The mission of the French Agency for Environmental and Occupational Health Safety (Afsset) is to assist in the areas of environmental and occupational health safety and assess potential health risks. It provides the competent authorities with all information required on these risks, as well as the expertise and technical support needed to draft legislative and statutory provisions and implement risk management strategies (article L. 1336-1 of the French Public Health Code).

Within the framework of the Occupational Health Plan 2005-2009 (PST), Afsset was requested by the French Ministry of Work to carry out the scientific expert appraisal activities required to set Occupational Exposure Limits (OELs).

Presentation of the question

On 7 February 2005, the Directorate General for Health (DGS), the Directorate General for Work (DGT) and the Directorate for Economic Studies and Environmental Evaluation (D4E) requested Afsset to assess the health risks linked to short asbestos fibres (SAFs) (length $L < 5 \mu m$, diameter $d < 3 \mu m$, with a ratio $L/d \geq 3$). An additional mission letter addressed to the Agency from the Directorate General for Pollution and Risk Prevention (DPPR), the DGS and the DGT, dated 16 May 2007, requested that the field of investigation be extended to include thin asbestos fibres (TAFs) ($L \geq 5 \mu m$, $d < 0.2 \mu m$ and $L/d \geq 3$).
In February 2009\(^1\), Afsset published an opinion accompanying a collective expert appraisal report instructed by its Committee of Specialised Experts (CES) “Assessment of risks associated with air environments” in which they answered the questions raised on the following 3 topics:

- the assessment of the toxicity of SAFs and TAFs;
- the determination of the possibility of characterising the particle size distribution of fibres according to exposure scenario (general population or workers) and the type of asbestos (chrysotile or amphibole);
- the assessment of the risks to human health linked to SAF exposure (not included in current regulations) and to TAF exposure (not included in current occupational regulations) and the redefinition, if necessary, of the protection threshold for the general population.

The funding ministries would also like the relevance of current regulatory provisions to be examined, especially:

- the current protection threshold for workers, set at 100 fibres per litre (0.1 f/cm\(^3\)) for asbestos over 1 hour;
- the absence of adequate counting for SAFs compared to that for TAFs in the occupational environment;
- an analysis of the possibilities and limitations offered by Transmission Electron Microscopy (TEM) so that all asbestos fibres can be better counted, including thin fibres, in comparison with Phase Contrast Microscopy (PCM).

With the support of the CES "Expert appraisal with the view to setting Occupational Exposure Limits for chemicals in the workplace", Afsset received a mission to give its opinion on the need to recommend another OEL by indicating the level or levels, the recommended reference period or periods and the most suitable measurement technique for the professional environment.

**Context**

An international benchmark method, using PCM, was selected at the end of the 1960s by the World Health Organization, following a consensus based on metrological considerations. It defines the characteristics of the fibres to take into account when measuring the concentration of airborne fibres in the workplace. A fibre was thus defined as any elongated solid particle, natural or artificial, with parallel sides, a diameter less than 3 \(\mu\)m, a length greater than 5 \(\mu\)m and a length-width ratio greater than 3.

A publication by Dodson *et al.* (2003)\(^2\) discusses this definition and investigates the pathogenicity of asbestos fibres based on their dimensional parameters. This article, which is a critical literature review, analyses and highlights the potential impact asbestos fibres less than 5 \(\mu\)m in length can have on health. The authors conclude that current data supports the hypothesis that asbestos fibres result in a pathological outcome regardless of their length. They therefore suggest that the exclusion of SAFs from the genesis of asbestos-related diseases is questionable.

\(^{1}\) Afsset expert appraisal report on the "Taking into account the dimensional criteria for the characterisation of health risks linked to asbestos inhalation", February 2009

Organisation of the expert appraisal

The expert appraisal was carried out in compliance with French Standard NF X 50-110 "Quality in Expert Appraisal Activities – General Requirements of Competence for Expert Appraisals (May 2003)" with the objective of respecting the following points: competence, independence, transparency and traceability.
These problems fall within the remit of the CES "Expert appraisal with the view to setting Occupational Exposure Limits for chemicals in the workplace". This committee appointed a number of rapporteurs (five experts from the CES "Expert appraisal with the view to setting Occupational Exposure Limits for chemicals in the workplace", two experts from the "thin and short asbestos fibre" working group and five agents from Afsset) to carry out the expert appraisal activities.
The methodologies and scientific findings were regularly submitted to the CES. The reports produced were the subject of discussions during telephone conferences and plenary meetings (with 7 revisions for the section relating to health effects and 4 for the section concerning measurement methods being made between May 2008 and April 2009) and the conclusions presented and approved by the CES "Expert appraisal with the view to setting Occupational Exposure Limits for chemicals in the workplace" on 27 April 2009.
This expert appraisal is thus the result of work performed by a group of experts with complementary competences.
The present opinion is based, as far as the scientific issues are concerned, on the final report from the collective expert appraisal ("Expert appraisal with the view to setting Occupational Exposure Limits for chemicals in the workplace", dated April 2009, which assessed health effects and methods for measuring exposure levels of asbestos fibres in the workplace), which was approved by the CES during their meeting on 27 April 2009.

Opinion and recommendations of Afsset

1 - Points to be considered when setting an OEL

Based on the conclusions of the collective expert appraisal report of the CES "Expert appraisal with a view to setting Occupational Exposure Limits for chemicals in the workplace", Afsset considers that:

- given the fact that all known and commercialised mineral varieties of asbestos fibres have the potential to induce cancer in humans through inhalation, it is not necessary to differentiate between them when making a recommendation for an Occupational Exposure Limit;
- given the carcinogenic potential of thin asbestos fibres, this dimensional class is to be included when measuring dust levels in the workplace;
- given that the limit of 5 μm in length used to differentiate between a "short" fibre (L < 5 μm) and a "long" fibre (L > 5 μm) does not correspond to demonstrated scientific safety data, the carcinogenicity of SAFs, even if remains difficult to assess, cannot be excluded;
- given the current state of data that is available and that relates to the carcinogenicity of asbestos fibres in humans, the toxicity of these fibres acts via a mechanism of action without a threshold;

the current OEL set for asbestos fibres must be reassessed.

To set a new OEL, the risk manager must take into account the following points:
- no human health protection threshold can be determined for asbestos fibres whatever their type or dimensional characteristics;
- available data on the carcinogenicity of these fibres is judged as sufficient to derive a dose-effect relationship at low doses and to calculate a single risk excess;
- the assessment of individual additional risks of cancer retained by Afsset allows the risk of lung cancer as well as that of mesothelioma to be taken into account, following exposure to asbestos.

After analysing all of the excess health risk models currently available in the literature, and by considering the occupational exposure scenarios, Afsset is retaining the 1997 Inserm model\(^3\) (from the US EPA model, 1996) due to the fact that:

- it has the advantage of being based on French mortality data;
- the superiority of other models could not be demonstrated with regards to the limitations and uncertainties associated with derivation methods at low doses.

This model was applied to a group of exclusively male workers, aged between 20 and 65, and a majority exposure to a variety of chrysotile fibres, under a continuous asbestos exposure scenario (40 hours per week and 48 weeks per year or 1920 hours per year). Its application thus leads to an excess risk of death from mesothelioma or lung cancer pertaining to the population of French workers of:

- \(10^{-4}\) for an exposure concentration of 3 fibres per litre (indicating a probability of 1 additional death from lung cancer or mesothelioma for every 10,000 people exposed to this level of concentration);
- \(10^{-5}\) for an exposure concentration of 0.3 fibres per litre (indicating a probability of 1 additional death from lung cancer or mesothelioma for every 100,000 people exposed to this level of concentration);
- \(10^{-6}\) for an exposure concentration of 0.03 fibres per litre (indicating a probability of 1 additional death from lung cancer or mesothelioma for every 1,000,000 people exposed to this level of concentration).

These three values constitute the references that Afsset is suggesting to risk managers for setting an OEL.

Furthermore, in so far as that there appears to be no quantitative evidence concerning acute toxicity linked to asbestos fibres, the setting of a Short-Term Exposure Limit is not recommended.

In the absence of dermal penetration data for asbestos fibres, the assigning of the mention of "skin" is not retained.

### 2 - Points to be considered for setting an exposure measurement method

Concerning the assessment of exposure measurement methods, no method currently available (PCM\(^4\), ASEM\(^5\), indirect ATEM\(^6\) and direct ATEM) is considered ideal for measuring occupational exposure to asbestos fibres, especially exposure to the finest of these fibres.

Adaption of the ATEM methods, using the indirect route (in order to alleviate the risk of fibre loss and changes in their particle size distribution during the preparation phase) or direct ATEM (to obtain optimal splitting of the deposit on the filter during sampling), should eventually allow

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\(^4\) Phase Contrast Microscopy

\(^5\) Analytical Scanning Electron Microscopy

\(^6\) Analytical Transmission Electron Microscopy
these methods to become valid for use in the occupational environment so that the exposure of operators to asbestos fibres, whatever their dimensional characteristics, can be assessed. Furthermore, with a view to existing measurement techniques and the systematic presence of asbestos fibres with a length greater than 5 µm for all occupational activities linked to asbestos in the workplace, it is proposed not to include short asbestos fibres in exposure measurements in the workplace.

3 - Additional Information
Upon completion of this expert appraisal, Afsset considers it important to draw the attention of risk managers to the following points:

- the estimations that come from the application of the Inserm model:
  - consider the mean values established from cohorts presenting with varied conditions as a result of exposure. These mean values are therefore susceptible to reasonably wide variations and cannot be considered as absolute values;
  - correspond to uninterrupted exposure to indicated concentrations (an adjustment of these estimations with regards to real exposure scenarios for asbestos fibres remains possible);
  - are below the threshold currently set in regulations relating to the protection of the population (either 5 fibres per litre or 5 × 10⁻³ f/ml)⁷ even when taking the higher value (10⁻⁴) for the suggested excess risk;

- the 8-hour OEL for asbestos fibres is currently 0.01 f/ml⁸ (or 10 fibres per litre) in Germany, in Switzerland and in the Netherlands, which is arrived at by applying Inserm's conservative model of an estimated excess risk of 3.3 × 10⁻⁴ (indicating a probability of 3.3 additional deaths from lung cancer or mesothelioma for every 10,000 people exposed to this level of concentration according to the scenario of 40 hours per week and 48 weeks per year or 1920 hours per year from the age of 20 until 65).

4 - Conclusion
Taking into account the current state of knowledge and the outcomes from this collective expert appraisal, when setting the new French OEL for asbestos, Afsset recommends that the following parameters be considered:

- the effect of asbestos fibres being cumulative and with no evidence having been found of acute toxicity when performing a wide review of the literature, Afsset recommends the setting of the next OEL for asbestos over a corresponding typical 8-hour working day;

- the 8-hour OEL of 10 f/l (0.01 f/ml) is currently the lowest regulatory value of many European countries. Afsset considers that this value can constitute a relevant step in the progress towards a reduction in the risk of asbestos exposure in France. However, for this powerful carcinogen that has no threshold, Afsset recommends retaining a target value of 0.03 f/l, which corresponds to a level of risk of 10⁻⁶, according to the retained model;

- given the carcinogenic potential of thin asbestos fibres, this dimensional class is to be included in the measurement of dust levels in the workplace. A modification of currently used metrological techniques is thus essential. Afsset recommends adapting the ATEM

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⁷ At the present time, background outdoor pollution levels for the Parisian conurbation are clearly lower than that those permitted under regulations. It was estimated at 0.3 f/l for fibres > 5 µm and 1.9 f/l for SAPs, or approximately 2 f/l for the entire distribution range of asbestos fibre particle sizes.

⁸ Asbestos fibre measurements were carried out using PCM.
method (direct or indirect) so that it can be used as an application in the occupational environment.

Finally, Afsset feels it is important to remember that:

- the ALARA\(^9\) (As Low As Reasonably Achievable) principle must be applied for a carcinogenic substance that does not have a threshold;
- due to the fact that available data does not justify the setting of a STEL, it is recommended\(^{10}\) that the concentration corresponding to 5 times the 8-hour OEL over a 15-minute period is not exceeded, in order to limit the significance of exposure levels over short periods of time.

5 - Additional Afsset recommendations

In view of the current scientific data available and on the basis of the collective expert appraisals on asbestos fibres carried out by Afsset, the agency recommends an update of the characterisation and counting techniques for short asbestos fibres be encouraged so that occupational exposure can be more precisely characterised. The objective of this recommendation is to improve knowledge on the dose-effect relationships, especially for exposure during epidemiological studies, and thus contribute to the reduction in the inaccuracies of quantitative assessments of the health risks at low doses.

