbestos are able to cause lung cancer, but exposure must have been sufficiently high to have caused asbestosis. Incidence is greatly increased due to smoking;
- There is no evidence of an increased risk of lung carcinoma at low levels of exposure to asbestos as encountered by the general population in urban areas;

- There is significant evidence that crocidolite is the main fibre associated with mesothelioma. The association between amosite and mesothelioma is minimal relative to crocidolite. Cases due to tremolite have occurred mainly where exposure has been to chrysotile contaminated with tremolite, whereas there is little evidence of an association with uncontaminated chrysotile. It is important to recognise those cases of non-asbestos related mesothelioma ;
- There is no further evidence of increased risk of mesothemioma at low levels of exposure to asbestos encountered by the general populaiton in urban areas compared to rural areas, and there is no risk to the general public except where buildings containing crocidolite are disturbed - wholesale removal of chrysotile from buildings is considered unnecessary;
- There is evidence of smoking increasing the risk of lung cancer from asbestos, although there is little evidence for the importance of other factors such as trace elements, waxes and oils;
- There is slight evidence to show the existence of incidence of other types of cancer related to exposure to asbestos, particularly that of the upper respiratory tract;
- There is no evidence to suggest increased risk of cancer from asbestos-contaminated food, water through oral administration;
- There is no risk of lung fibrosis from low levels of exposure to asbestos as encountered by the general population, other than through para-occupational exposure;
- Pleural plaques (symmetrical and bilateral) are associated with exposure to amphiboles or chrysotile contaminated with amphibole fibres.

- SPAIN
- Anon.
- 1996
- DIFFERENCES IN PATHOGENIC POTENTIAL BETWEEN ASBESTOS FIBER TYPES

Key information:

- **Nature of document:** Scientific review of research and data
- **Type of asbestos considered:** Chrysotile and amphiboles
- **Further differentiation between fibres:** Differentiation is made between crude and processed forms of chrysotile in the context of studies that are reviewed; there is no direct reference made to fibre length other than 'adaptive clearance of chrysotile'
- **Type of scientific evidence:** Review of experimental and epidemiological evidence
- **Assertions are based on:** Findings of other documents (see below)

This paper briefly reviews recent experimental and epidemiological data with regard to the differing pathogenic potential among asbestos fibre types. It highlights the increasing reports of causal agents for mesothelioma, other than asbestos, including exposure to both organic and inorganic agents such as fibrous zeolite, ionising radiation and biogenic silica, as well as viruses.

In terms of experimental evidence, the paper notes that past studies have not been consistent with epidemiological observations indicating greater potency of amphibole fibres than chrysotile in inducing pathogenesis. More recent work using both fibre mass and fibre number units of dose have confirmed the greater pathogenicity of amphiboles. In particular, confirmation is provided by invitro models and inhalation experiments by Yegles et al (1993) and McConnell et al (1994).

The paper goes on to present a fairly comprehensive review of epidemiological data published after 1976 which indicates firm differences in biological effects and potency of chrysotile and amphibole fibre types. Reference is made to 25 reports from human studies on:

- morbidity and mortality data in chrysotile-only users; and
- analysis of mineral lung content.

Most recent data available on retention of asbestos fibres in lung tissue supports earlier findings of the possible adaptive clearance of chrysotile fibres and that adverse effects are associated with those fibres retained (ie amphiboles).

A further conclusion is that mesothelioma is unlikely to arise with regard to present day threshold limit values (TLV) for chrysotile. This is supported by several key workers in this field (Churg, 1988; McDonald, 1995)

Reference is made to reports by the following authors with regard to morbidity and mortality data, and analysis of mineral lung content:

- Wagner, J.C. et al (1988);
- Klinerman, J. (1988);

- Dunnigan, J. (1988);
- Hughes, J.M. et al (1987);
- Gardner, M.J. and Powell, C.A. (1985);
- Ohlson, C.G. and Hogstedt, C. (1985);
- Berry, G. and Newhouse, M.L. (1983);
- Thomas, H.F. et al (1982);
- McDonald, A.D. and Fry, J. (1982);
- Acheson, E.D. et al (1982);
- McDonald, A.D. and McDonald, J.C. (1978);
- Welss, W. (1977);
- Wagner, J.C. et al (1988);
- Wagner, J.C. et al (1986);
- Churg, A. (1985);
- Churg, A. (1988);
- Jones, J.S.P. et al (1980);
- McDonald, A.D. (1980);
- Churg, A. (1982);
- Wagner, J.C. et al (1982);
- Wagner, J.C. et al (1982);
- Gylseth, B. et al (1983);
- Rowlands, N. et al (1982);
- McDonald, A.D. et al (1982);
- Gibbs, A.R. et al (1989).

- SPAIN
- McDonald, J.C., Liddell, F.D.K., Dufresne, A.M, and McDonald, A.D.;
- 1993
- The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88 (British Journal of Industrial Medicine 1993; 50:1073-1081)

Key Information:

- **Nature of document:** Presentation of epidemiological data;
- **Types of asbestos considered:** Chrysotile asbestos;
- **Further differentiation between fibres:** 'Commercial' chrysotile is referred to in the context of further research on the possible role of fibrous tremolite and amphiboles in pathogenesis;
- **Type of scientific evidence:** Presentation of results of analysis of mortality for the period 1976-1988 inclusive, obtained by the subject-years method for a cohort of some 11,000 men born 1891-1920 and employed for at least one month in the chrysotile mines and mills of Quebec;
- **Assertions based on:** Findings of the epidemiological study only.

Following recommendations that research o the health effects of of exposure to various types of asbestos fibre and to the elucidation of exposure-response relations, a comprehensive series of studies directed at all aspects of chrysotile asbestos began in 1966. Over the past 25 years, this research has widened in scope to include the effects of exposure to amphibole fibres and other types of industry. Central to this work has been the continuing observation of mortality in a large birth cohort of around 11,000 men born 1891-1920 and employed for at least one month in the chrysotile mines and mills of Quebec, which was established in 1966 and has been followed ever since. Of 5351 men surviving in 1976, only 16 could not be traced; 2508 were still alive in 1989, and 2827 had died. By the end of 1992, a further 698 were known to have died giving an overall mortality of almost 80%.

This report presents the results of analysis of mortality for the period 1976-1988 inclusive, obtained by the subject-years method, using Quebec mortality as a reference. The findings presented in this report focus on the broad pattern of mortality in male cohort members who survived into 1976, with analysis by the subject-years method, comparing the numbers of deaths observed against the numbers expected form the experience of the general population of Quebec.

The method of study can be divided into four main areas:

- ascertainment of deaths and cause of death;
- estimation of the level of dust exposure for each member in the cohort, taking into account the fraction of the year worked, the average dust concentration for the particular job and year, and the weekly hours worked during the period in question;
- establishment of smoking histories;
- statistical analysis of mortality for 1976-1988 using the subject-years method, and using Quebec death rates as a reference.

Much emphasis has been placed on the optimal use of all available dust measurements to evaluate for each cohort member his exposure to asbestos in terms of duration, intensity and timing.

Standardised mortality ratios (SMRs) 20 years or more after first employment were similar to those for the period 1951-75. For example, all causes 1.07 (1951-75, 1.09). However, the SMR for lung cancer increased from 1.25 to 1.39 and deaths from mesothelioma increased from 8 to 25. Among men whose exposure by age 55 was at least 300 million particles per cubic foot x years (mpcf.y), the SMR (all causes) was elevated in the two main mining regions, Asbestos and Thetford Mines, and for the small factory in Asbestos; so were the SMRs for other causes. However, except for lung cancer, there was little evidence of gradients over four classes of exposure, divided at 30, 100 and 300 mpcf.y. Mortality from pneumoconiosis was strongly related to exposure and the trend for mesothelioma was very similar. Mortality was generally related systematically to cigarette smoking habit, recorded in life from 99% of survivors in 1976; smokers of 20 or more cigarettes had the highest SMRs for lung cancer as well as other causes. For lung cancer, SMRs increased five-fold with smoking, but the increase with dust exposure was comparatively slight for non-smokers, lower for ex-smokers, and negligible for smokers of at least 20 cigarettes per day. Therefore asbestos-smoking interaction was less than multiplicative.

Of the 33 deaths from mesothelioma in the cohort to date, 28 were miners and millers and five were employees of a small asbestos products factory where commercial amphiboles had been used. These mesotheliomas were primarily of the pleura. Preliminary analysis also suggests that the risk of mesothelioma was higher in the mines and mills at Thetford Mines than at those at Asbestos. More detailed studies of these differences and of exposure-response relations for lung cancer are under way. In particular, these 33 cases are the subject of a detailed study which focuses on the possible role of fibrous tremolite and amphiboles and to exposure-response.

