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Geneva, 13–17 February 2006
Item 5 (c) of the provisional agenda*

Listing of chemicals in Annex III of the Rotterdam Convention: Consideration of the draft decision guidance document for chrysotile asbestos

Report of the World Health Organization Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes

Note by the secretariat

The annex to the present note contains the report of the World Health Organization (WHO) Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes, held in Lyon, France, from 8 to 12 November 2005.

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* UNEP/FAO/RC/CRC.2/1.

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WORLD HEALTH ORGANIZATION

WHO Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes
8-12 November 2005, Lyon, France

SUMMARY CONSENSUS REPORT[1]

Introduction

1. The WHO Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes was convened at IARC in Lyon, in response to a request from the Intergovernmental Negotiating Committee (INC) for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Annex 1). The substitutes considered by the WHO workshop included the 12 chrysotile substitutes identified by the INC for priority assessment by WHO, 2 substances from a second list provided by the INC to be assessed if resources allow, and one further substance for which data was submitted in response to WHO's public "call for data" for the workshop.

2. The workshop opened on 8 November with a one-day session devoted to taking statements from observers mainly representing various commercial interests, along with some government observers and the Rotterdam Convention Secretariat. In addition a statement submitted by a labour organization was read by the workshop Secretariat. Observers were invited to submit any comments on the pre-workshop working drafts in writing. Invited specialists and observers did not participate the evaluations of the substitutes (Part 2 of the following report), or the final agreement of Part 1. A list of participants appears at Annex 2.

Part 1: Methodological Aspects

3. The workshop considered the mode(s) of action of fibre carcinogenesis and the developments in the field after the IARC 1996 report, but did not produce a formal assessment of the state of the art. The workshop established a framework for hazard assessment based on: epidemiologic data (whether data are sufficient to determine carcinogenicity); in vivo animal data (whether there is a indication of carcinogenicity or lung fibrosis); mechanistic information (whether critical indictors of carcinogenicity exist, e.g. positive results for genotoxicity in *in vitro* tests); and physico-chemical and biopersistence data as determinants of dose at the target site and possible indicators of carcinogenic potential . The workshop conclusions on each of these factors appear in the following paragraphs.

[1] This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization.

4. In light of the workshop scope to assess fibrous forms of the substitutes, the workshop confined its considerations to effects related to cancer, focusing on lung cancer, mesothelioma and lung fibrosis. Further, noting that substitutes may be used in a variety of applications with different exposure potential, either alone or in combination with other substances, the workshop did not embark on risk assessment, but rather, limited its work to assessing the hazard.

5. Epidemiologic studies on fibres have a clear advantage over toxicological studies in that they involve studies of humans. They also have the advantage that they study the effects of exposure in the real world where the effects of these exposures may be mitigated or enhanced by other factors. Despite these obvious advantages, the presence or absence of evidence of risk from epidemiologic studies does not always override contrary findings from toxicological studies. The interpretation of either positive or non-positive epidemiologic findings needs to be carefully considered in light of the strengths and weaknesses of the study design.

6. In *in vivo* animal studies, carcinogenic response (lung cancer, mesothelioma) and fibrosis were considered to be the key effects; epithelial cell proliferation; and inflammation were not regarded to be equally important indicators of human health hazard. From studies with asbestos, it is apparent that the sensitivity of the rat inhalation studies to fibre induced lung tumours is clearly lower than that of humans. This holds true when the effect is related to exposure concentrations and lung burdens. The workshop discussed the hypothesis that differences in sensitivity could be due to greater lung mass and/or longer life span in humans, however the question remains open as to whether this sensitivity difference remains if individual or rat or human lung cells are taken as a basis for comparison. In comparison, testing of fibres by intraperitoneal injection represents a useful and sensitive assay, which also avoids confounding effects of granular dusts.

7. Genotoxic potential in experimental systems can be assessed via cell-free *in vitro* assays, *in vitro* tests with cultured cells, and via *in vivo* studies, usually in mice or rats. Fibres may act in principle on all steps in tumour development. However, of these interactions the *in vitro* genotoxicity tests are mainly indicative of genotoxic effects involved in the first steps of tumour initiation. Effects related to bio-persistence of fibres (such as continuous "frustrated phagocytosis") and secondary genotoxicity arising from reactive oxygen species and reactive nitrogen species and mitogen release by macrophages and inflammatory cells are not detected in routinely used genotoxicity tests. Therefore, negative results indicate a lack of primary genotoxicity, but do not exclude effects on later steps of carcinogenesis. A completely inert fibre that could be used as a negative control in the above-mentioned assays has not been identified.