Four copies produced,

The Director General

\begin{figure}
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\includegraphics[width=0.1\textwidth]{signature.png}
\end{figure}

Martin GUESPEREAU

\(^{9}\) As Low As Reasonably Achievable

\(^{10}\) For more details refer to the "collective expert appraisal report with the view to setting the Occupational Exposure Limits for chemicals in the workplace", dated December 2008, detailing the recommendations on Occupational Exposure Limits with the view to limiting the effects and the number of peaks in exposure during the working day (section 1)
Expert appraisal for establishing
Occupational Exposure Limit values
for chemicals

Asbestos fibres: assessment of the health effects and
methods used for measuring exposure levels
in the workplace

Collective expert appraisal
REPORT

CES "Expert appraisal for establishing occupational exposure limit values for
chemicals"
April 2009
Keywords

OEL, limit values, setting, exposure levels, occupational environment, thin asbestos fibres, short asbestos fibres, expert appraisal, health effects, mesothelioma, metrology, measurement methods, workplace, reference value, PCM, ASEM, ATEM
APPROVAL OF THE EXPERT APPRAISAL REPORT BY THE COMMITTEE OF SPECIALISED EXPERTS

This collective expert appraisal report was approved by the CES "expert appraisal for establishing occupational exposure limit values for chemicals" (OEL committee) on 27 April 2009.

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Mrs DIERS Brigitte;
Mrs DONNADIEU-CLARAZ Marie;
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Collective expert appraisal: review and conclusions

COLLECTIVE EXPERT APPRAISAL:
REVIEW AND CONCLUSIONS

Relating to the "expert appraisal for establishing occupational exposure limit values for chemicals"

Relating to the assessment of the health effects and methods used for measuring exposure levels in the workplace for asbestos fibres

This document summarises and presents the investigations of the Committee of Specialised Experts.

Presentation of the question

On 7 February 2005, the Directorate General for Health (DGS), the Directorate General for Work (DGT) and the Directorate for Economic Studies and Environmental Evaluation (D4E) requested Afsset to assess the health risks linked to short asbestos fibres (SAFs) (length $L < 5 \, \mu m$, diameter $d < 3 \, \mu m$, with a ratio $L/d \geq 3$). An additional mission letter addressed to the Agency from the Directorate General for Pollution and Risk Prevention (DPPR), the DGS and the DGT, dated 16 May 2007, requested that the field of investigation be extended to include thin asbestos fibres (TAFs) ($L \geq 5 \, \mu m$, $d < 0.2 \, \mu m$ and $L/d \geq 3$).

In February 2009, Afsset published an opinion accompanying a collective expert appraisal report instructed by its Committee of Specialised Experts (CES) "Assessment of risks associated with air environments" in which they answered the questions raised on the following 3 topics:

1 Afsset expert appraisal report relating to "Taking into account the dimensional criteria for the characterisation of health risks linked to asbestos inhalation", February 2009
Assess the toxicity of SAFs and TAFs;

Determine the possibility of characterising the particle size distribution of fibres according to exposure scenarios (general population or occupational environment) and the type of asbestos (chrysotile or amphibole);

Assess the risks to human health linked to SAF exposure (not included in current regulations) and to TAF exposure (not included in current occupational regulations) and redefine, if necessary, a new protection threshold for the general population.

The funding ministries also wanted the relevance of regulatory provisions currently in force examined, especially:

- the current protection threshold for workers, set at 0.1 f/cm$^3$ of asbestos over 1 hour;
- the absence of adequate counting of SAFs and TAFs in the occupational environment;
- An analysis of the possibilities offered by Transmission Electron Microscopy (TEM) so that all asbestos fibres can be better counted, including thin fibres, in comparison with Phase Contrast Microscopy (PCM), as well as its limitations;

With the support of the Committee of Specialised Experts (CES) "Expert appraisal for establishing occupational exposure limit values for chemicals" (OEL committee), Afsset received a mission to give its opinion on the need to recommend another OEL by indicating the level or levels, the recommended reference period or periods and the most suitable measurement technique for the occupational environment.

**Scientific Context**

An international benchmark method, using PCM, was set up at the end of the 1960s by the World Health Organization, following a consensus based on metrological considerations. It defines the characteristics of the fibres to be taken into account when measuring the concentration of airborne fibres in the workplace. A fibre was thus defined as any elongated solid particle, natural or artificial, with parallel sides, having a diameter below 3 μm, a length above or equal to 5 μm and a length-width ratio above 3.

A publication by Dodson *et al.* (2003)\(^2\) discusses this definition and investigates the pathogenicity of asbestos fibres based on their dimensional parameters. This article, which is a critical literature review, analyses and highlights the potential impact asbestos fibres below 5 μm in length can have on health. The authors conclude that current data supports the hypothesis that asbestos fibres result in a pathological outcome regardless of their length. They therefore suggest that the exclusion of SAFs from the genesis of asbestos-related diseases is questionable.

On 9 February 2009, in its collective expert appraisal report on short and thin asbestos fibres, Afsset recommended, particularly for the occupational environment:

- carrying out measurements systematically including fibres with a length above or equal to 5 μm, thus taking into account TAFs (L ≥ 5 μm, d < 3 μm);

not taking into account SAFs in the counting of fibres for regulations in the occupational environment when the systematic presence of asbestos fibres with a length above 5 μm in occupational activities linked to asbestos in the work place will indirectly cover a possible health risk linked to SAFs.

Organisation of the expert appraisal

Afsset entrusted the Committee of Specialised Experts (CES) "Expert appraisal for establishing occupational exposure limit values for chemicals" (OEL committee) with the investigation into questions relating to the recommendations that could be made in view of establishing an occupational exposure limit for asbestos fibres. This committee commissioned several rapporteurs (five experts from the OEL committee, two experts from the "short and thin asbestos fibres" working group and five Afsset agents) to carry out this appraisal.

The expert appraisal work was regularly submitted to the OEL committee (with regard to the methodology used and the scientific approach). The reports produced take into account the observations and additional comments of the other members of the OEL committee.

These expert appraisal activities are therefore a result of work by a group of experts having complementary competences. They were carried out in compliance with the French NF X 50-110 Standard "Quality in Expert Appraisal Activities" with the objective of respecting the following points: competence, independence, transparency and traceability.

Description of the method

1- For the assessment of health effects:
The OEL committee used the Afsset collective expert appraisal report of November 2008 relating to short and thin asbestos fibres\(^3\) in order to study the toxicity of asbestos fibres as well as original articles describing the pathogenic power of these fibres. The assessment of health risks has been carried out by carefully listing the models proposed in the literature and recognised internationally. Two models have been used; that of Inserm 1997\(^4\) from US-EPA 1986 and that suggested in 2000 by Hodgson and Darnton\(^5\). The data has been carefully analysed and the conclusions as well as the limitations have been clearly retranscribed and have been the subject of careful reading by several members of the OEL committee. The interpretations and critical reading of all of the data have been presented several times to the entire OEL committee.

The summary report on the assessment of the health effects of asbestos fibres has been presented for discussion to the OEL committee at several meetings on 17 March, 22 May, 11

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\(^3\) Afsset (Agency for Environmental and Occupational Health Safety) 2008. Taking into account the dimensional criteria for the characterisation of health risks linked to asbestos inhalation: Reassessment of toxicological, metrological and epidemiological data with a view to health risk assessment for the general population and workers, November 2008.


September and 4 December 2008, and 5 February and 2 April 2009.

2 - For the assessment of methods of measuring exposure levels in the workplace:

The listing of different methods and protocols used to measure exposure levels of fibres in the workplace has been mainly taken from the Afsset collective expert appraisal report of November 2008 relating to short and thin asbestos fibres.

The possible application of these methods for the measurement of occupational exposure to asbestos fibres for the purposes of comparison with occupational exposure limits has been assigned to two rapporteurs. Furthermore, they could discuss the choice among all of the existing fibre counting and identification methods with the Afsset working group set up for the expert appraisal relating to short and thin asbestos fibres. The presentation of this work was the subject of discussions with other OEL committee experts at several meetings on 4 December 2008 and 5 February and 2 April 2009.

The OEL committee approved:
- the review of the assessment of health effects from asbestos fibres during its meeting on 2 April 2009;
- the review relating to methods of measuring exposure levels in the workplace for asbestos fibres during its meeting on 2 April 2009.

The review and conclusions of the collective expert appraisal were approved by the OEL committee on 20 May 2009.

Conclusions of the collective expert appraisal

In light of available data, the OEL committee retained the following facts:

- all known and commercialised mineral varieties of asbestos are likely to cause cancer in humans by inhalation. A single value will be recommended to protect from the effects of all mineral varieties;
- given the carcinogenic potential of thin asbestos fibres, this dimensional class is to be included when measuring dust levels in the workplace;
- SAFs are not to be counted in the occupational exposure measurements. Indeed, due to the systematic presence of asbestos fibres with a length above 5 \( \mu \text{m} \) in occupational activities linked to asbestos in the workplace, the OEL that will be suggested will indirectly cover a possible health risk linked to SAFs.

The OEL committee therefore considers it necessary to reassess the OEL currently in place for asbestos in order to take account of the carcinogenic effect of TAFs.

Following analysis of all of the literature, and the current state of available data, the OEL committee considers that:
• no threshold value for health effects being proven, in terms of known carcinogenicity of asbestos fibres in humans, the toxicity of these fibres occurs according to a mechanism of action without threshold;

• the available data on the carcinogenicity of asbestos is sufficient to derive a dose-effect relationship for low doses and their correlation to a potency slope factor.

In these conditions and in accordance with its working methodology, the OEL committee has decided not to recommend values for establishing occupational exposure limits for asbestos fibres but to assess additional individual risks of cancer, taking into account both the risks of lung cancer and mesothelioma.

After analysing all of the excess health risk calculations available in the literature, and by considering the occupational exposure scenarios, the OEL committee has chosen to retain the 1997 Inserm model due to that fact that:

- it has the advantage of being based on French mortality data;
- it uses simple and easy to understand hypotheses;
- the superiority of the more complex model of Hodgson and Darnton could not be demonstrated with regard to the limitations and uncertainties associated with each of these models.

However, the OEL committee has recalculated the potency slope factors in order to ensure that the estimations from the Inserm model are in agreement with those of the Hodgson and Darnton model.

The application of the Inserm model, which applies to a group of exclusively male workers and a majority exposure to a variety of chrysotile fibres (asbestos fibres considered as having the lowest carcinogenic potential), under a continuous asbestos exposure scenario (40 hours per week and 48 weeks per year i.e. 1,920 hours per year) from the age of 20 to 65 years, thus leads to an excess risk of mortality by mesothelioma or lung cancer compared to the French worker population of:

- $10^{-4}$ for an exposure concentration of $3.10^{-3}$ f/ml;
- $10^{-5}$ for an exposure concentration of $3.10^{-4}$ f/ml;
- $10^{-6}$ for an exposure concentration of $3.10^{-5}$ f/ml.

When there appears to be no quantitative evidence of acute toxicity linked to asbestos fibres, the setting of a STEL is not recommended.

In the absence of skin penetration data for asbestos fibres, the assigning of a "skin" notation has not been retained.
Finally, the OEL committee feels that it is important to remember that:

- the ALARA\(^6\) principle must be applied for a carcinogenic substance that does not have a threshold value;
- when available data does not allow or justify the setting of a STEL, it is recommended that the value corresponding to five times the 8-hour OEL should not be exceeded over a 15-minute period\(^7\), in order to limit the extent of exposure levels over short periods of time.

Concerning the assessment of exposure measurement methods, the OEL committee believes that none of the methods (PCM\(^8\), ASEM\(^9\), indirect ATEM\(^10\) or direct ATEM) is ideal for measuring occupational exposure to asbestos fibres, especially exposure to the thinnest of these fibres, for the purposes of comparison to the OEL.

Adaptation of the ATEM methods, using the indirect route (in order to alleviate the risk of fibre loss and changes in their particle size distribution during the preparation phase) or direct ATEM (to obtain optimal distribution of the deposit on the filter during sampling), should eventually allow these methods to become valid for use in the occupational environment so that the exposure of operators to asbestos fibres, whatever their dimensional characteristics, can be assessed.

Maisons-Alfort, France, 20 May 2009

On behalf of the experts of the OEL committee,

François Paquet, Chairman of the OEL committee

\(^6\) As Low As Reasonably Achievable

\(^7\) For more details, refer to the collective appraisal report for establishing Occupational Exposure Limit values for chemicals, dated December 2008, detailing the recommendations on Occupational Exposure Limits with the view to limiting the significance and the number of exposure peaks during the working day (section 1)

\(^8\) Phase Contrast Microscopy

\(^9\) Analytical Scanning Electron Microscopy

\(^9\) Analytical Transmission Electron Microscopy
Preamble

The French system for establishing OELs comprises three clearly distinct phases:

- an independent scientific expert appraisal phase (the only phase entrusted to Afsset);
- a phase to draw up a draft regulation for binding or indicative limit values undertaken by the French Ministry of Work;
- a phase of consulting with social partners, when the draft regulation is presented to the French High Council for Occupational Risk Prevention (CSPRP) and the French National Commission for Occupational Health and Safety in Agriculture (CNHSTA). The aim of this phase is to discuss the effectiveness of the occupational exposure limits and to determine potential deadlines for application, according to technical and economic feasibility problems.

The organisation of the scientific expert appraisal phase required to establish Occupational Exposure Limits (OELs) was entrusted to Afsset within the framework of the Occupational Health Plan 2005-2009 (PST).

OELs, such as those recommended by the Committee of Specialised Experts (CES) "Expert appraisal for establishing occupational exposure limit values for chemicals" (OEL committee), are the levels of concentration of pollutants in the workplace atmosphere that should not be exceeded over a determined reference period, and below which the risk of adversely affecting health is negligible. Even if reversible physiological changes are sometimes tolerated, no organic or functional impairment, whether it be irreversible or prolonged, is permitted at this level of exposure for the large majority of workers. These concentration levels are determined by considering that the exposed population (workers) is a population that does not include either children or the elderly.