The proportion of mortality from mesothelioma in chrysotile miners and millers only, has reached 0.4%, although this is much lower than that already found in cohort exposed to commercial amphiboles at a much earlier stage of mortality.

The risk of lung cancer in relation to exposure to asbestos and smoking cannot be examined adequately by the subject years method. Instead forms of analysis are required that are capable of assessing the separate ad combined effects of duration ad intensity of exposure to asbestos, with appropriate allowance for a number of time related variables, and with regard to cigarette smoking. This work is to be reported at a later date.

- AIA/EAC
- Eds. Gibbs, G.W., Valic, F., and Browne, K.
- August 1994
- HEALTH RISKS ASSOCIATED WITH CHRYSOTILE ASBESTOS (in Annals of Occupational Hygiene, 1994, 38(4):399-426)

Key information:

- **Nature of document:** A presentation and review of a number of papers, research and results presented at a workshop
- **Type of asbestos considered:** Chrysotile and amphiboles separately, including tremolite
- **Further differentiation between fibres:** Reference is made to chrysotile contaminated with tremolite ('commercial'); reference is also made to fibre size in terms of experimental data presented at the workshop, that fibres < 5 μm do not appear to cause fibrosis or pulmonary tumours, and that to produce neoplasia, fibres > 20 μm may be needed. Furthermore, there was a view that fibres < 5 μm were considered to have carcinogenic potential, albeit low
- **Type of scientific evidence:** Presentation of a range of evidence based on exposure-response relationships (mortality/morbidity and cancer incidence), experimental and epidemiological studies
- **Assertions based on:** The findings of a number of authors, including amongst others, Liddell, F.D.K., Gibbs, G.W., Weill, H., Elmes, P., Hughes, J., Wagner and Pooley, and Churg, A.

This document is a report on a workshop held in Jersey (Channel Islands) in November 1993. It presents papers presented at the workshop, which was attended by 41 scientists and 11 observers and sponsored by the Scientific Committee on Mineral Fibres of the International Commission on Occupational Health (ICOH) in collaboration with the International Programme on Chemical Safety (IPCS -UNEP/ILO/WHO).

Some of the main findings and conclusions based on information presented at this workshop can be summarised as follows:

- health risks must be evaluated with respect to chrysotile as mined, with its associated minerals and contaminants, and that tremolite in chrysotile deposits should be more thoroughly characterised, based on results of epidemiological studies;
- especially for the textile industry, reliable measurements of long chrysotile fibres are needed. This is because differences in fibre dimension have been suggested for the apparent large difference in lung cancer risks between the textile and other industry sectors using chrysotile;
- workplace exposure standards, which are based on epidemiological studies in which past particle count measurements have been converted to their membrane equivalent, are subject to an element of uncertainty. However, approximate conversions may be made provided they are industry and/or process specific - this has been done for a limited number of chrysotile industries;
- recent concentrations in well-controlled plants, as in Japan, have shown 98% of values to be less than 0.3 f/ml, compared to industries studied epidemiologically in the past, which have measured hundreds of f/ml;
- little data exists on the level of exposure to chrysotile in households;

- for lung cancer in the various chrysotile industries, the slopes of exposure-response curves were shallow, in comparison to those of the textile industry, with minimal risk of lung cancer associated with exposure to chrysotile at or below lifetime cumulative exposures of 30 f/ml.yrs - no increased risk associated with chrysotile was discovered at considerably higher exposures in the mining sector;
- in the mortality study of approximately 11,000 Quebec chrysotile miners and millers born 1891-1920, the interaction between exposure to chrysotile and smoking habit was more than additive, but less than multiplicative;
- studies on 14 cohorts of asbestos cement workers suggest that a non-threshold model for lung cancer may not be appropriate, and that additional studies are required to verify this observation;
- three main studies of friction manufacturing workers show that if there are any effects on mortality due to work in the manufacture of friction materials, the effects must be negligible. Overall, there is only one confirmed case of mesothelioma within this industry, for which the only known exposure was chrysotile;
- within the textile industry, one cohort study showed the rate of increase in the risk of lung cancer with fibre exposure to be steeper than that of other cohorts using mainly chrysotile. This result follows that of previous studies, which had experienced greater exposures with amphiboles. Furthermore, that the differences were due to differences in the size distributions of fibres or that they were in some way related to the use of oils on fibres requires investigation;
- in terms building occupants, estimation of lung-cancer risks involves assumptions, particularly with regard to the type of dose-response slope used to estimate risk. It is the majority view that such selection should reflect the group to which the risk estimate is to apply, and that the use of a linear non-threshold model may have no basis at low levels of exposure;
- it is the majority view that, based on extensive literature, differences exist in the risk of mesothelioma associated with different types of fibre; that there was at least a 10 fold lower risk of mesothelioma in workers exposed to chrysotile in comparison to amphiboles; that with current chrysotile levels, the occurrence of mesothelioma would be unlikely, which is supported by observations in Quebec miners and millers where mesotheliomas were associated with significantly high concentrations of both chrysotile and tremolite in the lung - similar to those discovered in cases of asbestosis;
- asbestiform tremolite was suggested as being responsible for a significant number of mesotheliomas associated with chrysotile exposure in the Quebec chrysotile mining industry, although the actual role requires clarification;
- it was suggested that the large quantity of epidemiological evidence on mesothelioma should be used to quantify the risks for various situations, as the potential for chrysotile to induce this disease is related to type of chrysotile as mined and distributed;
- there was a majority opinion that continuous deposition or long retention of chrysotile ('pure' or contaminated) is necessary for mesothelioma induction;
- prevalence rates for all markers of morbidity have been shown to increase with an increase in exposure, and which increase more steeply within the textile, rather than mining industry. Furthermore, the presence of long

fibre tremolite or other amphiboles may lead to a steeper exposure-response slope;

- inhalation studies using animals, have shown chrysotile to cause fibrosis, as well as benign and malignant pulmonary tumours. Some studies have shown the risks of these diseases to be dose-related;
- tumour incidence depends on dose, source and preparation of fibres employed - few mesotheliomas are induced through inhalation studies in comparison to inoculation, although in one study, erionite (non-asbestos fibre) has produced approximately 100% tumours;
- studies in rats using inhalation and intra-cavitray injection of chrysotile, amosite and crocidolite provide no overall indication of a lower carcinogencity potential per chrysotile fibre than with amphiboles, providing that equal numbers of fibres and sizes were used, although chrysotile content of the lungs was low;
- using intra-tracheal and other artificial routes of administration, it is not possible to extrapolate results directly to humans, as factors that affect deposition and retention are not entirely accounted for;
- it has been difficult to confirm, in inhalation experiments, that long thin fibres more readily induce mesotheliomas as indicated in injection experiments, although fibres less than 5 μm in length do not appear to lead to fibrosis or pulmonary tumours;
- in terms of cellular studies, it seems likely that the increased clearance and dissolution of chrysotile may render it less potent, as an initiator of lung cancer and mesothelioma in human cells, than amphiboles;
- based on studies of human lungs, for nearly all types of exposure, the relative proportion of amphibole retained greatly exceeds that in the original dust and the proportion of chrysotile is much less.

- AIA/EAC
- Meldrum, M., for the UK Health & Safety Executive
- August 1996
- REVIEW OF FIBRE TOXICOLOGY

Key information:

- **Nature of document:** Scientific review of over 130 medical and scientific reviews and papers on epidemiological studies, exposure-response relationships, tumour incidence, mortality/morbidity studies, and animal experiments, etc
- **Type of asbestos considered:** Chrysotile and amphibole asbestos separately
- **Further differentiation between fibres:** There is some differentiation between 'pure' and 'commercial' chrysotile with regard to the different industries ranging from mining and milling though to textile manufacture as reported in the papers under review; in terms of size, longer fibres are considered more hazardous than short (< 5μm), and that there is little evidence for a role for diameter
- **Type of scientific evidence:** This document reviews a range of evidence from epidemiological studies through to tumour incidence and animal experiments on asbestos and other mineral fibres
- **Assertions based on:** Findings of a large selection of studies and reviews, including Churg (1991, 1993), Davis et al (1984-93), Doll et al (1985), Donaldson et al (1988), HSE (1987, 1990), Hughes et al (1986-1994), McDonald et al (1983-1993), Wagner et al (1960-1988), IPCS (1986-1993), etc

The aim of this document, by the UK Health and Safety Executive, is to present the HSE position on fibre toxicology. One of the primary objectives is to summarise recent views and evidence relating to the dose-response relationships for the main types of asbestos-related disease. This is because such toxicological and epidemiological evidence can serve as a point of reference for evaluating the human health hazards of other fibres. The purpose of this document is not to provide a comprehensive coverage of asbestos epidemiology, but to focus primarily on those properties of fibres that influence their toxicological hazard. The review is based on primary literature sources, together with recent 'state-of-the-art' reviews where available.