8. The chemical composition of the substitutes is a key factor influencing structure and physico-chemical properties, such as surface area, surface reactivity, solubility, etc. Attention should be paid not only to the chemical composition of the fibres, their major and trace elements, but also to contaminants or accompanying elements, including their speciation. Fibre-derived free radical generation favours DNA damage and mutations. Surface properties are a determining factor in the inflammatory response. In relation to fibre dimension and deposition, one can assume that there exists a continuous variation on the carcinogenic potency of respirable fibre,

which increases with length. Biopersistence of a fibre increases tissue burden, and therefore, may increase any toxicity the fibre might possess. For synthetic vitreous fibres, there is evidence in animals that the potential for carcinogenicity increases with biopersistence. This has not been demonstrated however for other fibres.

9. For all fibres, the fibres must be respirable to pose an appreciable hazard. Respirability is mainly determined by diameter and density, thus with a given fibre diameter a higher specific density is associated with lower respirability (note the specific density of most organic fibres is lower that the specific density of inorganic fibres.

Part 2: Hazard Assessment

10. The workshop decided to group substitutes roughly into hazard groupings of high, medium and low. However for some substitutes there was insufficient information to draw any conclusion on hazard and in this case the workshop categorized the hazard as indeterminate (a category which is not comparable to the other groupings). The hazard groups high, medium and low should be considered in relation to each other, and did not have reference to formal criteria or definitions, as such. For details of each substance, the reader is referred to the full workshop report (to be published subsequently). It is important to note that for each substitute, the fibre dimensions of commercially available products may vary and the workshop did not assess this variation. The substitutes are listed below in alphabetical order.

11. **para-Aramid** releases respirable fibres with dimensions similar to known carcinogenic fibres. p-Aramid fibres have induced pulmonary effects in animal inhalation studies. Biopersistence was noted. The workshop considered the human health hazard to be **medium**.

12. Most natural deposits contain **attapulgite** fibres which are < 5 µm in length and at workplaces the mean fibre length was less than 0.4 µm. The hazard from exposure to respirable attapulgite is likely to be **high for long fibres, low for short fibres**. This assessment is mainly based on findings in long-term inhalation experiments in animals, in which tumours were seen with long fibres; no tumours were seen in studies with short fibres.

13. The nominal diameter of **carbon fibres** ranges from 5 to 15 µm. Workplace exposure in production and processing is mostly to non-respirable fibres. The workshop considered that the hazard from inhalation exposure to these fibres to be **low**.

14. Most **cellulose** fibres are not respirable; for these the hazard is **low**. For respirable fibres, the available data do not allow the evaluation of the hazard; the hazard is thus **indeterminate**.

15. The dimensions of **graphite whiskers** indicate high respirability and they have a long half time in the lungs. However in the absence of any further useful information, the hazard from inhalation exposure was considered to be **indeterminate**.

16. **Magnesium sulphate** whiskers did not induce tumours in limited inhalation and intratracheal administration studies, were negative in limited short term tests, and are very quickly eliminated from the lung. It was discussed whether the hazard grouping should be **low or indeterminate**, and on the basis of the data available, in the time available, consensus was not reached.

17. For respirable **polyethylene**, **polyvinyl chloride**, and **polyvinyl alcohol** fibres, the data was insufficient for hazard classification, and the working group thus considered the hazard **indeterminate**.

18. In facilities producing **polypropylene** fibres, exposure to respirable fibres occurs. After intratracheal administration, respirable polypropylene fibres were highly biopersistent, however no fibrosis was reported in a sub-chronic animal study. However the data are sparse and the human health hazard potential was considered to be **indeterminate**.

19. The workshop considered that respirable **potassium octatitanate** fibres are likely to pose a **high** hazard to humans after inhalation exposure. At workplaces there is exposure to respirable fibres. There was a high and partly dose-dependent incidence of mesothelioma after intraperitoneal injection in two species (high incidence indicating high potency). There is evidence of genotoxicity. Biopersistence was noted.

20. Wool-like **synthetic vitreous fibres** (including glass wool/fibrous glass, mineral wool, special purpose vitreous silicates, and refractory ceramic fibres) contain respirable fibres. For these fibres, the major determinants of hazard are biopersistence, fibre dimensions and chemical/physical properties. It was noted that the available epidemiologic data are not informative, due to mixed (vitreous fibre) exposures or other design limitations. Based on inhalation exposure studies, intraperitoneal injection studies and biopersistence studies, it was concluded that the carcinogenic hazard could vary from high to low, with **high** for the biopersistent fibres and **low** for non-biopersistent fibres..