These concentration levels are determined by the OEL committee experts, based on available information from epidemiological, clinical or animal toxicological studies. The identification of these security concentrations for human health generally requires the application of correction factors to values identified directly by the studies. These factors allow the taking into account of a certain number of uncertainties inherent to the extrapolation process that is carried out when undertaking an assessment of the health effects of chemical substances on humans.

Two types of values are recommended by the OEL committee:

- an 8-hour Occupational Exposure Limit value: This is, unless otherwise indicated, the limit of the time-weighted average of the concentration of a chemical in the air within the breathing zone of a worker over the course of an 8-hour working day.

With current scientific understanding (in toxicology, medicine and epidemiology) the 8-hour OEL is supposed to protect, over the medium and long term, the health of workers exposed regularly and throughout their working life to the chemical concerned.
- a Short Term Exposure Limit (STEL): This is a limit value corresponding to exposure measured over a 15-minute reference period (unless otherwise indicated) during the exposure peak, irrespective of its overall duration. It aims to protect workers from any harmful health effects (immediate or short-term toxic effects, such as irritation) due to peaks in exposure.

These two types of values are expressed either:

- in mg/m³, i.e. milligrams of chemical per cubic metre of air and in ppm (parts per million), i.e. in cubic centimetres of the chemical per cubic metre of air, for gases and vapours;
- in only mg/m³ for liquid aerosols and solids; or
- in f/cm³, i.e. fibres per cm³ for fibrous materials.

The 8-hour OEL can be exceeded over short periods of time during the working day on the condition that:

- the weighted average of the values over the entire working day is not exceeded.
- the STEL is not exceeded, if one exists.

In addition to the OELs, the OEL committee also assesses the need to assign a "skin" notation if significant skin penetration is possible. This notation shows the need to take into account the cutaneous exposure route in the exposure assessment and, if necessary, implement appropriate prevention methods (such as the wearing of protective gloves). Skin penetration of substances is not taken into account in the determination of atmospheric limit value levels and can thus potentially lead to health effects independent of these atmospheric values.

The OEL committee also assesses applicable benchmark methods for measuring exposure levels in the workplace. Different protocols are classified according to the methods used. These methods are then assessed and classified according to how they conform to the 2006 Standard EN 482: "Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents". Classification is made according to two categories:

- category 1 for fully validated methods: reliability, precision, specificity, sensitivity, conservation of samples, etc.
- category 2 for indicative methods (validation criteria are not detailed in the protocol or are not sufficiently explained).

Category 1 methods are those that are recommended in preference for exposure measurements in reference to regulatory binding OELs. In the absence of category 1 methods, category 2 methods are recommended for exposure measurements in reference to regulatory indicative OELs.
Abbreviations

ACGIH: American conference of governmental industrial hygienists
AEV: average exposure value
AFNOR: French Association for Standardisation
ASEM: Analytical Scanning Electron Microscopy
ATEM: Analytical Transmission Electron Microscopy
CES: Committee of Specialised Experts
CI: Confidence interval
DFG: Deutsche Forschungsgemeinschaft (Germany)
DNA: deoxyribonucleic acid
EC: European Commission
EINECS: European inventory of existing commercial substances
ELINCS: European list of notified substances
FRp: Fibres regulated in the occupational environment
GESTIS: Gefahrstoffinformationssystem (information system on hazardous substances)
HSE: Health and Safety Executive (Great Britain)
IARC: International Agency for Research on Cancer
IDLH: immediately dangerous to life or health (values defined by NIOSH)
INRS: French National Research and Safety Institute
LOAEL: lowest observed adverse effect level
LOD: limit of detection
LOQ: limit of quantification
MAK: Maximale Arbeitsplatz-Konzentration (maximum concentration in the workplace)
MDHS: methods for the determination of hazardous substances (methods defined by the HSE)
MW: molecular weight
NI: no information
NIOSH: National institute for occupational safety and health (USA)
NOAEL: No observed adverse effect
NOEC: No observed effect concentration
OEL: Occupational Exposure Limit
OSHA: occupational safety and health administration (USA)
PBPK: Physiologically Based Pharmacokinetic
PCM: Phase Contrast Microscopy
PEL: permissible exposure limits (values defined by the OSHA)
PNSM: programme national de surveillance du mésothéliome (French National Programme for Mesothelioma Monitoring)
ppm: parts per million
REL: Recommended exposure limits (values defined by NIOSH)
RR: Relative risk
SAF: short asbestos fibres
SCOEL: Scientific Committee for Occupational Exposure Limits
STEL: Short Term Exposure Limit
TAF: thin asbestos fibres
TSH: Thyroid Stimulating Hormone
TWA: time weighted average
WHO: World Health Organization
Glossary

8-hour Occupational Exposure Limit: This is the average value over time of concentrations to which a worker is effectively exposed over the course of an 8-hour shift.

BMD: (Benchmark dose): the dose corresponding to a fixed response level in principle (generally 1, 5 or 10%), calculated from the exposure effects relationship in animals or humans.

CAS number (Chemical Abstracts Service number) of a chemical substance: this is the registration number of this substance in the Chemical Abstracts Service database, which is a division of the American Chemical Society. A unique and specific number is thus assigned to each substance that has been described in the literature.

EC number: this is either the EINECS number or the ELINCS number. The EINECS number identifies the substance in the Inventory of Existing Commercial Chemical Substances in Europe before 18 September 1981. The ELINCS identifies the substance in the list of chemical substances introduced onto the European market after 18 September 1981 and notified in accordance with the Directive 67/548/EEC.

Example PSF = 10^{-5} is the additional probability of 0.00001 compared to the baseline risk of contracting cancer linked to the studied exposure.

Index Number: this is the number assigned to dangerous substances registered on the list in Appendix I of Directive 67/548/EEC.

IER (Individual Excess Risk) = PSF x IC. This is the product of the PSF and the dose received by an individual. It is, from a theoretical point of view, the additional probability of observing a harmful effect linked to the agent studied in an individual.

LOAEL: this is the lowest dose leading to an effect considered to be harmful and statistically significant in comparison with the reference.

NOAEL: this is the maximum dose not leading to statistically significant harmful effects in comparison with the reference, from the identification of the LOAEL. In other words, it is the dose tested that directly precedes the LOAEL.

OEL: this is a value that must never be exceeded and which is measured over a maximum duration of 15 minutes: the sample is limited to the duration of the exposure peak (when this is technically possible) without exceeding 15 minutes.

PSF (Potency Slope Factor): Probability for an individual to develop cancer linked to an exposure equal to, on average over the course of their life, a unit dose of the toxic substance.

STEL: this is a limit value corresponding to a 15-minute reference period (unless otherwise indicated) during the exposure peak.
Preface

The initial aim assigned to the writers of this report was essentially to evaluate, with regard to the work carried out by the Afsset working group on the toxicity of thin/short asbestos fibres (Afsset, 2005; Afsset, 2008), the following elements:

- the relevance of the current French OEL (0.1 f/cm³ per hour), knowing that this limit excludes the counting of short asbestos fibres (SAFs) as well as thin asbestos fibres (TAFs);
- the consistency of the current OEL in light of the expert appraisal carried out and the different varieties of asbestos by studying possible differential toxicity according to the type of asbestos (chrysotile versus amphiboles);
- the assessment of different measuring methods and their adaptation for taking into account the dimensional characteristics of the asbestos fibres (long, thin, short).

Of course, precision of the general information about asbestos and its effects on health are key in the development of the justification. Throughout this report, it is frequently recalled that this is necessary for an understanding of the presentation.

This report does not aim to describe all publications relating to the effects on health following occupational exposure to asbestos, a known human carcinogen. The main effects of exposure to asbestos on human health, i.e. asbestosis, benign pleural diseases, bronchopulmonary cancer and mesothelioma, are well known and not discussed in this report.

It is noted that on 24 March 2009, the International Agency for Research on Cancer (IARC) recognised two new cancers - cancer of the larynx and ovarian cancer - as being possibly caused by exposure to asbestos fibres. In light of available scientific data, the IARC concluded "insufficient evidence" of the link between asbestos exposure and these two cancers. Since these results were only officially published in "Lancet Oncology" in May 2009 and the official update of the asbestos monograph is only intended for publication by the IARC in 2010, the group of Afsset experts have not taken this new data into account.
PART A - Assessment report about effects on health
1 Consensus on the definitions

So as to be clear on the different dimensional classes of fibres that will be dealt with in the rest of this report, it is desirable to give some definitions.

1.1 Definition of a fibre

As a reminder, a fibre is defined as a particle having a length/width ratio > 3/1 ("aspect ratio" or form factor) and approximately parallel sides. The L/d > 3/1 ratio is essentially based on a consensus set up by hygienists. Mineralogists often prefer to use a 5/1 or even a 10/1 ratio to define a fibrous structure.

1.2 WHO definition of a fibre

The characteristics of the fibres to be taken into account when measuring the concentration of airborne fibres by PCM are defined by a WHO reference method. Thus, this standardised method defines a fibre as any elongated solid particle, natural or artificial, with parallel sides, having a diameter below 3 µm, a length above 5 µm and a length-width ratio above 3. We note that the resolution of optical microscopy limits the observation of fibres with a diameter > 0.25 µm. The WHO fibres are frequently called respirable fibres in the literature. This assimilation can be erroneously interpreted, as the dimensions of fibres likely to settle in the alveolae are not limited to those defined according to the WHO criteria and particularly include fibres with a length below 5 µm (Inserm; 1997).

It is noted that fibres measured through occupational health (FRp) correspond to the WHO definition of a fibre.

1.3 Short and thin asbestos fibres: SAF/TAF

For the remainder of this report, the OEL committee has chosen to adopt the definitions of fibres used by the Afsset working group (Afsset, 2008).

An SAF is defined by a length below 5 µm, a diameter below 3 µm and a length/width ratio above 3. In practice and according to the specified L/d ratio, the diameter will not exceed 1.67 µm. Currently, SAFs are not taken into account during regulatory measures carried out through occupational health or in the general environment. No consensual definition exists for the dimensions of "short" or "long" fibres, including in experimental work. A limit of 5 µm in length is frequently cited but it is not internationally recognised for comparative analysis of toxicity as a function of dimensional parameters. This limit of 5 µm has been arbitrarily chosen by the scientific community and managers in the 1960s for its convenience of use in metrological analysis and optical microscopy.

A TAF is defined as any asbestos particle having a length above 5 µm, a diameter below 0.2 µm and a length/width ratio above 3. Currently, TAFs are only taken into account during regulatory measures in the general environment. For TAFs, the limit of 0.2 µm diameter to define this particle size class corresponds to the resolution limit of optical microscopy. This limit is not internationally used for the comparative analysis of toxicity as a function of dimensional parameters.
2 General information

2.1 Identification

2.1.1 Names and chemical compositions of different types of asbestos

The term "asbestos" describes a variety of hydrated silicates naturally formed during the metamorphism of rocks. An appropriate mechanical operation transforms these silicates into mineral fibres that can be used industrially.

Two varieties of asbestos can be distinguished: serpentine and amphibole.

The mineral crystalline structure of serpentine rock is commonly called chrysotile. The amphiboles include five distinct species: anthophyllite, amosite, crocidolite, actinolite and tremolite, differing from each other by their chemical composition (Inserm, 1997) (table I).

Table I: Different varieties and species of asbestos (Kirk - Othmer, 1978)

<table>
<thead>
<tr>
<th>Species</th>
<th>CAS No.</th>
<th>Variety</th>
<th>Chemical composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysotile</td>
<td>12007-29-5</td>
<td>Serpentine</td>
<td>3MgO.2SiO₂.2H₂O</td>
</tr>
<tr>
<td>Anthophyllite</td>
<td>17068-78-9</td>
<td>Amphibole</td>
<td>7MgO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Amosite</td>
<td>12172-73-5</td>
<td>Amphibole</td>
<td>11FeO.3MgO.8SiO₂. H₂O</td>
</tr>
<tr>
<td>Actinolite</td>
<td>13768-00-8</td>
<td>Amphibole</td>
<td>2CaO.4MgO.FeO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Tremolite</td>
<td>14567-73-8</td>
<td>Amphibole</td>
<td>2CaO.5MgO.FeO.8SiO₂2.H₂O</td>
</tr>
<tr>
<td>Crocidolite</td>
<td>12001-28-4</td>
<td>Amphibole</td>
<td>Na₂O.Fe₃O₅.FeO.8SiO₂.H₂O</td>
</tr>
</tbody>
</table>

Composition variations, impurities

The chemical composition of chrysotile varies slightly according to the deposits in comparison with the ideal composition Mg₃(Si₂O₅)(OH)₄ with 37-44% SiO₂, 39-44% MgO and 12-15% H₂O. The mineral is often accompanied by impurities linked to substitutions or to macroscopic inclusions representing 20% by weight, sometimes more. Iron and aluminium are the most common impurities; others are calcium, chromium, nickel, manganese, sodium and potassium.