In respect to the health effects of asbestos, the main findings of this review can be summarised as follows:

- that all forms of asbestos may cause asbestosis, lung cancer and mesothelioma, but that the level of hazard is dependent on fibre type (amphiboles > chrysotile) and fibre size distribution (long > short). Any useful comparisons of disease incidence for different occupational cohorts should therefore account for both fibre type and airborne size distribution;
- it is concluded that there will be a threshold level of exposure below which no form of asbestosis will occur, of which the value together with the slope of the dose-response curve depend on fibre type and size-distribution in the occupational setting;
- an association exists between asbestosis and lung cancer, in that both demonstrate similarities in dose-response relationships with respect to exposure to asbestos, latent periods of development, dependence on fibre type and size, and origins in the same underlying chronic inflammatory

condition, suggesting that asbestos-induced lung cancer, as with asbestosis is threshold-dependent. Hence, any exposure to asbestos too low to induce chronic inflammation, will not result in any increased risk of lung cancer;

- the available toxicological evidence does not lend support to the no-threshold model for asbestos-induced lung cancer, as proposed by Doll and Peto (1985) during their risk assessment for chrysotile-induced lung cancer;
- despite the large quantity of evidence for high and prolonged exposure to chrysotile, few cases of mesothelioma can be attributed to this form of asbestos - the reverse of which is true for amphiboles. This trend can be explained by the lower degree of biopersistence seen with chrysotile asbestos. Hence, for a fixed level of exposure, amphiboles pose a greater risk for developing mesothelioma compared to chrysotile;
- studies suggest that amphibole asbestos may result in the development of mesothelioma at lower levels of cumulative exposure than that required for lung cancer, although no reliable exposure-response curve can be produced for asbestos-induced mesothelioma in animals or humans. Furthermore, although a threshold could be assumed on theoretical grounds, there is insufficient evidence to identify a threshold level of exposure below which there would be no risk from exposure to asbestos.

The review goes on to consider other issues with regard to general fibre toxicology:

- animal studies;
- mechanisms of fibre pathogenicity;
- fibre toxicity testing strategy;
- relationship between fibre size and toxicity.

More general conclusions include:

- the pulmonary clearance of chrysotile is more rapid than for amphibole fibres of similar dimensions;
- results from animal studies on the ability of fibres to induce mesothelioma using different routes of administration, including intrapleural (IPL) and intraperitoneal (IP) administrations, should be treated with some caution. For the purpose of evaluating potential effects of fibres on human health, small and repeated doses over a period of time through intratracheal (IT) instillation should provide the most meaningful results. However, as the inhalation route is of most relevance to human exposure to fibres, animal studies using this route should provide a more suitable basis for hazard identification and for investigating dose-response relationships. Studies using rats are able to demonstrate the known hazards of asbestos for human health, although very few mesotheliomas can be produced via this route and so large group sizes of over 100 animals are required;
- there is good evidence to suggest that longer fibres are more toxic than equivalent masses of shorter fibres of the same composition. Experimental evidence suggests that short fibres of less than 5 μm pose very little concern for disease development;
- in terms of fibre toxicity, there is little evidence for the role of fibre diameter. Hence, concern should continue to focus on those fibres deemed

to be respirable - for mineral fibres this would include all fibres less than 3 μm in diameter with regard to counting purposes.

- FRANCE
- J. Bignon
- January, 1997
- "ASBESTOS, THE TRUE RISKS AND THE FALSE PROBLEMS" (in Recherche et Santé No. 69)

Key information:

- **Nature of document**: Scientific magazine article (scientific review of available data)
- **Type of asbestos considered**: Chrysotile and amphibole
- **Further differentiation between fibres**: Particle size and length considered
- **Type of scientific evidence**: Epidemiological and clinical mortality studies and
- experimental data
- **Assertions based on/References**: R. Doll, UK, 1955; C. Wagner, South Africa, 1966 (no further details available)

In the last few years, asbestos has been the subject of numerous debates in France. However, its qualities such as fire resistance are often forgotten and the real risks are, most of the most, only presented to workers who are professionally exposed to asbestos. However, the new 1996 regulations should protect them.

The numerous clinical, epidemiological and experimental studies that have been carried out during the last 50 years have resulted in a sound knowledge of the health risks posed by the inhalation of asbestos:

- Non-tumorous pathologies: after penetration in the respiratory system, a part of the fibres is evacuated and the other, the finer fibres will reach the alveols provoking an inflammatory reaction. The long fibres (> 5μm) retained in the lungs can provoke, after a few years, a pulmonar fibrosis. In case of exposure to high doses, we can observe inflammation of the pleura. Nowadays pulmonar fibrosis is rarely observed.

- Respiratory cancers: Studies (R. Doll, UK, 1955; C. Wagner, South Africa, 1966) have shown the relation between professional exposures and the development of respiratory cancers. (I) Lung cancers: Each year in France, about 25,000 death are caused by lung cancer, most often linked to tobacco smoking. However 5-10 % of lung cancers in non-smokers is due to exposure to asbestos. Another type of cancer is mesothelioma which appears 30-40 years after the beginning of exposure to asbestos.

For 1996, 1,950 death have been linked to exposure to asbestos. (1,200 lung cancers and 750 mesothelioma). In order to comply with the precautionary principles, the experts (INSERM) considered that, taking into account the absence of data concerning the risk of lung cancer at low doses exposures, it is not possible to attack the hypotheses of a linear dose/risk relation for such exposures. The figure of 1200 lung cancers correspond with this type of estimates based upon epidemiological studies of asbestos workers and by extrapolating the data obtained for high doses to low doses (less than 1,000 fibres/litre). Nevertheless, because of the uncertainties concerning the

response to very low exposure (<25 microfibres of chrysotile per litre air) it is impossible to demonstrate by epidemiological data that such an exposure could be responsible for a detectable significant excess of lung cancer.

In great Britain report of "Health and Safety Executive" published in 1996, gives different opinion considering that lung cancer does not appear but as a consequence of an inflammatory reaction of the alveols caused by the fibres provoking a more or less developed pulmonar fibrosis, this implicates exposures at relatively high doses. As a consequence the hypothesis of a threshold is a necessary inducement of lung cancer.

However, mesothelioma can develop at much lower doses, maybe ten to a thousand times lower than for broncho-pulmonary cancer. Nevertheless, there is a consensus to consider that mesothelioma is essentially associated with exposure to amphibole asbestos or mixtures of chrysoltile-amphiboles, unfortunately often used in the industry. The study carried out with Professor Valleron (INSERM U263) clearly shows that in France there are three to four times less mesothelioma compared to the number in the UK and this is correlated to an impact of amphiboles which is three times lower in tonnage.

It has been though for a long time that the length and diameter of fibres were the main physical characteristics to explain the carcinogenic potential. This is true at the cellular level, notably for the mesothelial cells where the fibres provoke genetic abnormalities when entering in contact with chromosomes.

In the organ, it is different. There is a consensus existing admitting that the difference between chrysotile and amphibole is justified for the lungs where the two variety of asbestos persist in different ways. Chrysotile is very sensitive to acidity inside the macrophage. Therefore, the chrysotile fibres would undergo a lixiviation of the magnesium which results in their dissolution. On the other hand, amphiboles are not sensitive to acidity and their durability *in vivo* is considerably longer. Therefore, chrysoltile fibres are less associated with the development of mesothelioma in humans.

- AIA (EAC)
- EAC-AIA
- January 31, 1997
- RECENT INFORMATION ON AMPHIBOLE ASBESTOS AND CHRYSOTILE

Key information:

- **Nature of document:** Scientific review of research and data on amphibole and chrysotile asbestos
- **Type of asbestos considered:** Asbestos in general, with emphasis on chrysotile
- **Further differentiation between fibres:** fibre lengths are considered as part of the studies reviewed
- **Type of scientific evidence:** Review of experimental, epidemiological, exposure data and tumor registers/incidence
- **Assertions based on:** Findings of several other documents described in four different categories of 'science', 'socio-economic aspects', 'legal elements' and 'general'

This report is a review of recent information on amphibole and chrysotile asbestos, focusing on four separate areas of importance:

- recent scientific findings;
- socio-economic considerations for EU and developing countries, as EU policy on health and environment is increasingly based on risk assessment and cost-benefit analysis;
- important regulatory declarations; and
- general thoughts on the desirability and feasibility of a zero risk society.