21. Natural **wollastonite** contains respirable fibres. In occupational settings exposure is mainly to short fibres. In chronic studies wollastonite did not induce tumours after intraperitoneal injection in animals; however, samples of wollastonite were active in different studies for genotoxicity. After considering this apparent discrepancy it was concluded that the hazard was likely to be **low.**

22. In a limited study with intraperitoneal implantation **xonotlite** did not induce tumours. After intratracheal injection in a chronic study no inflammatory or fibrotic reaction of the lung was observed. The chemical composition of xonotlite is similar to wollastonite, but it is more rapidly eliminated from the lung. The workshop considered the human health hazard to be **low.**

Further Information

The full report of this workshop will be published after scientific and language editing.

Secretariat for the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

UNEP

Plant Protection Service
Plant Production and Protection Division
Food and Agriculture Organization of the United Nations (FAO)
Viale delle Terme di Caracalla
00100 Rome, Italy

Tel: (+39 06) 5705 3441
Fax: (+39 06) 5705 6347
E-mail: pic@fao.org

Chemicals
United Nations Environment Programme (UNEP)
11-13, Chemin des Anémones
CH – 1219 Châtelaine, Geneva, Switzerland

Tel: (+41 22) 917 8183
Fax: (+41 22) 797 3460
E-mail: pic@unep.ch

Geneva, 25 March 2004

Subject: Chrysotile asbestos – assessment of alternatives.

Dear Dr Meredith

I refer to the request of the Intergovernmental Negotiation Committee at its tenth session to the World Health Organisation to conduct an assessment of alternatives to chrysotile asbestos. At this meeting, the WHO agreed that such an assessment would be able to be conducted, however requested that the fifth session of the Interim Chemical Review Committee for the Rotterdam Convention would consider the alternatives proposed by governments and develop a priority risk.. The Interim Chemicals Review Committee considered the alternatives proposed by governments, and developed a priority list for consideration by the WHO. They also developed a list of additional alternatives which were prioritised.

These alternatives are identified in the attached document, which is an extract from the report of the Interim Chemical Review Committee. I therefore invite the WHO to proceed with the agreed assessment of the proposed alternatives to chrysotile asbestos. If possible, it would be appreciated if an update on the progress of the assessment could be provided to the Intergovernmental Negotiating Committee at its eleventh session.

Please do not hesitate to contact us should you have any questions in regard to this letter.

Yours sincerely,

Mr James B Willis
Executive Secretary

Address Dr T. Meredith
Coordinator
IPCS / World Health Organization
CH-1211 Geneva 27 – Switzerland

cc Ms Carolyn Vickers

Annex I

Report of the contact group on chrysotile

1. The contact group considered the list of substitutes for chrysotile asbestos proposed by Governments for assessment by the World Health Organization (WHO). WHO indicated that it welcomed the guidance provided by the group on important alternatives used by Governments.

2. The list was prioritized initially on the basis of the number of Governments which had nominated the substances. Information on which substances had previously been assessed in environmental health criteria reports by IPCS was also considered. Where possible, the group's knowledge of important uses was also considered.

3. The first group of substances are listed on a priority basis, in the order in which the contact group would like them to be considered by WHO. The second group of substances, which were proposed by only one country, had undergone no previous assessment by WHO and could be considered if resources allowed.

Group 1: Substances identified and prioritized for assessment by WHO

Aramid and para-aramid fibres
Fibrous glass (glass fibres, glass wool)
Carbon/graphite
Ceramic fibres
Wollastonite
Cellulose fibres
Mineral wool (rock wool, slag wool)
Polyvinyl alcohol (PVA) fibres
Polypropylene fibres
Polyvinyl chloride (PVC) fibres
Attapulgite
Polyethylene fibres

Group 2: Substances identified as alternatives to chrysotile, to be assessed if resources allow

Aluminium silicates, basic magnesium sulphate whisker, erionite, ductile iron, mica, phosphate, polyacryl nitryl, polytetrafluoroethylene, potassium titanate whisker, semi-metallics, silicon carbide whisker, steel fibres

World Health Organization

Workshop on Mechanisms of Fibre Carcinogenesis and Assessment of Chrysotile Asbestos Substitutes

Lyon, 8-12 November 2005

LIST OF PARTICIPANTS

Members[1]

Elke Dopp
University Hospital Essen
Institute of Hygiene and Occupational Medicine
Hufelandstrasse 55
D-45122 Essen
Germany