The chemical compositions of amphiboles are more complex and more variable than that of chrysotile. The predominant cations are Mg²⁺, Fe²⁺, Fe³⁺, Na⁺, and Ca²⁺ (see table II)
Table II: Typical chemical compositions of amphiboles (Kirk-Othmer, 1978)

<table>
<thead>
<tr>
<th></th>
<th>Crocidolite %</th>
<th>Amosite %</th>
<th>Anthophyllite %</th>
<th>Actinolite %</th>
<th>Tremolite %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SiO₂</td>
<td>49-53</td>
<td>49-53</td>
<td>56-58</td>
<td>51-52</td>
<td>55-60</td>
</tr>
<tr>
<td>MgO</td>
<td>0-3</td>
<td>1-7</td>
<td>28-34</td>
<td>15-20</td>
<td>21-26</td>
</tr>
<tr>
<td>FeO</td>
<td>13-20</td>
<td>34-44</td>
<td>3-12</td>
<td>5-15</td>
<td>0-4</td>
</tr>
<tr>
<td>Fe₂O₃</td>
<td>17-20</td>
<td>-</td>
<td>-</td>
<td>0-3</td>
<td>0-0.5</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>0-0.2</td>
<td>-</td>
<td>0.5-1.5</td>
<td>1.5-3</td>
<td>0-2.5</td>
</tr>
<tr>
<td>CaO</td>
<td>0.3-2.7</td>
<td>-</td>
<td>-</td>
<td>10-12</td>
<td>11-13</td>
</tr>
<tr>
<td>K₂O</td>
<td>0-0.4</td>
<td>0-0.4</td>
<td>-</td>
<td>0-0.5</td>
<td>0-0.6</td>
</tr>
<tr>
<td>Na₂O</td>
<td>4-8.5</td>
<td>trace</td>
<td>-</td>
<td>0.5-1.5</td>
<td>0-1.5</td>
</tr>
<tr>
<td>H₂O</td>
<td>2.5-4.5</td>
<td>2.5-4.5</td>
<td>1-6</td>
<td>1.5-2.5</td>
<td>0.5-2.5</td>
</tr>
</tbody>
</table>

Other impurities, particularly organic, can occur in chrysotile as well in the other amphiboles, during transport or industrial transformation.

2.1.2 Crystalline structure

The crystalline structure of a fibre determines the form and size of the fibres.

The Inserm collective expert appraisal (Inserm, 1997) specifies that this crystalline structure is a significant element of differentiation between chrysotile and amphiboles.

The crystalline structure of chrysotile is in overlapping layers or sheets. It is based on a non limited layer of silica \((\text{Si}_2\text{O}_5)_n\) in which all the silica tetrahedra point in the same direction. On one of the faces of this layer, and connecting the silica tetrahedra, a layer of brucite \((\text{Mg(OH)}_2\) is found, in which two of the three hydroxyl groups are replaced by oxygen atoms at the points of the tetrahedra. The superposition anomalies, as well as the internal constraints between the layers, curve the layers forming cylinders called fibrilles.

Amphiboles consist of two chains or ribbons based on \(\text{Si}_4\text{O}_{11}\) units separated by a band of seven cations forming the base unit. Two hydroxide groups are attached to the central cation and are entirely contained in the structure composed of a stacking of ribbons. The bond between ribbons is chemically weak and crystals easily show cleavage parallel to the ribbons. Minor isomorphic substitutions can also occur with \(\text{Al}^{3+}, \text{Ti}^{4+}, \text{K}^+\) and \(\text{Li}^+\). Unlike chrysotile, amphiboles do not have a single fibrille as a structural unit. All amphibole fibres are straight and do not show the typical curvature of chrysotile.

2.1.3 Physicochemical properties

Asbestos fibres are minerals with exceptional physical and chemical properties. They do not burn, they are remarkably resistant to diverse chemical attacks depending on the species, and show a heightened mechanical resistance to traction. These properties have led to the development of the use of asbestos fibres in multiple forms, for manufacturing numerous widely consumed industrial products or in the construction of buildings (Inserm, 1997).

Several physicochemical parameters play a role in the toxicity of asbestos fibres, including the chemical composition, the presence of impurities, dimensional characteristics, surface characteristics, and the solubility in the biological environment (from a biopersistance angle).
2.1.3.1 Dimensional characteristics

Asbestos fibres can be very short, and many are shorter than 5 μm. They can also exceed several millimetres (maximum 40 mm and 70 mm, respectively for chrysotile, amosite or crocidolite).

The minimum diameter of isolated chrysotile fibres is around 0.02 μm. Electron microscopy shows that the majority of chrysotile fibres are hollow cylinders, of which the length to width ratio (also known as the form factor or elongation ratio) can be 100:1.

The diameters of amphibole fibres are around ten times larger, with significant variations from one variety to another and from one deposit to another (crocidolite 0.06 μm to 1.2 μm, amosite 0.15 μm to 1.5 μm, and anthophyllite 0.25 μm to 2.5 μm).

2.1.3.2 Surface characteristics

The surface of the fibres can be considered according to different points of view, for example surface geometry (external surface of the fibres or stacks of fibres, m²), specific surface (m²/g), or even reactive surface (surface capable of interacting with other biological or chemical molecules, or of producing active species with oxygen). The fibres can thus adsorb metals, biological macromolecules or organic molecules; the adsorbed species can in turn modify the properties of the fibre and its toxicity.

Chrysotile fibres have a positive surface charge, whereas in the case of amphiboles it is negative. The specific surfaces of amphiboles are much weaker than those of chrysotile. Gas adsorption determination gives, for example, a specific surface of 3 to 15 m²/g for crocidolite fibres compared with 30 to 50 m²/g for chrysotile.

2.1.3.3 Other characteristics of asbestos

All forms of asbestos are resistant to strong bases. Chrysotile is sensitive to acids, even weak ones, and to heat: magnesium atoms are released, leaving a silica residue. Amphiboles show variable resistance to acids, crocidolite being more resistant than amosite.

Despite their high thermal resistance, the different forms of asbestos all begin to decompose above 1,000°C. Their thermal decomposition is gradual and the kinetics are specific to each species. Chrysotile is completely dehydroxylated at 800°C with the formation of a complex amorphous product (forsterite). The major thermal decomposition products of amphiboles are Na-Fe Pyroxene (inosilicate of NaFe3+Si2O6), magnetite and vitreous silica if the transformation is carried out in the absence of oxygen.

Regarding mechanical resistance properties, the traction resistance varies notably according to the amphibole species, chrysotile being at an intermediate level. The following ranking is accepted: crocidolite > chrysotile > amosite > anthophyllite > tremolite > actinolite.

2.2 Classifications and occupational tables

Asbestos is a known human carcinogen.

European classification (28th adaptation to Directive 67/548/EC): Carc. Cat. 1, R45; T: R48/23

General system: tables 30 (occupational ailments following the inhalation of asbestos dust; created in August 1950, last updated by Decree 2000-343 of 14 April 2000) and 30b (bronchopulmonary cancer caused by the inhalation of asbestos dust; created in May 1996, last updated by Decree 2000-343 of 14 April 2000).
3 Existing OELs

It should be noted that the current occupational exposure limits for asbestos fibres apply to the measurement of asbestos fibres with a length above 5 μm, a diameter below 3 μm (and above 0.2 μm due to the resolution limit of optical microscopy), and with a length/width ratio above 3 (WHO fibres). For information, the exposure limits, listed in the Gestis database, are given in a table in Appendix 4.

3.1 European OELs


The nature of the exposure limit: binding

8-hour OEL: 0.1 fibre/ml

3.2 French exposure limits

Decree no. 2006-761 of 30 June 2006 relating to the protection of workers against the risks linked to the inhalation of asbestos dust and modifying the French labour code (second part: State Council Decrees)

The nature of the exposure limit: binding

1-hour OEL: 0.1 fibre/ml

3.3 American OELs

ACGIH TLV-TWA (2000): 0.1 fibre/ml

NIOSH (REL over 100 minutes for a sample of 400 litres; 2001): 0.1 fibre/ml

OSHA (PEL over 8 hours; 2001): 0.1 fibre/ml (fibre > 5 μm). The OSHA (2001) provides a STEL (30 minutes) of 1.0 fibre/ml (applicable in the construction and shipbuilding industries).

The Mine Safety and Health Administration (MSHA) set regulatory exposure limits (Federal Register, 2008) of 0.1 f/ml (for a reference period of 8 hours) and 1 f/ml (for a reference period of 30 minutes).
4 Summary of the SCOEL report

No SCOEL report relating to asbestos.
5 Toxicokinetics - Metabolism

The fraction deposited in the respiratory tract is partly eliminated, degraded or transferred to other organs (translocation). The mechanisms likely to be involved are numerous and depend particularly on the physicochemical properties of the fibres or the variety of fibres deposited: partial decomposition, phagocytosis by macrophages or other cells, transport - active (for example by macrophages or by mucociliary escalator) or inactive (by diffusion) - defibrillation (longitudinal), fracture (transversal), etc.

The scientific community agrees on the fact that the toxicokinetic characteristics and the toxicity of the fibres are partly linked to the dimensions and durability of the fibres. Other parameters such as the surface reactivity of the fibres (according to their composition) must affect these mechanisms but have been less studied to date (Donaldson and Tran, 2004).

This chapter does not aim to give a general review of the toxicokinetic and metabolism issues of asbestos fibres but is concerned particularly with the specific data regarding the influence of dimensions and more particularly for SAFs and TAFs. The points are partly taken from the working group report to which it is useful to refer for a more exhaustive description of the studies (Afsset, 2008).

5.1 Human toxicokinetic data

Once deposited in the lung, the asbestos fibres are likely to spread out into the body (Miserocchi et al., 2008). They are found particularly in lymphatic ganglions linked to the pulmonary system, in the kidneys, the liver, in the urine and as far as the foetus in pregnant women who have been exposed.

The human data is difficult to use (EPA, 2005, p. 6.41) for several reasons:

1) it is not possible to assess the pulmonary load over time since only an autopsy can do this;
2) the conversion technique of the samples can modify the result: it has been shown that several methods of fixing tissues accelerate the decomposition of asbestos fibres;
3) preparation and analysis methods of the samples vary;
4) the possibilities of reconstructing past exposures of subjects are limited;
5) the sampled pulmonary sites vary generally from one laboratory to another (and the characteristics of deposit or retention depend on the location; see Churg and Wood, 1983).

5.1.1 Pulmonary toxicokinetics of fibres in humans

The significance of purification phenomena should not be neglected in the case of very old exposures and/or exclusive exposures to chrysotile. Preferential purification of short fibres is considered by Morgan et al., (1983) (Mc Donald, 1980). Chrysotile shows lower biopersistence than amphiboles and, in cohorts mainly exposed to pure chrysotile or chrysotile - amphibole mixtures, significant proportions of amphiboles are often found during the analysis of pulmonary samples, even when the smallest range of sizes are taken into account. The half-life of fibres in the lungs was set at years for amphiboles and months for the small chrysotile fibres (Churg and Wright, 1994). Albin et al. (1994) show a relatively rapid turn-over for chrysotile and a much slower rate for crocidolite and tremolite in the lungs of workers from the asbestos cement sector, mainly exposed to chrysotile. Consequently, a low pulmonary concentration of chrysotile fibres does not exclude the possibility of a significant previous exposure (Churg, 1988; Pooley and Wagner, 1988). Finkelstein and Dufresne (1999) show, however, that the biopersistence of chrysotile in the lungs of subjects from mining towns of Quebec increases with length; the half-life of chrysotile fibres longer than 10 μm being around 8 years. Half-lives
of 7 to 8 years are reported for crocidolite in the lungs of workers exposed in the Wittenoom mine (De Klerk et al., 1996) and of 20 years for amosite in shipyard and insulation workers located on the north-west coast of the United States (Churg and Vedal, 1994).

Regarding the dimensions, in pulmonary samples, SAFs are always associated with the presence of long asbestos fibres, although the latter are sometimes in low percentages. No observation exists that mentions only SAFs, the relative proportions of SAF-long fibres being, however, dependent on the analytical methodology. In the lungs of workers exposed to crocidolite in Wittenoom, there is a very good correlation between the concentrations of SAFs and long asbestos fibres (De Klerk et al., 1996) (fibres L < 4 µm vs L > 4 µm: rpearson\(^1\) = 0.95). There is also an excellent correlation between the concentrations of "short" fibres (L < 8 µm) and "long" fibres (L > 8 µm) of amosite in the lungs of shipyard or insulation workers located on the north-west coast of the Pacific (r = 0.99). McDonald et al. (2001) report correlation coefficients of 0.6 and 0.9 respectively between the concentrations of short fibres (L < 6 µm), intermediate fibres (L from 6 to 10 µm) and long fibres (L > 10 µm) in young adults suffering from mesothelioma.