In terms of recent scientific findings, this report reviews 12 significant reports between 1991-97:

- A report by HEI-AR considers that the added lifetime risk of cancer for occupants in well-maintained public and commercial building is estimated to be relatively low compared to other pollutants, and that there is insufficient risk to warrant arbitrarily removing intact ACM from such buildings. However, relative risks to those involved in repair and maintenance are higher and thus should be the focus of any remedial action, whereas those involved in asbestos removal are at the highest risk of exposure and should receive adequate protection to avoid high exposure. The report states that determining exposure risks, and consequent management and control are site-specific tasks. It highlights inadequacies of existing data and recommends further research on the characteristic sources and patterns of both long and short-term exposure for differing classes of building occupants (including effects of remedial strategies), to improve analytical methods and to gain a greater understanding of biomedical effects through comparative analysis;
- A report by INSERM in 1992 on the risk assessment of cancer from exposure to chrysotile focused on present use. However, this report together with 1996 INSERM report did not suggest a ban on the use of chrysotile asbestos;
- In 1992, the US Journal of the National Cancer Institute stated that the predicted rate of asbestos-linked disease had not materialised and that risk

estimates were not realistic as they failed to account for the carcinogenicity of substitutes and that there was concern that such estimates were based on wrong assumptions;

- A workshop on the health risks associated with chrysotile asbestos (Annals of occupational hygiene, August 1994) presented various findings on such risks: few data exists on levels of exposure to chrysotile in households; that the estimation of lung cancer risks for building occupants involves assumptions - the clear opinion being that use of the linear non-threshold model may have no basis at low levels of exposure; that differences exist in the risk of mesothelioma associated with different fibre types, requiring further clarification; that of the Quebec cohort of 11,000 mine and milling workers, there was no trend of increasing lung cancer risk, although SMRs for men exposed below 300 mppcf.y was 1.27 - this study was one of a few large cohort studies that found smoking to be an important risk factor for many causes including lung cancer;
- a study by Peto et al (1995) analysiing mesothelioma mortality in the UK to assess the present and future state of the mesothelioma epidemic, concluded that it is important that building workers as the highest risk group, should be aware of the risks and take appropriate precautions;
- in response to the study by Peto et al, Damhuis & Planteydt (1995) found that incidence rates of pleural mesothelioma in the Netherlands contradict UK projections. This was due to the later introduction of legislative measures compared to UK asbestos regulations. Furthermore, Weill & Hughes (1995) suggested the difference in patterns between US and UK incidence could be explained by the greater exposure to amphiboles in the UK in the 1970s;
- The National Academy of Medicine in France...;
- A discussion paper prepared by ERM on the risks of chrysotile asbestos and RCF....;
- A scientific report by a working party (G2SAT, June 1996) on the monitoring of air quality in the workplace found varying degrees of pathogenicity of artificial mineral fibres. However, RCF - favoured as a substitute fibre for asbestos - was found to pose the greatest risk;
- The recent findings of the HSE review of fibre toxicology (1996)...;
- The WHO evaluation of the health risks of chrysotile asbestos (1996) involved in the industrial production and utilisation of chrysotile.....;
- A review of the INSERM report by the Expert Panel on Asbestos Risk (RPAR, 1996) is generally critical of the report and concludes that little new information is presented and that INSERM fails to address the relevance of the available studies in considering whether current exposures are associated with any increased risk;
- A report by the HSE examining the impact on the cancer risks on asbestos workers after the introduction of the 1969 UK regulation on asbestos....;

In summary of recent scientific findings on the health risks of asbestos, the report highlights:

- the importance of accounting for differences in composition, properties ad health effects of both chrysotile and amphiboles;
- that asbestosis and lung cancer are not likely to arise in the working population at the present levels of exposure through manufacturing and use of bonded chrysotile-containing products;

- that chrysotile alone is the causal agent in very few cases of mesothelioma;
- the majority of asbestos-related pathogenesis is a result of past high levels of exposure prior to the introduction of strict controls;
- that presence of asbestos-containing materials in well-maintained buildings does not represent a public health hazard;
- that extrapolation of high occupational exposure studies to low doses can lead to significant overestimates;
- that the hazards to health posed by alternative raw materials are not sufficiently known and therefore require further study.

Furthermore, this report highlights the necessity to take into account recent work undertaken by ERM to which EAC-members made a significant contribution, as they underline the efforts made by industry to continuously respond to new scientific findings and technologies.

Relevant reports and articles referred to in this report in the context of risks to health:

- Asbestos in public buildings and commercial buildings: a literature review and synthesis of current knowledge. US Health Effects Institute - Asbestos Rsearch (HEI-AR), September 1992;
- Risk assessment of cancer resulting from exposure to chrysotile-asbestos in the present conditions of use. Report by INSERM - France, September 1992;
- Predicted rate of asbestos linked disease has not materialised: experts say risk estimates were not realistic. April 1992;
- Health risks associated with chrysotile asbestos - the Annals of Occupational Hygiene No. 38, August 1994;
- Continuing increase in mesothelioma mortality in Britain. J Peto et al - The Lancet, March 1995;
- Amiante et protection de la population exposee a l'inhalation des fibres d'amiante dans les batiments publics et prives. Academie Nationale de Medecine - France, April 1996;
- Risks of chrysotile asbestos and RCF - Discussion paper. ERM, June 1996;
- Fibres minerales artificielles et amiante - Rapport du Groupe Scientifique pour la Surveillance des Atmospheres de Travail (G2SAT) - France, June 1996;
- Review of fibre toxicology. Health & Safety Executive - UK, August 1996;
- Chrysotile asbestos evaluated by health experts - press release. WHO, September 1996;
- Review of the INSERM report on the health effects of exposure to asbestos by an international Expert Panel on Asbestos Risk (EPAR) at the request of the Royal Society of Canada for Health Canada, December 1996;
- Report on cancer risks on asbestos workers after the 1969 Regulation on Permissible Levels on Asbestos at Workplaces in UK. Health & Safety Executive (HSE), January 1997.

- SPAIN
- Liddell, D.
- November 1991
- HEALTH EFFECTS OF HISTORICAL EXPOSURES TO ASBESTOS (in Health Risks from Exposure to Mineral Fibres: An International Perspective, Proceedings of the International Symposium on the Health Effects of Low Exposure to Fibrous Materials, 26-27 November 1991)

Key information:

- **Nature of document:** Scientific review of research results and data
- **Type of asbestos considered:** Chrysotile, amosite, tremolite, crocidolite
- **Further differentiation between fibres:** Chrysotile/chrysotile with proportions of amphiboles; no apparent reference to fibre size/dimensions
- **Type of scientific evidence:** Exposure data and experimental data (including carcinogenic potency of fibres/mortality studies), epidemiological studies, etc
- **Assertions based on:** The findings of all historical evidence from (circa) 1930 until 1992

This document is a scientific paper on the health effects of historical exposures to asbestos, as presented at the International Symposium on the Health Effects of Low Exposure to Fibrous Materials in November 1991.

Based on the following facts,

- that the excesses until 1977 of mortality from asbestosis, lung cancer and mesothelioma had been due to past exposures 20-60 years previously;
- that for this period, the average concentration of asbestos fibres in the occupational setting had been greater than 100 f/ml, but that levels were falling to around 1 f/ml by 1980, such that the risk of asbestos-related disease must also have been falling;
- that over 90% of commercially available asbestos has always been chrysotile;
- that the only major study of chrysotile workers showed that excess lung cancer was virtually confined to those workers who had been exposed to more than 1,000 f/ml.yrs;

this paper reviews all historical evidence from 1930 to 1992, and emphasises the knowledge gained relating to the strength, shape and slope of the relationships between asbestos exposure and the risks of mesothelioma and of lung cancer.

The paper presents information on the following:

- Historical backgroumd;
- Exposure-response relationships (mesothelioma andlung cancer);
- Differential carinogencity of chrysotile and amphibole asbestos (mesothelioma and lung cancer);
- Estimation of lung cancer risk.

The following conclusions are made by the author:

- present day asbestos-related cancer is more than likely related to exposures experienced during the 1935-65 period when the levels of respirable asbestos fibres in the occupational setting were approximately two orders of magnitude greater than those levels experienced in the 1980s. Hence, disease related to exposure to asbestos during present times will most probably be more than two orders of magnitude less;
- the risks of cancer depend not only on the degree of exposure to asbestos fibres, but on the fibre type and industrial process in which such fibres are used. Furthermore, the majority of disease has been caused by crocidolite (and amosite to a lesser degree);
- exposure-response relationships are extremely strong, and most likely to be linear;
- the risk of mesothelioma following exposure to chrysotile is very low (one order of magnitude less than from amosite, and two orders less than from crocidolite);
- the risk of excess lung cancer as resulting from exposure to chrysotile (textiles being the exception) is less, by more than one order of magnitude, than that from crocidolite exposure;
- on realistic assumptions, the risk of lung cancer from inhaling one chrysotile fibre is approximately one in a hundred-thousand billion - the risks of mesothelioma or asbestosis are even lower;
- the highest estimate of lung cancer risk from a single fibre (of crocidolite) is less than one in a thousand-billion.

Hence, the assumption that all forms of asbestos are equally hazardous and that one fibre can kill, as commonly believed following the 1977 New York Academy of Sciences Symposium on Health Hazards of Asbestos Exposure, are unfounded and inaccurate.

