

COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

Statement for Health and Safety Executive (HSE) on carcinogenic risks of three chrysotile-substitutes

Introduction

1. The COC has been asked by HSE to provide advice on the relative carcinogenic risks of three chrysotile-substitutes namely, polyvinyl alcohol (PVA) fibres*, p-aramid fibres, and cellulose fibres. The specific question referred by HSE asks whether these three materials pose less of a carcinogenic risk than chrysotile with respect to occupational and consumer health. In view of the urgency of providing DETR Ministers with advice on this issue of chrysotile-substitutes a subgroup of the COC gave initial consideration to the question posed by HSE at a meeting on the 22 May 1998. The subgroup considered four reports provided by HSE along with a number of published scientific investigations. These reports are listed below:

- i) Chrysotile and its substitutes: A critical evaluation. An Institute for Environment and Health unpublished report for the Health and Safety Executive, 6 April 1998.
- ii) A final report by ERM, Oxford for Directorate-General III of the European Commission, entitled "Recent Assessments of the Hazards and Risks Posed by Asbestos and Substitute Fibres, and Recent Regulation of Fibres Worldwide", November 1997.
- iii) A paper described as a constructive commentary on the June 1997 draft of the ERM report written by Gibbs, Davis, Dunnigan and Nolan, for the Quebec Ministry of Natural Resources, Department of Natural Resources, Canada and the Asbestos Institute, September 1997.
- iv) The opinion of the DGXXIV SCTEE, on a study commissioned by DG III of the European Commission on recent assessments of the hazards and risks posed by asbestos and substitute fibres prepared by ERM, February 1998.

2. The subgroup reviewed all four documents but placed most emphasis on the IEH report.¹ In addition, Dr L Levy, one of the authors of this report made a short presentation of the IEH findings to the subgroup.

3. Members of the subgroup considered all the submitted papers and agreed that it was not possible to undertake a full review of the literature in the time available. However, the subgroup agreed that it was possible to undertake a comparative risk assessment of the carcinogenicity of chrysotile-substitutes using available data on their

Throughout this statement the term "fibre" has been used to refer to airborne material derived from fibrous materials which may be spun woven or felted and used commercially. This is a much broader definition than the term "regulated fibre" as used by WHO or HSE for counting purposes which refers to particles of length $>5\mu\text{m}$ in length, $\leq 3\mu\text{m}$ in actual diameter, with an aspect ratio (length to diameter) of ≥ 3 . Throughout this statement the terms "regulated fibre" and "respirable fibre" can be used interchangeably.

physical properties (eg dimensions and potential for fragmentation) and information which indicated that exposures to respirable fibres would be significantly lower than the control limit for chrysotile of 0.5 f/ml. The subgroup also identified further information which should be provided to the COC in order for conclusions to be reached on the relative carcinogenic risks of the three materials under consideration compared to chrysotile.

4. The COC considered the minutes of the subgroup meeting, the report prepared by IEH for HSE and additional data identified by the subgroup at its meeting on 25 June 1998. The Committee also reviewed some additional written comments from IEH. Further confirmatory information on exposures to chrysotile-substitutes was forwarded to the Chairman. This statement reports the conclusions reached by the COC. A summary table of the evidence considered is appended as table 1, annex 1.