The particle size characteristics of fibres in the pulmonary tissue, as in air samples, are heavily dependent on the fibre type. Analyses consistently show that the average diameters of chrysotile and crocidolite fibres are rarely above 0.2 µm, which indicates a very high percentage of TAFs. The gradation of the diameter of the bare fibres and central fibres of asbestotic bodies according to the type of asbestos, mainly follows the following trend: chrysotile < crocidolite < amosite < tremolite < anthophyllite. The diameter, however, tends to increase with the length of the fibres (Case and Dufresne, 1997; Case et al., 2000; Nayebzadeh et al., 2001)

Long asbestos fibres, and in particular amphibole fibres, are found in the lungs of cases exposed through activities principally based on SAFs, such as servicing brake pads, which are known to only contain chrysotile (Finley et al., 2007). Indeed, during ASEM examination (fibres L >= 5 µm) of pulmonary tissue of 10 cases of mesothelioma for which the only known exposure to asbestos was through contact with brake dust, an excess of commercial amphibole fibres was observed in 5 of the 6 cases with a high fibre content (Butnor et al., 2003). Some asbestotic bodies, and therefore some long fibres, of chrysotile and tremolite (90% and 10% respectively) were shown in the lungs of a brake lining repairman (Levin et al., 1999). The presence of 25% long fibres of chrysotile and 40% long fibres of tremolite is also reported in the lungs of three workers exposed during the production or repair of brakes, all suffering from bronchopulmonary cancer (Churg and Wiggs, 1986).

### 5.1.2 Other locations

Compared to the number of studies devoted to the concentration and particle size analysis of fibres retained in the lungs, biometrological data regarding the dissemination of particles, the fibres inhaled in the body and their retention in extra-pulmonary sites are rare. Transpleural, lymphatic and systemic migration pathways have been mentioned as possible routes for dissemination of the fibres to these sites (Boutin et al., 1996), but no information currently exists allowing the dominant pathway to be determined.

In humans, asbestos fibres have been particularly identified in samples of lymphatic ganglions (Dodson et al., 1990; Sebastien et al., 1979), in healthy or diseased parietal pleura (Boutin et al., 1996; Suzuki et al., 1991; 2005; Dodson et al., 1990; LeBowffant et al., 1976; Sebastien et al., 1980), omentum and radix mesenteri (Dodson et al., 2000; 2001) and in the placenta and tissue samples of stillborn infants (Haque et al., 1992; 1996; 1998).

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\(^{11}\) Statistical term for measuring correlation (linear dependence) between two variables.
The migration of asbestos fibres to extra-pulmonary sites where they can accumulate involves both SAFs and long asbestos fibres. All of the studies consistently show that asbestos fibres of several tens of μm can be found in extra-pulmonary locations.

Although long asbestos fibres, and more particularly TAFs, are found in the parietal pleura, the proportion of SAFs, in particular chrysotile SAFs, is generally higher there than in the lungs. The dimensions of the fibres in the pleura and in the lungs are 2.3 μm and 4.9 μm respectively (average lengths) (Sébastien et al., 1980) and 3.82 ± 0.22 μm and 4.45 ± 0.45 μm respectively (Boutin et al., 1996). This is confirmed by Dodson et al. (2005) and Suzuki et al. (2005). The same is true for fibres found in lymphatic ganglia (Dodson et al., 2007), where some fibres > 5 μm can be observed at variable levels (up to 100%).

5.2 Animal toxicokinetic data

The analysis of publications concerning kinetic purification of fibres for short and higher durations has been carried out in the report of the working group "short and thin asbestos fibres" (Afsset, 2008). Only the main conclusions are reported.

In order to approach human exposure conditions, only experimental studies carried out by inhalation have been recorded. Studies in which the animals have been exposed to asbestos fibres by intratracheal instillation are not mentioned, but other reports analyse them (Inserm, 1997).

Regarding the long and medium term studies in rats in inhalation chambers, for amphiboles, the biopersistance of SAFs seems lower than that of long fibres (Davis et al., 1986; 199612 and Wagner, 1990b). The biopersistance of chrysotile SAFs also seems lower than that of long fibres (Platek et al., 1985; Davis et al., 1996). On the basis of this data, the SAFs seem less persistent than long fibres, regardless of the type of asbestos.

Long-term "nose-only" exposure studies in rats, allowing the relative biopersistance of SAFs to be assessed, are limited to 2 studies for chrysotile (Hesterberg et al., 1993; Bernstein et al., 2006), with samples of very short average lengths: 0.7 μm and 2.87 μm respectively (L geometric mean), and 1.1 μm and 4 μm respectively (L arithmetic mean). The value of the retention rates of SAFs, compared with other fibres, results in contradictory conclusions, not allowing the relative biopersistance of SAFs compared with other fibres to be concluded. However, inhalation chamber studies reinforce the hypothesis of a lower biopersistance for SAFs. From the data available for amphiboles, the interpretation is limited to the fact that fibres < 5 μm are more purified than fibres > 20 μm (Bellmann et al., 2002 and McConnell et al., 1994).

Regarding long-term studies in hamsters by inhalation, only two studies (McConnell et al., 1995; 1999) are available, of which only one assesses short chrysotile fibres of a length below 5 μm (duration of post-exposure monitoring defined as 2 months). The results show a slight decrease in the number of long fibres (> 5 μm) and a slight increase in the number of SAFs (< 5 μm). This data is compatible with the hypothesis of transversal fragmentation of chrysotile fibres (transversal fragmentation of long fibres thus increases the percentage of SAFs).

Concerning short-term studies in rats, according to the "nose-only" method, the analysis of four publications relating to amphiboles (Musselman, et al., 199413; Hesterberg et al., 1996, 1998b; Bernstein et al., 2005b) suggests that SAFs have a lower biopersistance than long

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12 Analogous data reassessed by Cullen et al. (2000)
13 Analogous data reassessed by Musselman et al. (1994)
fibres, in agreement with other results based on exposure by inhalation. For chrysotile, there are three studies from the same author (Bernstein et al., 2004; 2005a\textsuperscript{14} and 2005b) indicating an increased biopersistence of SAFs compared with long asbestos fibres.

On reading the results from experimental studies, several conclusions tend towards a higher biopersistence for long fibres, with, however, some slightly different or even contrary results, which suggest that other factors (concentration of fibres in the aerosol, treatment of fibres during preparation, etc.) are likely to influence the results.

5.3 Metabolisation

Asbestos fibres are not metabolised in the usual sense of the term: they undergo a change in the body, particularly due to defibrillation to a greater or lesser extent (in particular chrysotile), partial decomposition (noticeable for chrysotile; Hiroshima and Suzuki (1993), Langer et al., 1972; Jaurand et al., 1977; practically indistinguishable for amphiboles), and breaking of the longest fibres into shorter fibres.

\textsuperscript{14} Original data in Bernstein (2003) completed for this publication
6 General toxicity

The vast majority of points in this paragraph are from the Afsset report (2008).

6.1 Mechanistic knowledge

It is important to remember the current understanding of the toxicity mechanisms for asbestos fibres, in order to put the dimensional parameter into a more general context.

Experimental studies show that the biological effects depend on the dimensions of the fibres and are linked to their shape. Thus fibres of several tens of microns in length can reach pulmonary alveolae and are likely to penetrate into the epithelial cells.

The fibres are phagocytosed, not only by macrophages, but also by epithelial cells (bronchial, alveolar and mesothelial). This results in internalisation, a cellular response to stress, as well as disruption of cell division, shown in numerous studies. The mitotic disruptions are all the more significant since the sample has more long fibres. Studies carried out with macrophages have shown that the smaller fibres were phagocytosed by these cells, but that phagocytosis of long fibres could be limited. This "frustrated" phagocytosis, during which toxic factors could be secreted, damages the surrounding environment. In recent studies, the length limit of fibres phagocytosed by macrophages is estimated at around 20 µm (Moolgavkar et al., 2001; Daniel Maxim et al., 2003; Turim and Brown, 2003).

The surface properties of the fibres influence their reactivity. A very large number of studies exist on redox properties; they are associated with the presence of metals, particularly iron, playing a catalyst role, generating oxidants and free radicals. These molecules can cause oxidation of DNA bases. Such alterations have been observed in cultured epithelial cells exposed to asbestos fibres, as well as in animals. These effects appear to be more significant for long fibres, compared with short fibres, for an equivalent weight.

The surface properties of the fibres also impart their ability to adsorb biological macromolecules, proteins and DNA, as well as phospholipids. The pre-adsorption of proteins onto the fibres causes a change in the interactions between the fibres and the cells (Hill et al., 1995).

Asbestos fibres can also adsorb certain organic molecules. Polycyclic aromatic hydrocarbons, PAHs, have been detected on the surface of fibres. The explanation for the multiplicative effect of tobacco in smokers exposed to asbestos, compared to the risk of the onset of bronchopulmonary cancer, could be based in part on the hypothesis that the fibres can interact with PAHs (Kamp et al., 1998).

Finally, the chemical composition of fibres affects their resistance to decomposition; the differences in composition, but also in the structure, lead to a higher or lower biopersistance. Because of the differences in composition but also the structure, chrysotile is less resistant than amphiboles, particularly to acid pH and heat.
6.2 Toxicity in humans

6.2.1 General notions

The risks to health are clearly established in conditions of occupational exposure to asbestos. These arguments come from numerous studies, involving all types of study and all epidemiological methods: case studies, cohort and case-control studies, "ecological" studies and evolutionary tendency analysis. These studies have been carried out in different countries and have included extremely diverse populations and occupational groups. The health risks concern non-cancerous pleural and pulmonary disease, the risk of lung cancer and pleural and peritoneal mesothelioma (Inserm, 1997).

Epidemiological data, particularly from meta-analyses (Nicholson, 1986; Inserm, 1997; Hodgson et al., 2000) suggests that the exposure to chrysotile fibres causes a lower incidence of cancer than exposure to amphiboles, particularly for mesothelioma; this statement is debated for lung cancer. Furthermore, there is a known risk of developing cancer following inhalation of chrysotile fibres.

6.2.2 Discussion on the influence of dimensions

Analysis of the epidemiological studies discussing the influence of dimensions is described in the report mentioned in the preamble of the chapter (Afsset, 2008).

The study of health effects from occupational exposure to SAFs through epidemiological literature remains very fragmented. Indeed, few studies mention the presence of SAFs or, even more so, mention the distribution of the lengths of these fibres. Furthermore, the few studies available concern sectors where the exposure to SAFs is significant but never exclusive, due to the inevitable presence of fibres > 5 μm in length. In the ATSDR report (2003), it was thus highlighted that valid epidemiological data on this question is not available.

Analysis from the epidemiological data of possible effects of SAFs was based mainly on two possible indirect approaches. The first approach attempts to describe the data concerning industrial sectors, classified according to the knowledge, in principle, of SAF concentrations, concentrating on areas where these concentrations are described as being the highest. The second approach involves describing the differences in the observed risks in certain industrial sectors using comparative analyses, or even meta-analyses. Indeed, several hypotheses, including dimensional criteria, have been considered in order to explain the differences in mortality by cancer between sectors.

Regarding TAFs, epidemiological data is even more fragmented than for short fibres.

Analysis of epidemiological studies favours the existence of a significant excess risk of mesothelioma and/or bronchial cancer (which remains to be specified), in certain industrial sectors having the highest SAF concentrations and, more particularly, in the mining sector. However, the specific study of the textile sector cohort in South Carolina involving workers exposed to chrysotile fibres from the Quebec mines where the McDonald et al. cohort was set up, (1980; 1993; 1997a and 1997b) (mines) but with supposedly different dimensional characteristics (higher percentage of TAFs), shows a higher level of risk than in the mining sector. On the contrary, an excess risk has not been shown in the brake systems maintenance sector (high percentage of SAFs linked to a modification of physiochemical properties), for both mesothelioma and bronchial cancer.

For the positive studies in the sectors of interest with high SAF concentrations, the excess risk seems lower than in sectors having a greater proportion of fibres > 5 μm. However, the interpretation of these results is difficult, due to the variety of asbestos fibres used, the variation in exposure levels, the presence of different co-factors according to the industrial sectors, and finally the contamination of chrysotile by amphiboles at variable levels depending on the case. However, the inconsistency in taking into account these factors and the variable methodological quality of the studies, do not appear to be able to satisfactorily explain the differences noticed between the industrial sectors. The variation in particle size distributions of
asbestos fibres (particularly the proportions of SAFs) between the sectors and a lower toxicity of SAFs could lead to a plausible hypothesis to explain the differences in excess risk between these sectors. However, the small variations in the proportions of SAFs observed in the data acquired during this expert appraisal for several industrial sectors suggests a limited effect of these particle size variations compared to the differences in the health effects observed for the different industrial sectors.

The uncertainty that can be attributed to estimated exposure levels, the non-representative nature of the metrological data available and the presence, even in small quantities, of fibres > 5 μm in length in sectors where the excess risk is lower, do not however allow a categorical conclusion to be drawn concerning the absence or presence of a low carcinogenic effect of SAFs.

Recently published meta-analysis data is in agreement with these results, thus proving the differences in excess risks between these different industrial sectors, present in the mining sector, but absent or low in the asbestos cement or brake system servicing sectors.

