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-TiO₂.

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/m³ 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/m³ 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 Research 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 µm) 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/m³ 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/m³ (Jeffrey), 10.99 +/- 2.11 mg/ m³ (UICC/B) and 7.78 +/- 1.46 mg/ m³ (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/ m³. 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

<table>
<thead>
<tr>
<th>Ref</th>
<th>Industry</th>
<th>Number of workers</th>
<th>Follow-up period</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lung cancer</td>
</tr>
<tr>
<td>1</td>
<td>Cellulose acetate</td>
<td>9040</td>
<td>1972-82</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>2</td>
<td>Cellulose triacetate</td>
<td>1271</td>
<td>1954-76</td>
<td>0.8 (0.4-1.4)</td>
</tr>
<tr>
<td>3</td>
<td>Cellulose acetate and triacetate and polypropylene</td>
<td>10211</td>
<td>1947-86</td>
<td>0.8 (0.6-0.9)</td>
</tr>
<tr>
<td>4</td>
<td>Cellulose triacetate</td>
<td>3211</td>
<td>1970-89</td>
<td>0.7 (0.5-0.9)</td>
</tr>
</tbody>
</table>

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 –

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

Table 2: Cohort studies of chrysotile asbestos

<table>
<thead>
<tr>
<th>Location</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Mining</th>
<th>Textile</th>
<th>Mining</th>
<th>Textile</th>
<th>Cement</th>
<th>Friction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolina men</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carolina women</td>
<td>33</td>
<td>0</td>
<td>33</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Balangero</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Quebec</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New Orleans plant</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Connectic ut</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pleural mesothelioma</td>
<td>0.013</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Peritoneal mesothelioma</td>
<td>0.013</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Total expected mortality</td>
<td>410.1</td>
<td>225.4</td>
<td>5912.7</td>
<td>299.2</td>
<td>397.1</td>
<td>550.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average cumulative exposure f/ml/y</td>
<td>28</td>
<td>300</td>
<td>600</td>
<td>26</td>
<td>22</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma risk (*)</td>
<td>2.9-6.7</td>
<td>-0.11-0.24</td>
<td>0.04-0.08</td>
<td>3.6-11.0</td>
<td>-0.29-3.4</td>
<td>0.03-1.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer deaths obs/exp</td>
<td>74/32.2</td>
<td>19/17.3</td>
<td>587/431.6</td>
<td>38/13.8</td>
<td>42/32.4</td>
<td>49/35.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer risk (**)</td>
<td>4.6</td>
<td>0.03</td>
<td>0.06</td>
<td>6.7</td>
<td>1.3</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(*) 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

<table>
<thead>
<tr>
<th>Cumulative exposure (f/ml/year)</th>
<th>% excess per exposure (linear extrapolation)</th>
<th>Hodgson and Darnton’s estimate (extra cases x 100.000 exposed persons)</th>
<th>best estimate (and range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>500</td>
<td>Range from 1000-2500 for 10 f/ml/year to 25000-55000 for 100 f/ml/year</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>85 (range 20-250)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>4 (range &lt;1-25)</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>0.5</td>
<td>? (&lt;1-3)</td>
<td></td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Cumulative exposure (f/ml/year)</th>
<th>% excess per exposure (linear extrapolation)</th>
<th>Hodgson and Darnton’s estimate (extra cases x 100.000 exposed persons)</th>
<th>Data from Charleston considered to represent “exceptional circumstances” and excluded from estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>6-50</td>
<td>50-500 (cautious estimate up to 3000)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.6-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.06-0.5</td>
<td>2 (cautious estimate 30)</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>0.006-0.05</td>
<td>Cautious estimate 3</td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Cumulative exposure (f/ml/year)</th>
<th>% excess per exposure</th>
<th>Hodgson and Darnton’s estimate (extra cases x 100.000 exposed persons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>230</td>
<td>Up to 10000</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.3</td>
<td>100</td>
</tr>
<tr>
<td>0.1</td>
<td>0.23</td>
<td>10</td>
</tr>
<tr>
<td>0.01</td>
<td>0.0023</td>
<td>1</td>
</tr>
</tbody>
</table>
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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