Bice Fubini
University of Torino
Interdepartmental Center 'G. Scansetti' for
Studies on Asbestos and other Toxic Particulates
Via P. Giuria 7
I-10125 Torino
Italy

Andrea Hartwig
Technische Universität Berlin
Fak. III – Institut für Lebensmitteltechnologie
und Lebensmittelchemie
Sekr.: TIB 4/3-1
Gustav-Meyer-Allee 25
D-13355 Berlin
Germany

F. Javier Huertas
CSIC, Estacion Experimental del Zaidin
Department of Earth Sciences and
Environmental Chemistry
Prof. Albareda 1
E-18008 Granada
Spain

Marie-Claude Jaurand
Institut National de la Santé et de la Recherche
Médicale (INSERM)
Génomique fonctionelle des tumeurs solides
U674 - IFR 105 – CEPH – IUH
27, rue Juliette Dodu
F-75010 Paris
France

Aparna M. Koppikar
United States Environmental Protection Agency
National Center for Environmental Assessment
1200 Pennsylvania Ave, N.W.
Washington, D.C. 20460
USA

Dr Yasuo Morimoto
Department of Occupational Pneumology
University of Occupational & Environmental
Health
1-1 Iseigaoka, Yahatanishiku
Kitakyushu City 807-8555
Japan

Paul A. Schulte
National Institute for Occupational Safety and
Health (NIOSH)/CDC
Robert A. Taft Laboratories
4676 Columbia Parkway
Cincinnati OH 45226-1998
USA

Leslie Stayner
University of Illinois at Chicago
School of Public Health (M/C 923)
1603 West Taylor Street, Room 971
Chicago, IL 60612
USA

Peter Wardenbach

[1] Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

Federal Institute for Occupational Safety and Health (BAuA)
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund
Germany

Invited specialists[2]

Suresh Moolgavkar[3]
Fred Hutchinson Cancer Research Center
Division of Public Health Sciences
Fairview Avenue North, M2-B500
PO Box 19024
Seattle, Washington DC 98109-1024
USA

Hartwig Muhle[4]
Fraunhofer Institute of Toxicology and Experimental Medicine
Nikolai-Fuchs-Strasse 1
D-30625 Hannover
Germany

Jay Turim[5]
Sciences International Inc.
King Street Station
1800 Diagonal Road, Suite 500
Alexandria, VA 22314
USA

Observers

Observer for the American Forest & Paper Association, Inc. (AFPA)

David Bernstein[6]
40, chemin de la Petite-Boissière
CH-1208 Geneva
Switzerland

Observer for the European Ceramic Fibres Industry Association (ECFIA)
R.C. Brown[7]
6, Stocken Hall Mews
GB-Stretton LE15 7RL
United Kingdom

Observer for Health Canada, Government of Canada
Michel Camus
University of Montreal
3875, Rue Saint-Urbain
Montréal, Québec H2W 1V1
Canada

Observer for the Institute of Defense of National Property, Brazil
Carlos Crespo
Avenida 18 No 149
Rio Claro, São Paolo
Brazil

Observer for NYCO Minerals Inc.
Christophe de Bellefroid[8]
NYCO Minerals Inc.
45, av, de Cîteaux
B-1348 Louvain-la-Neuve
Belgium

Observer for the Belgian Ministry of Health
Frédéric Denauw
Direction générale environnement – Maîtrise des risques
Place Victor Horta 40
Boîte 10 B
B-1060 Brussels
Belgium

Observer for the US EPA IRIS Program

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[2]NOTE: Minor pertinent interests are not listed. Examples of minor interests include stock valued at no more than US$10 000 overall, research grants that provide no more than 5% of the unit's research budget, and consulting and speaking engagements, on matters not related to courts or government agencies, that do not exceed 2% of time or compensation. All consulting or speaking on matters before a court or government agency is listed as a significant pertinent interest.

[3]Is advising a law firm that is representing a corporation with asbestos interests.

[4] The Fraunhofer Institute is doing contract research for many companies that produce glass wool, rock wool, or ceramic fibres.

[5] Is advising a law firm that is representing a corporation with asbestos interests. Received research support from the Refractory Ceramic Fibers Coalition, an association of producers of refractory ceramic fibres.

[6] Consultant to the American forest and paper industry. Received research support from the chrysotile industry.

[7] Consultant to ECFIA. Partner owns shares in the Morgan Crucible Company, a producer of ceramic fibres.

[8] Employed by NYCO Minerals, a producer of wollastonite.