Recent work from the EPA (2003) and NIOSH (Gilbert et al., 2007; Stayner et al., 2007), on the modelling of the dose-effect relationship for bronchial cancer (and mesothelioma for EPA), using an employment-exposure matrix and consisting of ATEM metrological data, show interesting results. Taking into account the thinnest fibres has thus enabled significant improvements to be made in the accuracy of the models estimating the slopes for bronchial cancer and mesothelioma. Concerning short fibres, the results are less convincing, due to a strong statistical correlation between the number of fibres of different classes of length (< or ≥ 5 μm). In the study carried out for the EPA, taking into account the fibres of length < 5 μm does not improve the accuracy of the model and the authors believe that they should not be taken into account in the estimation of dose-effect relationships. The question of defining a dimensional class most representative of the health effects of asbestos fibres therefore remains open, even though the EPA data (fibres L > 10 μm and D < 0.4 μm) shows new elements.

Finally, the toxicity of SAFs assessed from an epidemiological point of view cannot be dismissed, although certain authors believe that it is limited. The existence of a non-zero but weak effect of SAFs thus seems to be a conservative hypothesis. Regarding TAFs, recent data, albeit few in number, confirms the existence of a significant carcinogenic effect.

6.3 Toxicity in animals

6.3.1 General points and methodological questions

In a similar way to human data, numerous in vivo and in vitro studies show the genotoxic and carcinogenic character of asbestos fibres. Reviews exist (Inserm, 1997; IARC, 1977) on the subject and the aim of this chapter, once again, is to discuss more specifically the results concerning the influence of dimensional parameters on the toxicity of asbestos fibres. The points are mostly taken from the Afset report (2008).

In the experimental studies, it is theoretically possible to know with precision the data based on pulmonary exposure and biometrology. It is nevertheless important to remember that some elements change the interpretation of the results.

6.3.1.1 Preparation of samples for animal experimentation

The samples of fibres should be prepared in order to be inhalable by the animal; however, it is difficult to obtain only short fibres, and the preparation methods are likely to modify the physicochemical characteristics (Wagner, 1990a).

In the case of asbestos, batches are prepared with this aim [International Union Against Cancer (UICC), National Institute of Environmental Health Sciences (NIEHS) and different industrial sources]; this allows better comparison between the studies carried out by different teams for various biological effects. However, these same samples could have been treated...
and contaminated (by metals for example), and thus their physicochemical properties could have been modified.

6.3.1.2 Exposure methods of the animals

The animals were exposed in inhalation chambers (historic studies) or "nose-only" (more recent studies); intratracheal instillation or intracavitary inoculation have also been used, each with its respective advantages and disadvantages.

6.3.1.3 Assessment of the exposure of animals

The comparison of the animal exposure assessment data between publications is difficult due to the heterogeneity of the methods used for measuring the fibres (PCM, SEM, TEM); moreover, the limit of counting fibres of length above 5 μm has not always been applied, as it has no scientific justification.

Furthermore, the selection of fibres from a "crude" sample aimed at keeping the fibres inhalable by the animal produces a sample of which the properties can differ from those of particles in the ambient air of the occupational or general environment.

6.3.1.4 Number of animals exposed and statistical use of the results

Numerous studies, particularly historic ones, have used a limited number of animals. Because of this, the increase in the frequency of tumours compared to the reference animals is not always statistically significant, through lack of statistical power.

6.3.2 Discussion on the influence of dimensions

6.3.2.1 Studies by implantation in the pleura of rats

Different studies, particularly those from the Stanton team (Stanton et al., 1972, 1972, 1981), have shown a lower toxicity for short fibres compared with long fibres. Numerous samples of fibres of diverse nature and structures were implanted into the pleura of rats, and the fibres split into 34 particle size classes according to their length and their diameter. In the treated animals, the percentage of mesotheliomas went from 0% to 72.4% (around 30 rats per test). The 34 dimensional categories were re-grouped into 11 categories and the correlation coefficients calculated between the particle size class and the number of mesotheliomas. The best correlation was obtained with the number of fibres measuring below 0.25 μm diameter and more than 8 μm length ("Stanton fibres"); a relatively good correlation was still observed in the other categories, for diameters up to 1.5 μm and lengths above 4 μm. Correlations were not observed for fibres 4 μm in length and > 1.5 μm in diameter.

In these studies, the following points seem to be determining factors:

- The demonstration of a tumorigenic potential depending on the dimensions of fibres regardless of their structure and their chemistry (this observation does not exclude a role for these two parameters).
- The existence of erroneous observations, for poorly defined reasons.
- Experimentation based on rats, a species later considered to be less sensitive to fibres, at least by inhalation, than humans.

The data from the Stanton team has been re-analysed by others (Bertrand and Pézerat, 1980; Oehlert, 1991). The number of "Stanton fibres" could have been a better indicator of the risk than the "average fibre dimension". Later studies have compared the effects of "long" and "short" asbestos fibre samples. Davis et al., (1986, 1988) have shown that the short fibres are capable of causing tumours at high doses, with higher induction times. The "short fibre" samples comprised, however, fibres of length above 5 μm, which could have played a role in the differences in response. Statistical analysis of data by Berman et al (1995) concludes that no univariate measure allows the tumoral response to be described correctly, although
consideration of the concentration of fibres > 20 μm in length gives the best correlation. Multivariate analysis suggests that asbestos fibres of length below 5 μm do not have carcinogenic potential; and that those that are either thin (diameter < 0.3 μm), or thick (diameter ≥ 5 μm) have a positive potential, which increases with length.

The significance of the number of "Stanton fibres" (L > 8 μm; d < 0.25 μm) has been mentioned in other articles where asbestos fibres were injected intrapleurally (Monchaux et al., 1981; Jaurand et al., 1987; Van der Meeren et al., 1992). The potential role of other parameters in the toxicity of fibres has been researched: it has been observed that the modification of the physicochemical characteristics of fibres was likely to modify the relationship between the number of fibres found in the lungs and the carcinogenic potential. In a study on various chrysotile samples, different tumorigenic potentials could furthermore be explained by a difference in chemical composition of fibres (Monchaux et al., 1981); however, the dimensions of fibres and the specific surface are also modified.

6.3.2.2 Intratracheal instillation studies

Many other studies have compared samples having a greater or lesser proportion of long fibres. The fibrosing potential of long fibres has been confirmed after intratracheal instillation of chrysotile in rats (Lemaire et al., 1985) or crocidolite in mice (Adamson and Bowden, 1987; Adamson et al., 1993), without however excluding a fibrosing potential of SAFs for significant and long-term exposures. Wagner (1990a, 1990b) compared the incidence of pulmonary tumours induced in rats after inhalation of crocidolite or erionite fibres ("short" or "long" samples in the two cases); there again, the "short" samples are slightly active or inactive; the same is true for mesotheliomas after intrapleural inoculation.

6.3.2.3 Intraperitoneal instillation studies

Several studies have explored the effects induced on mice by the intraperitoneal administration of single doses of long or short asbestos fibres (Goodlick and Kane, 1990; Donaldson et al., 1991; 1989). Long fibres caused noticeable local inflammatory reactions compared with SAFs. Although a single dose of SAFs seems to be without significant inflammatory repercussion, successive doses appear to increase the reactions. In these experiments, long asbestos fibres and SAFs were injected in equal number (480 μg and 120 μg respectively).

Likewise, the cellular proliferation was assessed by the incorporation of tritiated thymidine (Adamson and Bowden, 1987; Adamson et al., 1993). An increase in the percentage of positive pulmonary cells was observed in the treated mice; weak and short-lived for SAFs, less short-lived and more marked for long fibres, in comparison with the controls. Similar results were obtained through observation of subpleural cells and mesothelial pleural cells.

Finally, Davis et al. (1991a and b) compared the effects of six samples of tremolite after intraperitoneal injection in rats. These samples comprised either "asbestiform" fibres (3 samples), or fragments with length to width ratios above 3 (3 samples). The latter were less tumorigenic, but one of them caused an increased level of mesotheliomas. The authors found that the best correlation between the risk of mesothelioma and the logarithm of the number of fibres, according to their dimensions, involved fibres of length > 8 μm and of diameter < 0.25 μm (Stanton fibres). Samples containing a low number of long and thin fibres produced an increased percentage of mesotheliomas. These results led the authors to question the potential carcinogenic role of the cleavage fragments.

6.3.2.4 Inhalation study

Platek et al. (1985) exposed rats and monkeys to low concentrations of chrysotile (1 mg/m³) by inhalation for 18 months; the median length of the fibres was 0.67 μm. Only 0.66% of the fibres had a length above 5 μm (as determined by PCM). In these conditions, neither fibrosis nor pulmonary tumour was observed. After 11.5 years without exposure, the geometric mean of the length of the pulmonary fibres in the 9 monkeys (59 samples examined) was 3.5 μm, 35% of fibres being longer than 5 μm. Asbestotic bodies were observed, but no fibrosis (Stettler et al., 2008).
Finally, the results obtained in these primates involve exposure to a low concentration of heavily crushed chrysotile fibres, and after a relatively short exposure duration compared with human exposure. The authors believe that the consequences of these results, namely the absence of toxicity of these chrysotile fibres, are limited and should be considered in the context of the study.

6.3.2.5 In vitro study

In the literature, some studies have compared the effects of samples of different dimensions on cultured cells. The results are difficult to interpret, however the data shows an improvement in the correlation between cytotoxicity of fibres and the increase in the length or the decrease in the diameter (Brown et al., 1986; Goodglick and Kane, 1990; Hart et al., 1994).

A study was carried out on the detection of mitotic anomalies on cultures of rat pleural mesothelial cells exposed to different types of fibres. The results showed that the production of abnormal anaphases/metaphases was dependent on the number of fibres corresponding to criteria defined by Stanton (L > 8 μm d ≤ 0.25 μm) present in the sample (Yegles et al., 1995). From these results, it can be seen that the parameter of length is not the only thing that explains the effects observed, as the number of fibres in the same length category in samples termed either positive or negative is sometimes very close.

6.3.2.6 Biopersistance study

The main results from a toxicokinetic viewpoint are described in chapter 5.2. If biopersistance, as such, is a critical parameter of the toxic potential of fibres, there are some arguments for the impact, in terms of toxicity, of a short fibre being below that of a long fibre. However, taking into account the numerical distribution of fibres in different particle size classes within a sample, it must also be considered that the number of short fibres retained in the lungs is always in great excess compared with long fibres. Consequently, a dose of short fibres is much higher than that of long fibres. This difference is taken into account in estimating a toxic effect.

However, the interpretation of the results remains limited due to the following:

1. the preparation of samples, as mentioned throughout this section, is likely to modify the physicochemical characteristics of the asbestos fibres making it difficult to interpret, and particularly compare, the results of one study to another (particularly for the same type of asbestos).

2. metrological analysis remains marred by large variability and some authors use different analytical techniques (ASEM vs ATEM).

3. exposure durations and post-exposure durations can differ from one study to another and thus accentuate the difficulties in comparison between publications.

4. the limited amount of data comparing SAFs and long asbestos fibres as well as contradictory results limit the interpretation of biopersistance, etc.

In conclusion, it is impossible to use the results from experimental studies concerning biopersistance in order to estimate the harmfulness of SAFs compared with long asbestos fibres (length above 5 μm).

6.3.3 Discussion on the influence of other parameters

The toxic potential of asbestos fibres results from a combination of parameters, thus limiting the interpretation of results based only on the influence of the dimensions of fibres.

Numerous studies have been carried out on the role of physicochemical properties of fibres, likely to affect their reactivity in the biological environment. The composition seems important and is involved in their resistance to decomposition. Due to the differences in composition, but also the structure, chrysotile is less resistant than amphiboles, particularly to acid pH and heat. The different results obtained using modified fibres (chemical or adsorption of biological
molecules, etc.) that show a dependence of the biological response on the characteristics of the fibres, illustrate well the relationship between the physicochemical characteristics of the fibres and their effects. Other parameters include particularly the surface reactivity and the capacity of the fibres to adsorb other molecules, etc.

Thus, although the dimensions are a measurable parameter allowing quantitative variables between the fibres and the biological response to be linked, it is known that this dimensional parameter alone does not fully reflect the toxic potential of the particles. The toxicity of the fibres results from several parameters that vary non-independently (for example, reduction in size is likely to be associated with a change in the surface reactivity, the aggregation state; chemical treatment leading to an increase in the specific surface; interaction with biological macromolecules, etc.).

In conclusion, the toxic potential of fibres cannot only be thought of in terms of dimensions of the fibres, although this parameter seems, in itself, in numerous experimental situations, to be a good indicator of the biological response (Afsset, 2008).

In conclusion from the numerous animal studies analysed, it seems that for:

**Thin asbestos fibres**

The Afsset report (2008) highlights the low percentage of TAFs present within the samples tested in the experimental studies. Thus, it appears difficult to categorically interpret the data but it is true that some results agree in showing that TAFs are toxic in animals. Thus, comparative studies between samples containing a greater or lesser extent of TAFs show that the samples containing a higher percentage of this class were the most active. Statistical analyses have linked the highest probability of tumours to the classes representative of TAFs.

**Short asbestos fibres**

All of the results based on the search for the particle size classes most representative of the carcinogenic potential of asbestos fibres show that long fibres are more active than short fibres and that "short" fibres are: either less active, or inactive, compared with long fibres.

It should be noted that, despite an agreement between the studies for defining a dependence of the effects on dimensional parameters and the surface reactivity, the results based on the clearance of fibres, according to their dimensions, are sometimes divergent between the studies, making it seem that a relative half-life of the short fibres is either higher or lower than that of the long fibres (most often lower).