Background

5. The World Health Organisation's International Agency for Research on cancer (IARC) has classified chrysotile as a definite human carcinogen (group 1).^{1,2} The IARC working group agreed that chrysotile induced lung cancer and pulmonary mesothelioma in humans and also in experimental animals following inhalation exposure.² The European Union (EU), has classified chrysotile as a definite human carcinogen (ie category 1) and regulatory controls are set out in the Asbestos Directive (91/382/EEC) to limit its uses and control exposure. These measures have been enacted in the UK by the Control of Asbestos at Work Regulations (1987) as amended by the Control of Asbestos at Work (Amendment Regulations (1992)). These regulations set a control limit of 0.5 chrysotile fibres/ml of air averaged over any continuous period of 4 hours or 1.5 fibres/ml of air averaged over any continuous period of 10 minutes.³ The Asbestos (Prohibitions) Regulations (1992) ban the import, supply and use of amphibole forms of asbestos, including crocidolite and amosite asbestos. These regulations also ban some specific uses of chrysotile. However chrysotile is now the only type of asbestos that can be supplied and used within the EU. We understand that currently eight out of fifteen Member States have already instituted either total bans or restrictions on chrysotile which exceed the requirement of the current EU Directive. Research undertaken by Peto J et al has suggested that annual male mesothelioma deaths due to exposure to asbestos fibres (eg crocidolite and chrysotile) will increase to around 2,700-3,300 by the year 2020.⁴ This prediction is based on an analysis of death certificates and the known long latency period involved in asbestos fibre related disease. The majority of individuals at risk would have probably been occupationally exposed to asbestos prior to the 1960s. HSE report that occupational categories with intermittent exposure to asbestos such as plumbers, carpenters and electricians may be at increased risk of asbestos related disease.⁵ There remain many hundreds of thousands of tonnes of asbestos installed in buildings and workplaces across the UK. This material will be progressively removed, presenting considerable management and control problems. Continuing new use of chrysotile, in building products in particular, compounds the overall management problem.

6. We consider that any comparative assessment of the carcinogenic risks posed by chrysotile-substitutes and chrysotile cannot be based predominantly on an epidemiological assessment since the substitute fibres have only been used for periods of up to approximately 20 years and occupational hygiene controls have been placed on these

materials. Hence exposures to these materials have been of shorter duration and lower intensity compared to exposures to chrysotile which occurred prior to establishing modern hygiene controls on the use of asbestos. Thus we have placed most emphasis on a review of data on fibre dimensions and potential for fragmentation, evidence of biological effects and biopersistence in experimental animal systems and information on likely occupational exposures in use and compared these data to that on chrysotile.

Carcinogenicity of fibres

7. General perspectives on the properties of hazardous fibres have been reviewed in the IEH report.¹ A comprehensive review of fibre toxicology has also been published by HSE.⁶ We consider that the definition used by the WHO and HSE to identify "regulated fibres" can be used to assess the potential hazard associated with chrysotile-substitutes. Thus a potential carcinogenic hazard may exist with fibres of length $> 5\mu\text{m}$, diameter $\leq 3\mu\text{m}$ and with an aspect ratio of $\geq 3:1$. The length of regulated fibres known to be capable of inducing lung cancer are $>10\mu\text{m}$ and $>8-10\mu\text{m}$ for the induction of mesothelioma.⁶ The potential for fragmentation (ie fibrillation producing potentially hazardous fibrils) also needs to be considered. We note that the predominant physical determinant of deposition in the lung is fibre diameter. For inhaled mineral fibres, the maximum alveolar deposition occurs with fibres of diameters of about $1\mu\text{m}$, whereas fibres of diameter $>3\mu\text{m}$ are essentially non-respirable. Such fibres would not be expected to present a carcinogenic hazard to the lung or induce pleural mesothelioma. We therefore agree that consideration of information on fibre dimensions and information on evidence from animal studies should provide a basis for carcinogenic hazard assessment.

8. In order to characterise potential carcinogenic risks of fibres, information on actual exposures and the biopersistence of fibres are also required. We consider biopersistence to be dependent on (i) the mechanical clearance of fibres (ie mucociliary removal up the trachea), (ii) the solubility and fragmentation of deposited fibres and (iii) the biological removal of fibres by lung macrophages.⁶ A low biopersistence suggests that the fibre is cleared from the lung and is thus likely to present a lower carcinogenic risk than a fibre of similar carcinogenic potential but which shows evidence of biopersistence.