Danielle DeVoney
United States Environmental Protection Agency
National Center for Environmental Assessment
1200 Pennsylvania Avenue, NW 8601D
Washington DC 20460
USA

Observer for Sama Mineração de Amianto Ltda
Milton do Nascimento[9]
Sama Mineração de Amianto Ltda
Rua Dr Fernandes Coelho
85 2º andar
São Paolo 05404-014
Brazil

Observer for the Chrysotile Institute
Jacques Dunnigan[10]
380 Chemin de North-Hatley
PO Box 123
Ste-Catherine-de-Hatley, QC, J0B 1W0
Canada

Observer for l'Agence Française de Sécutité sanitaire de l'environnement et du travail (AFSSET)
Anne-Marie Fillet
AFSSET
27-31 Avenue du Général Leclerc
F-94704 Maisons Alfort
France

Observer for International Ban Asbestos (IBAS)
Morris Greenberg[11]
14, North End Road
GB-London NW11 7SY
United Kingdom

Observer for the North American Insulation Manufacturers Association (NAIMA)
John Hadley[12]
Owens Corning Science and Technology Center
Granville, Ohio
USA

Observer for the Swiss Agency for the Environment, Forests and Landscape
Bettina Hitzfeld
Designated National Authority Rotterdam Convention
Swiss Agency for the Environment, Forests and Landscape SAEFL
Substances, Soil, Biotechnology Division
CH-3003 Berne
Switzerland

Observer for Future Pipe Industries Llc.
Mustafa Kabbara[13]
Future Pipe Industries Llc
PO Box 1371
Dubai
United Arab Emirates

Observer for the Research Institute of Occupational Health of the Russian Academy of Medical Science
Evgeny Kovalevskiy
State Run Organization Research Institute of Occupational Health
Russian Academy of Medical Science
The WHO Collaborating Center in Occupational Health
31, Prospect Budennogo
105275 Moscow
Russian Federation

Observer for the Russian Register of Potentially Hazardous Chemicals
Boris Kurlyandskiy
18/20, Vadkovskiy per
127994 Moscow
Russian Federation

Observer for the French Ministry of Health
Claude Lambré
Ministère de la Santé
DGS/CAS
14, avenue Duquesne
F-75350 Paris SP07
France

Observer for the Secretariat of the Rotterdam Convention

[9] Employed by Sama Mineração de Amianto, a producer of asbestos.
[10] Consultant to the chrysotile industry.
[11] Has advised plaintiffs seeking compensation for disease related to asbestos or mineral fibres. May receive travel support for this meeting from IBAS.
[12] Employed by Owens Corning, a producer of glass fibres.
[13] Employed by the Future Pipe Company, a producer of chrysotile cement pipe.

Sheila Logan
Secretariat of the Rotterdam Convention
United Nations Environmental Program
11-13 Chemin des Anemones
Chatelaine 1219
Geneva
Switzerland

Observer for Refractory Ceramic Fibers Coalition (RCFC)
Daniel Maxim[14]
15 N. Main Street
Cranbury, NJ 08512
USA

Observer for the European Tissue Symposium (ETS) and the Confederation of the European Paper Industry (CEPI)
Anthony S. Panepinto
Procter and Gamble
5299 Spring Grove Avenue
Cincinnati, OH 45217
USA

Observer for the Austrian Federal Ministry for Economic Affairs and Labour, Labourinspection
Reinhild Pürgy
Federal Ministry for Economic Affairs and Labour
Favoritenstrasse 7
A-1040 Wien
Austria

Observer for the Finnish Ministry of Social Affairs and Health
Antti Tossavainen
Finnish Institute of Occupational Health
Topeliuksenkatu 41
SF-00250 Helsinki
Finland

Observer for the International Federation of Building and Wood Workers
Lars Vedsmand
BAT-Kartellet
Kampmannsgade 4
DK-1790 Copenhagen V
Denmark

Observer for l'Agence Française de Sécutité sanitaire de l'environnement et du travail (AFSSET)
Antoine Villa
AFSSET
27-31 Avenue du Général Leclerc
F-94704 Maisons Alfort
France

WHO Secretariat

Antero Aitio
Robert Baan
Vincent Cogliano
Fatiha El Ghissassi
Yann Grosse
Béatrice Secretan
Kurt Straif
Carolyn Vickers

Administrative Assistance

Sandrine Egraz
Helene Lorenzen-Augros

[14] Employed by Everest Consultants, Inc. Consultant to RCFC, ECFIA, NAIMA, and NYCO Minerals.