Certain experimental results in animals or on cell cultures show a toxicity of samples comprising mainly short asbestos fibres (L < 5 μm), particularly in the case of exposure to high or repeated doses. However, samples of short fibres are also systematically linked to a residual percentage of long fibres and the increase in doses is accompanied by an increase in the absolute number of long fibres.

With regard to experimental studies on biopersistence, it seems that it is impossible to use the available results to estimate the harmfulness of SAFs compared with that of long asbestos fibres (length above 5 μm) due essentially to methodological reasons (preparation of samples, variability of analytical techniques used, exposure and post-exposure durations, limited amount of comparative data which is sometimes contradictory).

Based on the current state of knowledge, the main points to retain from reading these studies are:

- The limit of 5 μm in length used to differentiate between a "short" fibre (L < 5 μm) and a "long" fibre (L > 5 μm) does not correspond to demonstrated scientific safety data for fibres of length below 5 μm;
- It should be stressed that there is no study comparing the potential of "long" fibres with that of "short" fibres, all things being otherwise equal, as the selection of fibres, according to the dimensions, generally requires treatments likely to cause other differences between
the samples. The preparation of the samples notably changes the surface reactivity of the fibres. Furthermore, the samples of SAFs have, almost systematically, a residual percentage of fibres above 5 \(\mu m\) in length, and vice versa, thus limiting the interpretation of the results.

**Physicochemical properties affecting the toxicity**

Taking only the dimensional characteristics of the fibres into account is not sufficient to explain their toxic potential. Data also exists showing the importance of chemical and physicochemical characteristics. Publications generally mention the role of other parameters of the fibres (surface reactivity, chemical composition, interaction with PAHs, biological macromolecules, metals or other particles, etc). It therefore appears necessary to not only consider the type of fibres, but, if it has taken place, their treatment, particularly if it is likely to change the interactions with the biological environment.

### 6.4 Human-animal consistency

The consistency between toxicological studies carried out in humans or animals is more qualitative than quantitative, and it not necessarily homogeneous between the target organs (for example, the lungs and the pleura). Thus, the sensitivity of humans to lung cancer caused by the inhalation of asbestos fibres has been estimated at around 100 to 200 times higher than in rats; the concentration of crocidolite fibres in the lungs of rats during a negative study was more than 1,000 times higher than the median concentration in the lungs of workers occupationally exposed to asbestos suffering from mesothelioma (Pott et al., 1994; Muhle and Pott, 2000).

The rat and the hamster are the two species most frequently used in order to assess the carcinogenic potential of asbestos, by various exposure pathways. Of these two species, the rat seems most appropriate as it shows both pulmonary cancers and mesotheliomas, whereas the hamster does not trigger pulmonary cancer after exposure to high concentrations of either chrysotile or amosite. Primates would be an ideal animal model as they are the closest to humans, but they are not used due to their longevity (20 to 30 years to demonstrate the absence of a carcinogenic effect), the number of animals necessary (more than 200 animals of each sex) and the cost (ERG 2003, p. E-17, McConnell, 1999).

Inserm (1997) highlights that the epidemiological studies have shown an increased risk of mortality by pulmonary cancer or mesothelioma, regardless of the mineralogical origin of the fibres. The experimental results obtained in animals have shown the existence of a carcinogenic potential of asbestos fibres, regardless of exposure type, by inhalation or inoculation. Therefore there is a good balance between the experimental and epidemiological results.

### 6.5 General conclusion on the toxicity of asbestos fibres

The risks to health are clearly established in conditions of occupational exposure to asbestos. The health risks concern non-cancerous pleural and pulmonary disease, the risk of lung cancer and pleural and peritoneal mesothelioma (Inserm, 1997). The OEL committee decided to maintain a carcinogenic mechanism of action without threshold for asbestos fibres.

Publications discussing the influence of the dimensional parameter are difficult to interpret, particularly for SAFs (confusion factors, lack of metrology methods etc. for epidemiological studies, or preparation of samples, residual concentrations of long fibres, etc., for animal studies). Furthermore, taking only the dimensional characteristics of the fibres into account is not sufficient to explain their toxic potential. Data also exists showing the importance of
physicochemical characteristics. Indeed, publications generally mention the role of other parameters (surface reactivity, chemical composition, interaction with PAHs, biological macromolecules, metals or other particles, etc.) (Afsset, 2008).

Overall analysis of the literature leads to the following:

**For the variety of fibres**

Epidemiological data, particularly from meta-analyses (Nicholson, 1986; Inserm, 1997; Hodgson et al., 2000) suggests that the exposure to chrysotile fibres causes a lower incidence of cancer than exposure to amphiboles, particularly for mesothelioma; this statement is debated for lung cancer. Furthermore, there is a known excess risk of developing cancer following inhalation of chrysotile fibres.

**For SAFs**

Despite the numerous limitations in interpretation highlighted in the Afsset report (2008), the direct or indirect toxicity (saturation of purification systems increasing the toxicity of long fibres) of SAFs remains difficult to estimate but it cannot be dismissed following epidemiological or experimental studies. In the hypothesis of SAF toxicity, it would be certainly lower than that of long fibres but no weighting is currently definable. In the current state of knowledge, establishing a dose-effect relationship for estimating the toxicity of SAFs has not been carried out experimentally.

**For TAFs**

The epidemiological and experimental studies agree in showing the existence of a carcinogenic potential of TAFs. Statistical analyses have linked the highest probability of tumours to the classes representative of TAFs.

In the current state of knowledge, establishing a dose-effect relationship for estimating the toxicity of TAFs or a weighting attributable to the toxicity of TAFs compared with so called "WHO" fibres has not been carried out experimentally or validated epidemiologically (Afsset, 2008).
7 Setting Occupational Exposure Limits (OELs)

When proposing occupational exposure limits and determining the effects when no threshold limit has been established, the OEL Committee suggests that the Committee of Specialised Experts (CES) should analyse any models used to calculate excess health risks (mainly those published in the scientific literature) and propose to risk managers several exposure levels traditionally associated with excess risks of $10^{-4}$, $10^{-5}$ and $10^{-6}$, whenever possible (data judged to be of sufficiently high quality by the CES). The models used to calculate excess health risks designed using data collected from humans have been selected and described below. These models retained bronchopulmonary cancer and mesothelioma as a critical effect. It is not suggested that pleural plaques are retained as a critical effect.

7.1 Model used by Inserm to calculate excess health risks

The model developed by the Inserm expert appraisal in 1997 is based on the same hypotheses as those established by the US-EPA (United States Environmental Protection Agency) in 1986. It is a linear model relating to asbestos concentrations.

7.1.1 Relationship between cumulative asbestos exposure (f/ml x year) and relative mortality risk

7.1.1.1 Lung cancer

Inserm believes that the most appropriate model for describing the risk of dying from lung cancer attributable to asbestos exposure is a linear model without a cumulative exposure threshold.

Inserm therefore describes the relative risk of dying from lung cancer (RRp = number of cases observed / number of expected cases) in occupational cohorts as follows:

\[
RRp = \frac{\text{Observed cases}}{\text{Expected cases}} = 1 + (K_p) \times (EC)
\]

- \(EC = \sum f \times d\) is the cumulative exposure expressed as "f/ml x year", i.e. the total products resulting from exposure levels "f" (in f/ml) observed during the career history for periods "d" (years) during which these levels prevailed.

- \(K_p\) is the slope that produces the variation of the relative risk of dying from lung cancer by additional cumulative exposure unit (1 f/ml x year). Inserm opted for practicality\(^{15}\) by adopting a single value for the \(K_p\) risk coefficient, equivalent to + 1.0% irrespective of the geological origin of the fibres.

Equally, the extra numbers of lung cancer deaths attributable to asbestos exposure in occupational cohorts can be expressed as follows:

Attributable extra cases = Observed cases - Expected cases = \((K_p) \times (EC) \times (\text{Expected cases})\)

\(^{15}\) The Inserm report (French National Institute for Health and Medical Research) noted the heterogeneous nature of the slopes depending on, among others, the asbestos variety. However, \(K_p = 1\) was chosen to simplify the calculations.
7.1.1.2 Mesothelioma

According to Inserm, the model most suited to describing the risk of dying from mesothelioma attributable to asbestos exposure is a linear model that depends on the level of exposure in f/ml (cubic) based on the period of time that has elapsed since the exposure commenced, reduced by a 10-year period, and in which the excess risk of an individual remains until the end of the person’s life.

\[
I_m = \begin{cases} 
K_m f \left[ (T-10)^3 - (T-10-d)^3 \right] & \text{if } T > 10 + d \\
K_m f (T-10)^3 & \text{if } 10 + d > T > 10 \\
0 & \text{if } T < 10 
\end{cases}
\]

Here:

- \( I_m \): incidence of mesothelioma
- \( K_m \): constant (Km risk coefficient equivalent to 1.0 x 10^-8 for "chrysotile" asbestos exposure, 1.5 times higher for combined exposures (chrysotile and amosite) and three time higher for exposure to amosite alone).
- \( f \): exposure concentration in f/ml
- \( T \): time elapsed since the start of the exposure, in years
- \( d \): length of exposure, in years

Inserm retained "3" as the value to represent the increase rate of the incidence of mesothelioma and the time elapsed since the start of the exposure.

Therefore, the number of mesothelioma deaths due to asbestos exposure in a given population (\( N_m \)) is expressed as:

\[
N_m = I_m \times P \quad \text{(Eq. 2)}
\]

7.1.2 Method used to calculate "lifetime" risks

Inserm has used the all-causes mortality rates (\( t_w \)) amongst the French population to calculate the lifetime risks of an individual (all ages) and establish the number of people at risk of dying (\( P \)). The "lifetime" risks are therefore non-specific risks as they recognise that, as the age of the population advances, the size of the population at risk of dying for all causes will become smaller.

Equally, for a given category, the number of lung cancer deaths expected without any asbestos exposure is calculated using the lung cancer mortality rate (\( t_p \)) for this age category and size of the population at risk of dying (\( P \)).

The "lifetime" risk is generally calculated up to the age of 80 (Inserm 1997; Hodgson 2000). The number of additional deaths attributable to asbestos exposure is therefore obtained by adding the number of deaths calculated in each of the age categories from the start of the exposure until reaching the age of 80.

The individual excess risk (IER) of dying from lung cancer or mesothelioma associated with asbestos exposure is then calculated by establishing a ratio between the number of excess deaths and the size of the population in question.

7.1.3 Exposure and risk calculation scenarios

The risk calculations were carried out for continuous chrysotile exposure (predominantly or exclusively) and several exposure scenarios have been envisaged in this expert appraisal. Only the occupational scenario will be explored in this chapter.

The excess risk of dying from cancer (either mesothelioma or lung cancer) up to the age of 80 was calculated by considering an asbestos exposure for 10,000 men subject to sustained occupational exposure (40 h/week and 48 week/year, i.e. 1,920 hours per year) of 0.1 fpcm/ml of chrysotile, "predominantly" or "exclusively", from the age of 20 to 65.
Taking into consideration the previous hypotheses and an exclusively male population, Inserm believes that for 10,000 men the estimated additional number of deaths due to asbestos exposure is 21 lung cancer deaths and 10 mesothelioma deaths, i.e. 31 deaths due to cancer.

Consequently, to provide a comparison with Hodgson & Darnton’s model presented below, these estimations were converted into individual excess risks \(10^{-4}, 10^{-5}\) and \(10^{-6}\) associated with various concentrations. As an example, taking into consideration the excess risk of mortality due to lung cancer, a continuous exposure at 0.1 f-pcm/ml was associated with an individual excess risk of \(21 / 10000\), i.e. \(2.1 \times 10^{-3}\). Therefore, after an individual excess risk adjustment of \(10^{-4}\), the associated concentration is \(4.7 \times 10^{-3}\) f-pcm/ml. This same reasoning was applied to the other diseases and individual excess risk values. The results are shown in Table V.

### Table V: Chrysotile concentration, expressed in terms of f-pcm/ml, associated with an increased excess risk of dying from lung cancer and/or mesothelioma, taking into consideration a sustained exposure from the age of 20 to 65, 40 hours a week for 48 weeks a year, in a population of exclusively male workers.

<table>
<thead>
<tr>
<th>Types of cancers</th>
<th>Lung cancer</th>
<th>Mesothelioma</th>
<th>Lung cancer and mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-pcm/ml concentration associated with a sustained exposure from the age of 20 to 65, 40 h/week, 48 weeks/year (occupational exposure)</td>
<td>(4.7 \times 10^{-3}) (IER (10^{-4}))</td>
<td>(1.0 \times 10^{-2}) (IER (10^{-4}))</td>
<td>(3.0 \times 10^{-3}) (IER (10^{-4}))</td>
</tr>
<tr>
<td></td>
<td>(4.7 \times 10^{-4}) (IER (10^{-5}))</td>
<td>(1.0 \times 10^{-3}) (IER (10^{-5}))</td>
<td>(3.0 \times 10^{-4}) (IER (10^{-5}))</td>
</tr>
<tr>
<td></td>
<td>(4.7 \times 10^{-5}) (IER (10^{-6}))</td>
<td>(1.0 \times 10^{-4}) (IER (10^{-6}))</td>
<td>(3.0 \times 10^{-5}) (IER (10^{-6}))</td>
</tr>
</tbody>
</table>

### 7.1.4 Limit

Inserm analysed and plotted the limits using source studies and the model set out in its expert appraisal (1997).