Consideration of individual chrysotile substitutes

9. We have used the criteria outlined in the above section to consider the relevant data identified in table 1 (Annex 1) to produce a short summary of the potential carcinogenic hazard and risk for each of the three chrysotile-substitutes. (All information has been derived from the IEH report, unless otherwise stated).

Polyvinyl alcohol (PVA) fibres

10. The respirable fraction of PVA fibres is likely to be very small. There is no evidence that PVA will fibrillate. The aspect ratio of the vast majority of airborne PVA fibres is likely to be below 3 suggesting that these fibres will have no potential for the induction of lung cancer or mesothelioma. Although no appropriate animal carcinogenicity bioassays are available, the information on PVA suggests a low carcinogenic hazard. However any PVA fibres deposited in the lung may degrade at a

slow rate. The evidence suggests a lower carcinogenic risk than chrysotile. We are also reassured to note that exposures to respirable PVA fibres are likely to be very much below 0.5 f/ml.⁷

p-Aramid fibres

11. The respirable fraction of p-aramid fibres is likely to be very small, but limited fibrillation may occur under certain conditions. The aspect ratio for airborne fibres is predominantly above 3.⁸ The formation of proliferative keratinising cysts (PKC) of the lung had been documented in a long term inhalation study in the rat, but these authors had used extreme abrasion of p-aramid fibres to produce a large number of respirable fibrils.⁹ Thus we consider exposure conditions in this study were unrealistic. The biological behaviour of PKC lung lesions is uncertain and a definitive diagnosis as to whether they are neoplasms cannot be ascertained at present.^{10,11} However, they have only been documented in rats at high exposures where the normal clearance mechanisms of the lung are overloaded and thus we consider them to be of no significance for human health assessment. The reports of the induction of a low level of peritoneal mesotheliomas in rats following intraperitoneal administration of p-aramid fibrous dusts in saline is not considered relevant to hazard assessment. In particular the sample of p-aramid administered to rats had been specially treated (which included drying, milling and ultrasonication) in order to prepare an aqueous saline suspension which could be administered to animals; despite this, the effect obtained was substantially lower than that seen with chrysotile.^{12,13} Thus, although there is some evidence of adverse biological effects with p-aramid there is no convincing evidence to suggest a carcinogenic hazard. The rate of degradation of p-aramid fibres in the rat lung has been documented to be faster than chrysotile fibres.¹⁴ The evidence suggests a lower carcinogenic risk than chrysotile. We are also reassured to note that exposures to p-aramid fibres are likely to be below 0.5 f/ml.⁷

Cellulose fibres

12. The respirable fraction of cellulose fibres is likely to be very small. It is possible that cellulose fibres could fibrillate, but in practice this appears to be extremely limited.¹⁴ The aspect ratio of airborne cellulose is likely to be variable according to industry and uses. No appropriate animal carcinogenicity bioassays are available. A recent investigation with cellulose fibres had documented evidence of a long biopersistence in the rat lung.¹⁶ However the COC agreed that this study was not relevant to consideration of the question posed by HSE. In particular, the investigators used excessively high doses of respirable cellulose fibres which resulted in overloading of the normal clearance mechanisms of the lung. Information on exposures in the IEH report indicate that respirable fibre counts are consistently below 0.05 f/ml, although occasional levels up to 0.2 f/ml had been documented. The COC undertook a review of the readily available epidemiological investigations considered in one review¹⁷ cited in the IEH report. Members concluded that these studies were inadequate and that it was unlikely that they could identify a carcinogenic response attributable to cellulose fibres.¹⁸⁻²¹

Discussion and conclusions

13. Our approach has been to undertake a comparative risk assessment based on the information presented to us. The key assumptions in our deliberation are that;

- (i) carcinogenicity associated with exposure to chrysotile has been clearly demonstrated,
- (ii) the physical properties (ie dimensions and potential for fragmentation) of chrysotile substitutes can be used to indicate potential hazard,
- (iii) adequate epidemiological data are unlikely to become available,
- (iv) occupational exposures to respirable PVA, p-aramid and cellulose fibres will be below the control limit for chrysotile of 0.5 f/ml (4h Time Weighted Average).