Chrysotile Asbestos

Environmental Health Criteria, No. 203
1998, xxi + 197 pages
ISBN 92 4 157203 5
Sw.fr. 42.-/US $37.80; in developing countries: Sw.fr. 29.40
Order no. 1160203

Summary of main findings and conclusions

This book evaluates the risks to human health and the environment posed by exposure to chrysotile asbestos. Also referred to as white asbestos, chrysotile is a naturally occurring fibrous hydrated magnesium silicate mineral having many commercial applications. Chrysotile is released to the environment from industrial sources. In addition, natural weathering of serpentine rock results in emissions to air and water.

Although the health risks associated with mixed exposures to the main commercial forms of asbestos (crocidolite, amosite, and chrysotile) are well known, the evaluation was undertaken in response to the continuing widespread production and use of chrysotile following the International Labour Organisation's recommendation to discontinue the use of crocidolite asbestos, and taking into consideration that amosite is virtually no longer exploited. The asbestos cement industry is singled out as by far the largest current global user of chrysotile fibres. Main applications include the production of corrugated sheets, flat sheets and building boards, slates, moulded goods, including low-pressure pipes, and high-pressure water pipes. Chrysotile is also used, in much smaller quantities, in the manufacturing of friction products, gaskets, and asbestos paper.

In assessing the health risks posed by chrysotile asbestos, the evaluation faced a number of methodological problems, including the industry-specific nature of exposure-response relationships, and difficulties with the interpretation of exposure data from older studies, which did not differentiate between exposures to amphiboles (crocidolite, amosite) and serpentine (chrysotile) fibres. Conclusions and recommendations reflect the consensus reached by a large group of scientists selected solely on the basis of their contribution to the open scientific literature. Some 500 references to the literature are included in this carefully documented assessment.

The report opens with a review of methods used for collecting and analysing samples, followed by a discussion of sources of occupational and environmental exposure. Studies indicate that exposure may occur during mining and milling, processing of asbestos into products, construction and repair activities, and the transportation and disposal of waste products containing chrysotile. Exposure to chrysotile fibres during the construction, maintenance, or demolition of buildings is judged likely to entail high risks. Subsequent sections summarize the levels of chrysotile detected in the environment and in various occupational settings, and review what is known about the uptake, clearance, retention, and translocation of inhaled or ingested fibres.

The most extensive sections review the results of toxicity studies conducted in laboratory mammals and *in vitro* test systems and of epidemiological studies in occupationally exposed workers. For humans, the report concludes that exposure to chrysotile asbestos poses increased risks for asbestosis, lung cancer, and mesothelioma in a dose-dependent manner, and confirms previous findings that asbestos exposure and cigarette smoking interact to greatly increase the risk of lung cancer. The report did not identify a threshold for carcinogenic risks. Evidence that exposure to chrysotile increases the risk of cancer at sites other than the lung was judged inconclusive.

To reduce the health risks posed by exposure, the report calls for the use of engineering and other control measures in workplace settings where occupational exposure continues to occur, and further concludes that, where safer substitute materials are available, these should be considered for use.

See also: Asbestos and Other Natural Mineral Fibres **(Environmental Health Criteria, No. 53)**

Annex II

EUROPEAN COMMISSION
DIRECTORATE-GENERAL HEALTH AND CONSUMER PROTECTION
Directorate C - Scientific Opinions
Unit C2 – Management of Scientific Committees; scientific co-operation and networks
Scientific Committee on Toxicity, Ecotoxicity and the Environment

Brussels, C2/GF/csteeop/**Asbestos 17122002**/D(02)

SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on

Risk to human health from chrysotile asbestos and organic substitutes

Opinion expressed at the 35th CSTEE plenary meeting

Brussels, 17 December 2002

I. Terms of reference

On the occasion of its 32nd plenary session CSTEE has been requested to comply with Directive 1999/77/EC which stipulates that new scientific evidence ought to be reviewed by January 1, 2003.

The terms of reference were discussed and it was noted that these terms should be the same as those which formed the basis of the CSTEE opinion in 1998, as follows:

On the basis of the available data, do any of the following substitute fibres pose an equal or greater risk to human health than chrysotile asbestos?

- *cellulose fibres*
- *PVA fibres*
- *p-aramid fibres*

Particular consideration should be given to the relative risk to para-occupational workers and other users of the asbestos-containing products in comparison to non-asbestos products.

The review reported in the present opinion summarises major scientific findings on chrysotile and organic substitutes reported during 1998-2002.

II. General reviews on mechanisms

A recent international Workshop discussed the underlying mechanisms and the information necessary to characterise the toxic effects of fibres and particles (Greim et al 2001). There was general agreement that several fibres (including asbestos) are carcinogenic in humans, leading to bronchogenic carcinoma and mesothelioma. Many fibres cause cancer in experimental animals, fibre length and fibre biopersistence being the crucial parameters. Biopersistence includes durability and clearance of the fibres from the lung, the latter again being related with fibre length. Fibres of a very low durability are not carcinogenic.

The Workshop confirmed previous conclusions that fibre length, biopersistence and inflammation are the major determinants of fibre toxicity and carcinogenicity and that overload condition do not occur in humans. Deposition, durability, and clearance select out the thin, durable, and long fibres, which are difficult to clear.

Fibres of a mean length of 17 μm or greater are more toxic than shorter fibres of a mean length of 7 μm or smaller.

Exposures resulting in a steady state lung burden that does not cause inflammatory reactions may be considered to define best the NOAEL of long-term

exposure. Thus information on dose response, biopersistence, kinetics of fibres in the lung and fibre geometry must be made available for appropriate risk characterisation of a fibre.

In vivo genotoxicity of fibres, including chrysotile, can arise via a) direct mechanisms (primary genotoxicity), involving the generation of fibre components of DNA-damaging, reactive oxygen and nitrogen species, or the direct interaction of fibres with chromosomes, or b) indirect (secondary genotoxicity), caused by DNA-damaging species arising as a result of chronic inflammation. The contribution of each of these pathways to the genotoxicity of a given fibre is of critical importance in the assessment of low-dose risks. Furthermore, since all fibres induce inflammation following chronic inhalation, but not all of them are carcinogens, inflammation does not seem to be the only crucial event in carcinogenicity.

The 2000 Workshop concluded that whether or not fibres have the potential to induce direct genotoxicity remains to be clarified. Since fibres induce inflammation that generates oxidants this adds to the steady-state level of oxidative adducts in cells caused by respiration. If exposure is low and does not induce inflammation, the antioxidative and DNA-repair systems may prevent additional mutations. Indirect genotoxicity becomes apparent when sufficiently high and continuous exposure induces chronic inflammation that overrides the defence mechanisms.

As far as chrysotile genotoxicity is concerned, the interaction of chrysotile fibres with the DNA in mammalian cells may result in chromosomal or mutational events that can initiate carcinogenesis or genetic damage (Env Health Criteria 203). However, the definite mechanisms initiated and sustained by chrysotile remain inadequately understood.

McDonald's group, in a series of original research articles (see Liddell et al (1997, 1998)) has proposed that chrysotile, at least in its pure form, has minimum, if any, potential to cause mesothelioma and that the overall carcinogenicity of chrysotile is much lower than that of amphiboles.

To evaluate the relevance of chronic animal studies on fibres to humans, Maxim and McConnell (2001) summarised the available information on fibre dosimetry (relation between exposure and fibre lung burden) and potency. Dosimetry models indicate that fibre deposition and clearance rates are lower in humans than in rats. Rats develop fibrosis at comparable lung burdens (>20 μg fibres per gram of lung) to those of humans. It was concluded that there is no reason to assume that humans are more sensitive to fibres than rats.

Oberdörster (2000) also discussed the role of dose, dimensions and durability of fibrous particles as key parameters for the induction of pulmonary effects. In particular, it was concluded that fibre persistence plays a most important role and

consequently biopersistence receives greatest attention in the search for new fibrous materials.

III. Genotoxicity and short-term toxicity studies

Chrysotile

Data on chrysotile genotoxicity reported since 1998 do not add any substantially new information on this question. The ability of chrysotile to induce inflammation, oxidative stress and genotoxicity in several *in vitro* and *in vivo* experimental systems has been confirmed [for example, Abidi et al, 1999; Okayasu et al., 1999; Levresse et al, 2000; Kienast et al., 2000; Tanaka et al., 1998; Morimoto et al., 1999]. Positive *in vitro* results confirm the potential of chrysotile to induce direct genotoxicity. On the other hand, the dose-response relationships governing *in vivo* genotoxicity are still unclear, with the consequence that the extent to which such effects reflect direct (presumably unthresholded) or indirect, inflammation-mediated genotoxicity remains uncertain.