14. We therefore *conclude*:

"The evidence presented to the Committee on fibre dimensions, studies in animals including that of biopersistence in the lung, indicate that the carcinogenic risk posed by PVA fibres, p-aramid fibres or cellulose fibres is likely to be less than that posed by chrysotile. Additional reassurance can be gleaned by noting that these materials are unlikely to form significant amounts of respirable fibres under normal working conditions and that occupational exposures to these materials will be below the control limit for chrysotile."

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References

1. Chrysotile and its substitutes: A critical evaluation. An Institute for Environment and Health unpublished report for the Health and Safety Executive, 6 April 1998.
2. World Health Organisation. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs volumes 1-42, supplement 7, Lyon, France, 1987.
3. HSE. EH40/95. Occupational exposure limits 1995. ISBN 07176-0876-X.
4. Peto J, Hodgson JT, Mathews FE and Jones JR. Continuing increase in mesothelioma mortality in great Britain. *The Lancet*, **345**, 535-539, march 4, 1995.
5. HSE press release 6 February 1995. HSE Campaign warns plumbers, carpenters and electricians of fatal asbestos danger. .
6. Meldrum M. Review of Fibre Toxicology. HSE Books, EH 65, 1996. ISBN 07176-1205-8.
7. Levy L (Personal communication to COC secretariat) 7 July 1998.
8. Minty CA, Meldrum M, Philips AM and Ogden T. p-Aramid respirable fibres. Criteria document for an occupational exposure limit. HSE Books EH65/17, pp1-30, 1995. (ISBN 0-7176-0941-3).
9. Lee KP, Kell DP, O'Neal FO, Stadler JC and Kennedy GL Jr. Lung response to ultrafine Kevlar aramid synthetic fibrils following 2-year inhalation exposure in rats. *Fundamental and Applied Toxicology*, **11**, 1-20, 1988.
10. Schwartz LW, Hahn FF, Keenan KP, Keenan CM, Brown HR and Mann PC. Proliferative lesions of the rat respiratory tract. In guidelines for Toxicologic pathology. Society of Toxicological Pathologists, pp8, Washington DC, USA, 1994
11. World Health Organisation. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans. Silica and some silicates, coal dust and para-aramid fibres, **68**, pp 409-439, 1997.
12. Pott F, Ziem U, Reiffer FJ, Huth F, Ernst H and Mohr U. Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Experimental Pathology*, **32**, 129-152, 1987.
13. Pott F, Roller M, Ziem U, Reiffer FJ, Bellmann B, Rosenbruch M and Huth F. Carcinogenicity studies on natural and man-made fibres with the intraperitoneal test in rats. IARC Scientific Publications, No 90, 173-179, 1989.
14. Searl A. A comparative study of the clearance of respirable para-aramid, chrysotile

- and glass fibres from rat lungs. *Annals of Occupational, Hygiene*, **41**, 217-233, 1997.
15. Levy L (Personal Communication to COC secretariat), 24 June 1998.
 16. Muhle, Ernst H and Bellmann B. Investigation of the durability of cellulose fibres in rat lungs. *Annals of Occupational, Hygiene*, **41**, supplement 1, 184-188, 1997.
 17. Davis JA. The toxicity of wool and cellulose fibres. *Journal of Occupational Health and safety - Australia and New Zealand*, **12**, 341-344, 1996.
 18. Solet D, Zoloth SR, Sullivan C, Jewett J and Michaels DM. Patterns of mortality in pulp and paper workers. *Journal of Occupational Medicine*, **31**, 627-630, 1989.
 19. Jarvholm B, Thoren K, Brodin I, Ericsson J, Morgan U, Tylén U, and Bake B. Lung function in workers exposed to soft paper dust. *American Journal of Industrial Medicine*, **14**, 457-464, 1986.
 20. Ericsson J, Jarvholm B and Norin F. Respiratory symptoms and lung function following exposure in workers exposed to soft paper tissue dust. *International Archives of Occupational and Environmental Health*, **60**, 341-345, 1988.
 21. Lanes SF, Cohen A, Rothman KJ, Dreyer NA and Soden KJ. Mortality of cellulose fiber production workers. *Scandinavian Journal of Work, Environment, and Health*, **16**, 247-251, 1990.

COMPARISON OF FIBRE RISKS

TABLE 1 ANNEX 1

FIBRE	HAZARD				ASPECT RATIO	EXPOSURE		COMPARATIVE RISK TO CHRYSOTILE			
	FIBRE DIMENSIONS			ANIMAL STUDY		BIOPERSISTENCE	ACTUAL	POTENTIAL		EPIDEMIOLOGY	
RISK FACTORS ⇒	Length <5 NC 8-10 LC 10-15 F	Diameter ≤3u *	Fibrillation	Effects reported.	>3:1**	Biopersistence in lung	Actual levels of respirable fibres.!!	Lung cancer	Mesothelioma	Lung cancer	Mesothelioma
CROCIDOLITE	>5u	<1u particularly from fibrillation	++++ depends on processing	F, LC,ME	>3:1	++++ Accumulate	< 0.2 f/ml (control limit 4 h TWA).!!!!	Human carcinogen	Human carcinogen	+++	++++
CHRYSOTILE	>5u	<1u particularly from fibrillation	+++	F, LC,ME	>3:1	+++ Accumulate	< 0.5 f/ml (control limit 4 h TWA).!!!!	Human carcinogen	Human carcinogen	++	++ (Role of amosite unclear)
PVA	>5u †	10-16u	Evidence suggests that PVA will not fibrillate.	No relevant study	<3:1	No relevant study. Respired fibres might degrade slowly	< 0.05 f/ml	Lower relative to chrysotile	Lower relative to chrysotile	No relevant study	No relevant study
ARAMID	>5u †	10-12u	Fibrils may be formed. Need extreme abrasion to produce many.	PKC at 100 & 400 f/ml.!!!	>3:1 (predominantly)	Faster biodegradation than chrysotile	< 0.5 f/ml	Lower relative to chrysotile	Lower relative to chrysotile	No relevant study.	No relevant study.
CELLULOSE	>5u †	12-40u	Possible but available exposure data suggests very limited in practice	No relevant study.	Variable according to industry	No relevant study. !!!!	< 0.5 f/ml	Lower relative to chrysotile	Lower relative to chrysotile	No evidence after many years of use, but available studies inadequate for evaluation.	

KEY (OVERLEAF)

KEY

Grey areas refer to data on two forms of asbestos fibres, crocidolite and chrysotile.

The number "+"s have been used to indicate potential for adverse effects.

* Mean actual diameters (respirable limit can be up to 7µm for low density fibres)** Aspect ratio of predominant airborne fibres.

! Data from Asbestos information Centre, Widnes, Cheshire. Fibre lengths; Aramid 3-12 mm(composites), 38 mm (textiles). PVA 4-6 mm, Cellulose 90% > 0.5 mm

NC= No concern. F= Fibrosis, LC = lung cancer, ME = mesothelioma, PKC = proliferating Kertinsising cysts.

!! Data refers to levels of respirable fibres (ie >5µm in length, ≤ 3 µm in actual diameter, with an aspect ratio of ≥ 3)

!!! The finding of a very slight increased incidence of mesothelioma in one study using intraperitoneal administration was considered irrelevant by the Committee. (see statement text for details).

!!!! The finding of a high biopersistence in the rat lung in one study was considered irrelevant by the Committee. (see statement text for details).

!!!! Historically and with poor control exposures were much higher.