In humans, 3 studies have detected increased levels of DNA damage (8-hydroxyguanine adducts and strand fragmentation) and higher frequencies of SCE in the blood cells of workers occupationally exposed to asbestos (primarily chrysotile, but also to other forms of asbestos, including crocidolite) [Marczynski et al., 2000a; 2000b; 2001; Takahashi et al., 1997; Lee et al., 1999]. Although levels of 8-hydroxyguanine were higher in asbestos-exposed workers than in unexposed controls, no correlation with the duration, level or latency of exposure was found, making the assessment of dose- and time-response relationships difficult.

Turning to short-term animal studies, Abidi et al (1999) investigated the mechanisms involved in chrysotile-induced fibrosis. Rats received 5 mg asbestos in 0.5 ml saline by intratracheal instillation. Thereafter, glutathione (GSH) was assayed in alveolar macrophages, blood and lung cytosol, while GSH peroxidase, GSH reductase, glucose-6-phosphate dehydrogenase and GSH-S-transferase and ascorbic acid were repeatedly determined between 1 and 150 days in different lung fractions. It was concluded that the observed depletion in GSH, ascorbic acid and alteration in GSH redox system enzymes might be involved in fibrosis and carcinogenesis by chrysotile.

Afaq et al (1998) measured the cytotoxic and oxidative responses in alveolar macrophages and peripheral blood cells in rats, 30 days after intratracheal instillation of 5 mg crocidolite, chrysotile and ultrafine titanium dioxide. In both cellular systems, cytotoxic reactions (LDH and acid phosphatase activities) as well as oxidative stress (decrease in GSH and ascorbic acid, changes in GSH peroxidase, GSH-reductase, catalase, formation of substances that react with hydrogen peroxide

and thiobarbituric acid) were recorded. The level of responses suggests a decreasing order of toxicity, with crocidolite > chrysotile > UF-TiO_2.

The clearance half-time of Brazilian chrysotile fibres in rats has been reported to be in the order of 10-15 days (Bernstein et al., 2000). Similar findings were observed in an ongoing study with Canadian chrysotile whose preliminary results were made available to the CSTEE (Bernstein, personal communication, 2002).

In rat pleural mesothelial cells Faux et al (2001) studied upregulation of epidermal growth factor receptor expression *in vitro*. Crocidolite and erionite increased expression whereas chrysotile and milled (non-fibrous) crocidolite did not.

Inhalation of 50 mg chrysotile/m^3 for 40 weeks marginally increased induction of lung tumours in rats after 3 and 10 mg/kg of the lung carcinogen N-nitrosoheptamethyleneimine given once a week for 10 weeks (Harrison et al 2000). The animals have been sacrificed after 15 months. The authors explain the weak effects of both lung carcinogens by the premature termination of the experiment.

Anthophyllite stimulated human PMN to produce reactive oxygen to a greater extent than chrysotile, crocidolite and amosite (Iwata et al 2002).

Rats were exposed by inhalation to 10 mg/m^3 of chrysotile asbestos for 5 hrs (Lasky et al 1998). Exposure induced fibroblast proliferation and morphometrically characterised lesions at the alveolar duct bifurcations. In the rat lungs an increase in the expression of PDGF receptor α mRNA, but not that of the β-receptor as well as the respective protein were noticed.

Rats exposed to either chrysotile or crocidolite asbestos fibres had greater amounts of monocyte chemoattractant protein-1 protein in their pleural lavage fluid produced by rat pleural mesothelial cells than controls (Tanaka et al 2000). Although a higher inducing potency of crocidolite was seen *in vitro*, there was no difference *in vivo*.

p-Aramid

One recent *in vitro* study with human lymphocytes exposed to p-aramid did not indicate induction of chromosomal damage [Warheit et al., 2001a].

Two studies in the rat have further demonstrated the ability of p-aramid fibres to undergo transverse breakage to shorter size and to cause transient inflammatory and fibrotic effects [Warheit et al., 2001a; Bellman et al., 2000]. In the latter study, male Wistar rats were exposed by inhalation to 50, 200 and 800 respirable fibre-shaped p-aramide/ml 5 days a week for 3 months to determine lung clearance. Alveolar clearance half times measured by γ tracers indicated dust overloading at the high dose at 0 and 3 months postexposure. At the end of exposure inflammatory

effects as measured by bronchoalveolar lavage as well as histopathological changes were seen at the highest and medium dose. At 3 months post exposure these effects were less marked. The NOAEL of this 3- month study was 50 respirable fibres per ml. Half-lives of alveolar clearance of >5μm fibres were 62, 76 and 173 days at lowest, medium and highest doses respectively. For fibres longer than 10 μm, half times were 58, 76 and 108 days and for fibres longer than 20 μm corresponding times were 46, 52 and 56 days, respectively.

Cellulose

Intraperitoneal injection of cellulose fibres to mice resulted in transient recruitment to the intraperitoneal cavity of inflammatory cells; similarly, inhalation of rats resulted in transient increase of inflammatory markers in bronchoalveolar lavage fluid [Cullen et al., 2000].

Findings of Warheit et al (1998) suggest that inhaled cellulose fibres have a slow clearance. These authors exposed rats to 300 and 575/ml Thermocell mechanical wood pulp cellulose fibres for 2 weeks. After 3 and 10 days, 1 and 3 months postexposure the lungs were evaluated for biopersistence and clearance and inflammation (bronchoalveolar lavage: cell differentials, acid LDH, protein, N-acetyl-glucosamidase, and alkaline phosphatase). Preliminary data show that a mild but transient pulmonary inflammation response occurred at 2 weeks of high exposure that returned to control levels within 10 days. The amount of fibres in the lungs did not decrease. The interim results suggest that inhaled cellulose fibres have slow clearance, but do not produce sustained pulmonary inflammatory effects after exposure has terminated.

Contrary to p-aramid, cellulose fibres do not react with components of lung fluids and are not shortened through enzymatic digestion. They induce a significant inflammatory response in laboratory animals, although less than crocidolite (Cullen et al 2000). They are released from cigarette filters and it has been postulated that they may affect the health of smokers (Pauly et al 2002).

Polyvinyl alcohol (PVA)

Samples of PVA fibres with diameters ranging from 13 μm down to less than 1 μm (industrially used fibres have diameters of a few μm, while the fibres of diameter <1 μm were prepared by special fibrillation treatment for the purpose of testing) were found negative for the induction of chromosome aberrations in a Chinese hamster cell line (Hatano Reserch Institute 1999; Hayashi & Arai, 2002).

No recent studies regarding the persistence of PVA have been found.

Comparison between chrysotile and p-aramid

In 1997, Searl compared rats exposed to chrysotile and to p-aramid by inhalation. The biopersistence in the lungs, of long (>15 um) chrysotile fibres was much greater than that of similar p-aramid fibres. No new studies focussing on a direct comparison have been reported. As noted above, the lower lung biopersistence of p-aramid fibres is due to cleavage/shortening of p-aramid fibres following reaction with lung fluids.

IV. Recent long-term experimental studies

Muhle et al (1987) compared a glass wool fibre (Code 104, Tempstran) a very durable and thin MMMF, with crocidolite and chrysotile (California, Calidria RG 144). In rats, inhalation of aerosol concentrations of 2.2-6 mg/m^3 for 1 year did not induce tumours, except that crocidolite resulted in bronchiolo-alveolar hyperplasia. Intraperitoneal injection of 0.5 mg of the three different fibre types showed a tumour rate of 55% for crocidolite, 17% for the glass fibre, and 6% for the Calidria chrysotile that was not significantly different from controls. Intraperitoneal injection of 1 mg UICC-chrysotile, Canada, led to a tumour rate of 84%. The authors explain this difference in carcinogenic potencies between UICC chrysotile and Calidria by the shorter persistence of the latter. It has to be noted that exposure of only one year in the inhalation experiments does not meet the criteria for a long-term carcinogenicity study in rats. Moreover, the lung burden of 1 mg crocidolite at the end of 1 year exposure was rather low (and no maximum tolerated dose has been determined). The authors conclude that the experimental conditions of the inhalation studies have been inappropriate to detect any carcinogenic potential of the fibres which were tested.

Ilgren and Chatfield **(**1997, 1998a,b) have re-evaluated a lifetime study on F344 rats exposed by inhalation to either Coalinga, Jeffrey or UICC/B chrysotile fibres that was performed at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program between 1978 and 1980. In this study, rats have been exposed (7h/day, 5 days/week) for 12 months to three well defined experimental chrysotile preparations: 11.36 +/- 2.18 mg/m^3 (Jeffrey), 10.99 +/- 2.11 mg/ m^3 (UICC/B) and 7.78 +/- 1.46 mg/ m^3 (Coalinga). Animals were sacrificed at 0, 3, 12 and 24 months. The first of the three reports is particularly concerned with fibrosis (Ilgren and Chatfield, 1997), the second on tumorigenic activity (Ilgren and Chatfield, 1998a), and the third on biopersistence (Ilgren and Chatfield, 1998b). The Coalinga fibre fraction consisted in fibres that were almost all less than 5 μm in length and were not contaminated with amphiboles. To obtain the short fibres, Coalinga chrysotile was subjected to additional milling and separation resulting in a fraction composed of fibres that were almost all less than 5 μm in length without contamination with amphibole (Pinkerton et al 1983). The two other fibres, Jeffrey and UICC/B standard, are both Canadian long fibre preparations with a minor degree of amphibole contamination. In contrast to both types of Canadian

fibres, the animals exposed to Coalinga fibres displayed no fibrosis (Ilgren and Chatfield 1997) and no tumours (Ilgren and Chatfield 1998). The authors' hypothesis was that short, amphibole-free chrysotile is the least tumorigenic form of asbestos. In previous studies, sufficient quantities of "pure" short fibre preparations, devoid of long fibres, were not available. The authors conclude that the long fibre Canadian chrysotile preparations produced marked pathological changes, whilst the short Coalinga sample did not result in fibrogenic and tumorigenic effects. The observed absence of biological effects noted with Coalinga has been attributed to its lack of biopersistence (Ilgren and Chatfield 1998). It is to be noted that the Coalinga fibres used in this experiment had been prepared *ad hoc* for experimental research.

Hesterberg et al (1998) exposed Fischer rats to fibre aerosols by nose-only inhalation for 6 h/day, 5 days/week for 2 years. The study was to compare chronic inhalation effects of X607 - a rapidly dissolving synthetic vitreous fibre – with the refractory ceramic synthetic vitreous fibre RCF1 and chrysotile asbestos. X607 was neither fibrogenic nor tumorigenic and induced only minimal lung cellularity that reversed after exposure was terminated. RCF1 and chrysotile asbestos induced pulmonary fibrosis and thoracic neoplasms (chrysotile inducing 32% more pulmonary neoplasms than RCF1). The authors conclude that biodurability, but not lung deposition and fibre length, explain the toxicological differences between the three fibres. Chemical analysis of fibres in the lung revealed rapid degradation of X607 compared to RCF1. At the end of the experiment, after 104 weeks exposure and 23 weeks recovery, the lungs retained (in millions) WHO fibres: 216 for chrysotile, 61 for RCF1 and 15 for X607. The differences were even larger at the end of exposure. In *in vitro* dissolution tests X607 underwent rapid dissolution and transverse fragmentation, RCF1 dissolved slowly and did not fragment, whereas chrysotile dissolution was negligible.

In a recent study, Cullen et al. (2002) reported an experiment with intraperitoneal injection of cellulose fibres to rats. Total doses between 1 million and 1 billion fibres were injected as 3 weekly aliquots. Nine of 50 animals at the highest dose developed peritoneal sarcomas.

IV Epidemiological studies: original investigations

Chrysotile

An excess of lung cancer (based on 22 cases vs 3 in a control group of similar size) was reported from a plant manufacturing a variety of asbestos products in China, in which chrysotile was used. The chrysotile originated from two mines in Sichuan (6000 tons of raw asbestos produced in 1996) and is reported to be amphibole-free. Purity was measured by x-ray diffraction analysis and analytical transmission electron microscopy method, and tremolite was below the detection

limits of these methods (0.001 %). Concentrations of asbestos in the working area were not measured: in 1999 the dust concentration largely exceeded 2 mg/ m^3. An unspecified number of lung cancers lacked histological confirmation (Yano et al 2001).

A study on pleural mesothelioma in workers at the Balangero quarry (NW Italy) detected 5 cases vs. 0.15 expected. None had evidence of other occupations entailing exposure to asbestos. Cumulative exposures were in the range 300-1000 f/ml/years (Silvestri et al. 1999). The quarry produced chrysotile, which was contaminated (0.2-0.5% by weight) with balangeroite (a fibrous magnesium-iron silicate first discovered at Balangero, morphologically similar to amphiboles).

p-Aramid

No formal epidemiological studies on long-term effects of p-aramid have been reported. One prevalence study in the early nineties suggested a high prevalence of respiratory irritation, cough, dyspnea, wheeze and increased phlegm, but there was potential for concomitant exposure to sulfuric acid and synthetic oils (Pal et al 1990).

Cellulose acetate and triacetate

Compared to 1998, one additional formal epidemiological study on the mortality experience of workers exposed to cellulose fibres study has become available from Canada (Goldberg and Theriault 1999). Overall findings do not suggest that exposure to cellulose fibres is associated to lethal neoplastic or non-neoplastic respiratory conditions. (see Table 1)

Table 1: Summary of relative risk levels

Ref	Industry	Number of workers	Follow-up period	Relative risk (95% CI)	
				Lung cancer	Non-malignant respiratory disease
1	Cellulose acetate	9040	1972-82	0.7 (0.5-0.9)	0.4 (0.2-0.5)
2	Cellulose triacetate	1271	1954-76	0.8 (0.4-1.4)	1.0 (0.4-1.9)
3	Cellulose acetate and triacetate and polypropylene	10211	1947-86	0.8 (0.6-0.9)	0.8 (0.6-0.9)
4	Cellulose triacetate	3211	1970-89	0.7 (0.5-0.9	Not given

1. Pifer et al J Occup Med 1986;28:438-444
2. Lanes et al Scand J Work Environ Health 1993;19:426-428
3. Goldberg & Theriault Am J Industr Med 1999;2:889-907
4. Gibbs et al J Environ Med 1996;38:693-697

Goldberg and Theriault did not detect any trend for lung cancer related to the duration of employment. Levels of fibre dust were not given.

Cellulose and plastic fibres have been found in resected human lungs, i.e. 83% non-neoplastic lung specimens and 97% malignant lung specimens (Pauly et al 1998). This study does not seem to have been replicated.

Polyvinyl alcohol (PVA)

A recent retrospective mortality cohort study on 447 exposed and 2416 non-exposed male workers did not detect any difference in mortality from all causes or mortality from lung cancer among the two groups. (Morinaga et al. 1999).

Types of asbestos fibres in the lung and cancer risk

In the last few years, a number of studies (eg McDonald et al 2001, Roedelsperger et al 1999) have investigated the association between mesothelioma and lung cancer risk and asbestos exposure estimated as concentration of fibres of different types in the lung tissue (usually expressed per microgram dry lung tissue). The design of these studies was case-control and in some of them (eg Roedelsperger et al) selection bias in the identification of cases and/or controls may have occurred. A marked difference in risk between individual or total amphiboles and chrysotile has been consistently observed. An association was reported for the former, but not between chrysotile concentration in the lung and risk for mesothelioma. It is commonly agreed that the lack of association for chrysotile ought to be viewed with caution, since, given its low biopersistence, concentration of chrysotile in the lung reflects relatively recent exposures.

V. Pooled analyses of cohort studies of workers exposed to asbestos

Studies allowing for an estimate of the cumulative exposure to different types of asbestos (crocidolite, amosite, chrysotile and amphibole, chrysotile alone) were included in a major analysis (Hodgson and Darnton 2000).

Six studies related to cohorts reported to be exclusively exposed to chrysotile. They regarded two cohorts of miners (respectively in Quebec Canada, Liddell et al 1997 and Balangero Italy, Piolatto et al 1990), one cohort of textile workers among whom male and female workers were analysed separately (in Charleston, US –

Dement et al 1994), workers of one cement asbestos plant in New Orleans, US (Hughes et al 1987) and one plant producing friction material in Connecticut, US (McDonald et al 1984). Within these studies, estimates of lung cancer risk have spanned over two orders of magnitude.

Major features of the six cohorts exclusively exposed to chrysotile are given in the Table 2 below.

Table 2: Cohort studies of chrysotile asbestos

	Carolina men	Balangero	Quebec	Carolina women	New Orleans plant 2	Connecticut
	Textile	Mining	Mining	Textile	Cement	Friction
Pleural mesothelioma	1	2	33	0	0	0
Peritoneal mesothelioma	1	0	0	-	-	-
Total expected mortality	410.1	225.4	5912.7	299.2	397,1	550.7
Average cumul. exposure f/ml/y	28	300	600	26	22	46
Mesothelioma risk (*)	0.013	0.003	0.001	0.000	0.000	0.00
Lung cancer deaths obs/exp	74/32.2	19/17.3	587/431.6	38/13.8	42/32,4	49/35.8
Lung cancer risk (**)	4.6	0.03	0.06	6.7	1.3	0.80
95% CI	2.9-6.7	-0.11-0.24	0.04-0.08	3.6-11.0	-0.29-3.4	0.03-1.80

(*) percentage total expected mortality per f/ml/y, adjusted for age at first exposure
(**) percentage expected lung cancer risk per f/ml/year

A sizeable number of mesotheliomas were observed only in the mining area of Quebec. As for lung cancer, the two most informative cohorts were the Quebec miners (lowest risk: 0.06% excess risk per f/ml/year) and the Charleston textile workers (highest risk: 4.6% and 6.7% excess cancer risk per f/ml/year in men and women respectively). Workers in Charleston were exposed to chrysotile originating from Quebec and subsequently processed. The difference in risk has not been satisfactorily explained. The very low number of mesotheliomas in Charleston may be indicative of removal of tremolite during processing (and therefore of the ability of "pure" chrysotile to produce lung cancer in man). It has also been suggested that lung cancers in Charleston could be attributed to mineral oils. However, mineral oils are not powerful lung carcinogens. In addition, in the Charleston cohort study**,** the consideration of exposure to mineral oils as a semiquantitative variable led to odds ratio estimates of 1.0, 1.1 (95% CI 0.6-2.2) and 1.5 (0.8-2.8) for slight, moderate and high exposure (no statistically significant trend). In their pooled analysis, Hodgson and Darnton (2000) have estimated an excess of lung cancers ranging between 1-20 (best estimates) cases per 100.000 exposed per f/ml/year (according to whether or not the Charleston cohort is included in the analysis), i.e. between one tenth and one fiftieth the risk estimated for amphiboles. Risks for lung cancer estimated in this pooled analysis are summarised in Tables 3-5 below.

From Tables 2 and 11 of Hodgson and Darnton's paper and Hodgson (personal communication): percentage excess risk and extra-cases are estimated from cumulative mortality rates in the UK). Exposure is assumed to be accumulated over short- up to 5 yr periods starting at age 30).

Table 3: Crocidolite

→ 5% excess lung cancer per f/ml x years exposure at historical occupational levels

Cumulative exposure (f/ml/year)	% excess per exposure (linear extrapolation)	Hodgson and Darnton's estimate (extra cases x 100.000 exposed persons) best estimate (and range)
100	500	Ranging from 1000-2500 for 10 f/ml/year to 25000-55000 for 100 f/ml/year
10	50	
1	5	85 (range 20-250)
0.1	0.5	4 (range <1-25)
0.01	0.05	? (<1-3)

Note: the "best estimate" model is non-linear (risk proportional to a power of exposure = 1.3). The highest suggested risks derive from a linear extrapolation

Table 4: Chrysotile (excluding data from Charleston)

→ 0.06 – 0.5% excess lung cancer per f/ml x years exposure at historical occupational levels

Cumulative exposure (f/ml/year)	% excess per exposure (linear extrapolation)	Hodgson and Darnton's estimate (extra cases x 100.000 exposed persons). Data from Charleston considered to represent "exceptional circumstances" and excluded from estimates
100	6-50	50-500 (cautious estimate up to 3000)
10	0.6-5	
1	0.06-0.5	2 (cautious estimate 30)
0.1	0.006-0.05	Cautious estimate 3
0.01		Negligible

Note: the "best estimate" model is non-linear (risk proportional to a power of exposure = 1.3). The "cautious" low dose estimates derive from a linear extrapolation

Table 5: Chrysotile (including data from Charleston). According to Hodgson and Darnton this estimate should only be applicable when there is simultaneous exposure to textile grade (i.e. long fibre) chrysotile + mineral oil or some analogous co-exposure. However, whether or not co-exposures explain the data from Charleston is open to debate

→ 2.3% excess lung cancer per f/ml x years exposure

Cumulative exposure (f/ml/year)	% excess per exposure	Hodgson and Darnton's estimate (extra cases x 100.000 exposed persons)
100	230	Up to 10000
10	23	
1	2.3	100
0.1	0.23	10
0.01	0.0023	1

According to the same pooled analysis, the risk for mesothelioma associated to chrysotile is much smaller (between 1/100 and 1/500) than the corresponding risk for the amphiboles. Nevertheless, globally, a sizeable number of pleural cancers have been occasionally found in cohorts exposed to chrysotile which was unlikely to be contaminated with tremolite.

Overall, a non-linear relationship is suggested by the authors of the review for all three cancer endpoints (pleural, peritoneal and lung cancer). Risk for lung cancer has been estimated to be proportional to a power of exposure of 1.3. This means that risks increase more steeply than exposure as exposure rises; extrapolation to low doses using these models gives lower risks than the traditional linear models. The authors rightly point out that these estimates are to be considered with caution because of a number of statistical and other uncertainties.

VI. Summary of major recent findings

- In recent years, a small but sizeable number of additional cases of pleural mesotheliomas among workers exposed to chrysotile originating in several locations have been reported in the epidemiological literature.
- Excess lung cancers were reported in a Chinese cohort of workers heavily exposed to asbestos said to consist of pure chrysotile.
- A pooled analysis of the literature has estimated quantitative lung and pleural cancer risks from chrysotile at different levels of cumulative exposure. For mesothelioma, the estimate of excess cases per 100.000 exposed for a cumulative exposure of 1 f/ml/years (i.e. 10 years of exposure to a concentration of 0.1 f/ml, which is an accepted standard in some countries) was within the range 1-20 (best estimate 5).
- In the same pooled analysis, corresponding estimates for lung cancer varied according to whether or not one particularly study (in which exposure to occupational carcinogens other than chrysotile has been postulated, but not proven) is included. For an exposure of 1 f/ml/years (as above), exclusion and inclusion of this particular study from the analyses led to estimates of additional lung cancer cases, per 100.000 exposed persons, of 2-30 and 100 respectively.
- No new epidemiological studies on the long-term effects of p-aramid and PVA have been reported. Results of a new cohort study on workers exposed to cellulose corresponded to those of three previous studies in that no excess cancer were detected. Thus, for none of the three substitutes there is evidence of carcinogenicity in humans.
- Short-term studies that compared effects of chrysotile with other fibres indicate that chrysotile is more hazardous than the major substitutes p-aramid, polyvinyl alcohol (PVA) and cellulose fibres (Harrison et al 1999). Chrysotile appears to be less hazardous than crocidolite and erionite.

- New studies on cellulose fibres indicate a relative long biopersistence of this material. In one study in rats, following intraperitoneal injection, this material produced peritoneal sarcomas.
- Chrysotile splits longitudinally and produces thin respirable fibres and is more biopersistent than most man-made fibres, although less persistent than amphibole asbestos. The substitutes usually break to produce shorter fibres.
- The basic principles of fibre toxicity are geometry and durability. Fibres of a mean length of 17 μm or greater are more toxic than shorter fibres of a mean length of 7 μm or smaller. Durability again is determined by fibre length.
- Despite the relatively short persistence of chrysotile fibres in the rat lung, it is known that chrysotile is carcinogenic in the rat by inhalation and intrapleural injection and that it produces lung and pleural cancer in man.
- Specially prepared Coalinga chrysotile fibres mostly less than 5 μm in length without contamination with amphibole did not result in fibrogenic and tumorigenic effects. The observed absence of biological effects noted with Coalinga has been attributed to the limited biopersistence of this very specific sample. In contrast, longer chrysotile fibres induce such effects. Coalinga fibrers do not represent the commonly used commercial chrysotile.

VII. Conclusions

The most recent scientific findings are in line with previous data. Thus, CSTEE reiterates its previous conclusion that the evidence for harmful potential is more extensive for chrysotile than for its organic substitutes.

In particular, there is sufficient evidence that all forms of asbestos, including chrysotile, are carcinogenic to humans. No evidence of fibre-caused cancer occurrence in humans is available for any of the three candidate substitutes. Admittedly, for cellulose fibres, this may reflect limitations in the design of the underlying studies, whereas the lack of epidemiological observations in persons exposed to PVA or p-aramid may be due to the relatively low exposure and/or short time elapsed since the onset of industrial uses of these materials.

Single- and repeated-dose experimental toxicity data on the three substitute fibres are still very meagre and do not allow for a proper comparison with chrysotile. A possible exception is p-aramid, which in a series of experiments in rats was shown to cause less inflammation and cellular proliferation than chrysotile given at similar doses. The *in vitro* ability of cellulose to induce certain inflammation-related changes and its relatively long persistence in animals gives cause for concern.

Fibre characteristics, such as size, respirability, biopersistence and fragmentability, indirectly provide elements for an overall comparison of potential

effects between different types of fibres. On the basis of such characteristics, current knowledge on the mechanisms of long-term toxicity of fibrous materials in humans is consistent with the inference that substitutes are less harmful than commercial chrysotile, which in turn is less harmful than the asbestos amphiboles.

The CSTEE also reiterates its recommendation that these conclusions should not be interpreted in the sense that environmental control of the workplaces where the substitute fibres are produced or used can be relaxed. Finally, the CSTEE strongly recommends expansion of research in the areas of toxicology and epidemiology of the substitute fibres as well as in the technology of development of new, thicker (less respirable) fibres.

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