#### 7.1.4.1 Characteristics of asbestos exposure in the populations studied:

In the studies analysing lung cancer, the exposure levels observed in the various cohorts ranged from a few f/ml to several dozen f/ml - with extreme values ranging from 1 f/ml (Peto, 1980) to over 250 f/ml (McDonald et al., 1979). Equally, in the mesothelioma studies, the exposure levels reported ranged on average from 15 to 35 f/ml. These figures report a particularly high (mean) occupational exposure. The actual effect of exposure levels, at comparable cumulative exposures, was therefore unable to be analysed at levels below 1 f/ml.

In the populations analysed, the exposure was permanent (at all times of the day, all days of the week and for all weeks worked during the year). The studies did not supply any direct information with regard to the risks associated with exposures unevenly distributed over time (discontinuous or sporadic exposures). They also did not provide any information on whether
exposures of this type were associated with higher lung cancer levels or, on the contrary, the risks were lower than with comparable cumulative exposures over a sustained period of time.

As the studies related to occupational exposure, in the vast majority of cases the exposure of the populations concerned commenced around the age of 20; very little information is available to determine whether the relative risks for lung cancer are altered if the exposure commenced at an older age.

As the populations studied were very frequently exposed to asbestos exposure throughout their working life and in view of the fact that the latency period for the onset of lung cancer is 20 to 30 years, on average, very little data exists to indicate whether the relative increased risk linked to asbestos exposure is present until the end of an individual's life or whether, on the contrary, it decreases a certain amount of time after the cessation of the exposure.

7.1.4.2 Recognising all types of asbestos exposure

The mineral varieties and physicochemical properties of asbestos fibres likely to be inhaled by workers may vary over the course of their professional career, in particular:

- virtually all the minerals include, possibly in a trace form, several different geological types of fibres (for example, asbestos commercially known as "chrysotile" often contains traces of tremolite).
- furthermore, the fibres used at a given period of time often contain a combination of fibres from various origins.
- the exposure of a given individual generally changes over the course of his/her career, as a result of carrying out different jobs, and changes to the industrial processes and procurement methods (even though such changes may only have lasted for a few months – changes of this nature are extremely difficult to quantify retrospectively).

7.1.4.3 Quantifying exposure

The exposure levels over the course of each member of the cohort's working life were necessarily quantified retrospectively. This raised the issue of the spatial and temporal representativity of the environmental measurements established and, consequently, their relevance in terms of determining an individual's cumulative exposure.

7.1.4.4 Recognising tobacco consumption

It was generally impossible to directly take into account an individual's tobacco consumption (which was, in most cases, necessarily retrospective) in the cohort studies. The expert appraisal of Inserm limited itself to indirectly recognising tobacco consumption by comparing the number of lung cancer deaths in each cohort with the expected number of deaths among the general population.

7.1.4.5 Risk slopes

For lung cancer, the Kp slopes take different values into account depending on the study concerned. The least steep slope was observed by McDonald et al. (1984) in a population manufacturing friction products using chrysotile (Kp = 0.01%); the steepest was observed by Finkelstein (1983) in asbestos cement workers exposed to mixed fibres (Kp = + 6.7%). The range between these two figures is considerable (670). The most extreme values have been widely debated in the epidemiological literature.

The main sources of inaccuracy for the Kp estimations are:

- the number of lung cancers observed in the various cohort studies is subject to random fluctuations.
- uncertainty with regard to the exposure.
7.1.4.6 Extrapolating the data to low doses

In 1997, when finalising its collective expert appraisal, Inserm stated that the exact shape (linear, supra-linear and infra-linear) of the dose-risk relationship was unknown for levels below 1 f/ml; it has, however, been clearly established above 1 f/ml and has been accurately described by a linear relationship for this range of exposures.

Inserm emphasised that the suggested extrapolation would not produce scientifically sound data but it should help to analyse the risks for control purposes. However, in the future, the use of extrapolated data may be challenged:

- if experimental data firmly establishes the existence of a safety threshold and determines the value of this threshold,
- if epidemiological data shows that under certain conditions asbestos exposure below 1 f/ml is "consistently" associated with higher lung cancer or mesothelioma risks than previously believed after extrapolating "high" exposure data to "low" exposures.

7.1.4.7 Measurement method

The use of epidemiological studies intrinsically implies that TAFs as such are not taken into account. These were cohort studies carried out on populations of workers from various industries exposed to asbestos (including textile manufacturing, friction products, insulation and cement). They were carried out in an occupational environment and the exposure was measured using Phase Contrast Microscopy (PCM). TAFs were therefore not determined. PCM is an indirect and partial method of measuring the risks associated with any particle size distribution of asbestos fibres. In fact, due to the technical limitations of PCM, only part of the distribution is measured and it is not highly sensitive to variations in the particle size parameters in the different studies; this yields significant statistical uncertainties and inaccurate analyses.

7.2 Model used to calculate excess health risks by Hodgson & Darnton (2000)

Hodgson and Darnton (2000) suggested a non-linear excess cancer risk model (pleural and peritoneal mesothelioma and lung cancer) based on a meta-analysis of the results observed in 17 cohorts. The model took into account the nature of the asbestos fibres and differentiated between three mineral varieties (crocidolite, amosite and chrysotile).

7.2.1 Relationship between cumulative asbestos exposure (f/ml) and excess cancer risks

7.2.1.1 Mesothelioma

According to Hodgson and Darnton, a non-linear model without thresholds for cumulative exposures is most appropriate for describing the risks of dying from mesothelioma attributable to asbestos exposure. This model integrates different parameters depending on the location of the mesothelioma (pleural or peritoneal) and is expressed as follows:

$$ PM = A_{pl}X^r + A_{pr}X^t $$

$PM$ represents the percentage of excess deaths due to mesothelioma compared to the expected mortality all causes considered.

$r$ and $t$ are dose-response slopes on a log-log scale for pleural and peritoneal mesothelioma respectively obtained using a Poisson regression.

$A_{pl}$ and $A_{pr}$ are proportionality constants of these Poisson regressions for pleural and peritoneal mesothelioma respectively.

The corresponding expected number of cancers (pleural or peritoneal) for a given cohort is conveyed as follows: $A_{pl}$ or $pr \times X^r \times t \times E_{Adj} / 100$
The parameters have been estimated to reduce as far as possible the deviation between the observed and predicted cancers for each cohort (pure fibres).

A sensitivity analysis tested the various values of the $r$ and $t$ slopes depending on the nature of the fibres and resulted in the authors retaining the following values as the best estimates for the slopes: $r = 0.75$ and $t = 2.1$; the highest estimate proposed was $r = 1$ and $t = 2.5$; the lowest was $r = 0.6$ and $t = 1.7$. The authors emphasised that the value of $t$ was statistically more uncertain due to the small amount of data available. These various scenarios yielded extremely variable values for $A_{pl}$ or $A_{pu}$, depending on the types of fibres (ranging from 0.00012 to 0.94); however, the details relating to this data cannot be presented herein.

It is the choice of $r$ and $t$ that determines the shape of the model's curve for low exposure levels. In this appraisal, the authors selected a value for $r$ below 1, which therefore supports a convex relationship (supra-linear) between the risks of pleural mesothelioma and a cumulative exposure. To support this hypothesis, the authors reported the findings from two studies (Berry 1991 and Coggon et al. 1995) to demonstrate that the risk of pleural mesothelioma increases relatively steeply at low exposures, and less steeply at high exposures.

The shape of the authors’ model means that each cumulative-exposure unit progressively implies lower risks for pleural tumours, and greater risks for peritoneal tumours.

The proposed model does not take the length of exposure or the age of the first exposure into account. The authors suggested using an adjustment factor derived from the HEI model (Health Effects Institute, 1991) to convert the estimated risk when the age of the first exposure is 30 into other exposure ages.

The authors cut off the mortality predictions at the age of 80, in common with other authors (Inserm, 1997).

### 7.2.1.2 Lung cancer

The authors suggested that the relationship between lung cancer and the cumulative exposure was of a concave type (infra-linear) and described it in the following formula:

$$P_L = A_L X^r$$

$P_L$ is the excess mortality (percentage) due to lung cancer compared to the expected mortality for lung cancer.

$r$ is the dose-response slope on a log-log scale for lung cancer obtained using a Poisson regression

$A_L$ is the proportionality constant of the same Poisson regression for lung cancer.

The number of expected cases of lung cancer for a given cohort is conveyed as follows: $A_L X^r E_{Adj} / 100$

$E_{Adj}$ represents the expected number of lung cancer deaths.

The parameters have been estimated in order to reduce as far as possible any deviation between the observed and predicted cancers for each cohort.

The authors determined values for $r$ between 1 (linear) and 2 depending on the type of fibre, i.e. chrysotile - without being able to distinguish between crocidolite and amosite (combined amphiboles). The corresponding values of $A_L$ ranged from 0.028 to 4.8.

### 7.2.2 Risk calculations

The risk was calculated for a sustained exposure to crocidolite, amosite and chrysotile for mesothelioma and to amphiboles and chrysotile for lung cancer. In terms of mesothelioma, and for exposures starting at the age of 30, the excess mortality (percentage) was applied to the expected mortality for all causes among 40 to 79 year olds (with a minimum 10-year
latency period and a cut-off point at the age of 80). The mortality data for men in Great Britain (1997) was used to estimate the number of lung cancer deaths. The number of extra deaths was assessed for exposures starting at the age of 30 and for maximum periods of 5 years. The individual excess risk (IER) of dying from lung cancer or mesothelioma due to asbestos exposure was calculated by comparing the number of extra deaths and the population numbers concerned. The results in terms of individual excess risks are summarised in the tables below:

**Table VI: Mesothelioma risks calculated according to the nature of the asbestos fibre and the cumulative exposure**

<table>
<thead>
<tr>
<th>Cumulative exposure</th>
<th>Nature of the fibre</th>
<th>Mesothelioma IER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>between 10 and 100 f/ml/year for each fibre</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crocidolite</td>
<td>4.10^{-3}</td>
<td></td>
</tr>
<tr>
<td>Amosite</td>
<td>6.5.10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Chrysotile</td>
<td>2.10^{-5}</td>
<td></td>
</tr>
<tr>
<td><strong>1 f/ml/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crocidolite</td>
<td>6.5.10^{-3}</td>
<td></td>
</tr>
<tr>
<td>Amosite</td>
<td>9.10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Chrysotile</td>
<td>5.10^{-5}</td>
<td></td>
</tr>
<tr>
<td><strong>0.1 f/ml/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crocidolite</td>
<td>1.10^{-3}</td>
<td></td>
</tr>
<tr>
<td>Amosite</td>
<td>1.5.10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Chrysotile</td>
<td>4.10^{-5}</td>
<td></td>
</tr>
<tr>
<td><strong>0.01 f/ml/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crocidolite</td>
<td>2.10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Amosite</td>
<td>3.10^{-5}</td>
<td></td>
</tr>
<tr>
<td>Chrysotile</td>
<td>1.10^{-5}</td>
<td></td>
</tr>
<tr>
<td><strong>0.005 f/ml/year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crocidolite</td>
<td>1.10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Amosite</td>
<td>2.10^{-5}</td>
<td></td>
</tr>
<tr>
<td>Chrysotile</td>
<td>Insignificant</td>
<td></td>
</tr>
</tbody>
</table>
Table VII: Lung cancer risks calculated according to the nature of the asbestos fibre and the cumulative exposure

<table>
<thead>
<tr>
<th>Cumulative exposure</th>
<th>Nature of the fibre</th>
<th>Lung cancer IER</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 and 100 f/ml/year for each fibre</td>
<td>Amphiboles</td>
<td>$1.5 \times 10^{-3}$</td>
</tr>
<tr>
<td></td>
<td>Chrysotile</td>
<td>$5 \times 10^{-5}$</td>
</tr>
<tr>
<td>1 f/ml/year</td>
<td>Amphiboles</td>
<td>$8.5 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td>Chrysotile</td>
<td>$2 \times 10^{-5}$</td>
</tr>
<tr>
<td>0.1 f/ml/year</td>
<td>Amphiboles</td>
<td>$4 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>Chrysotile</td>
<td>Insignificant</td>
</tr>
<tr>
<td>0.01 f/ml/year</td>
<td>Amphiboles</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>Chrysotile</td>
<td>Insignificant</td>
</tr>
<tr>
<td>0.005 f/ml/year</td>
<td>Amphiboles</td>
<td>Insignificant</td>
</tr>
<tr>
<td></td>
<td>Chrysotile</td>
<td>Insignificant</td>
</tr>
</tbody>
</table>

7.2.3 Limits

The limits of Hodgson and Darnton's meta-analysis are partly shared by the collective expert appraisal of Inserm (French National Institute for Health and Medical Research) (see paragraph 7.2.4), in particular:

- The characteristic features of asbestos exposure in the populations studied. The authors confirmed that their models were even more representative when they described the actual range of exposures represented in the cohort studies. The most delicate question obviously concerns the extrapolation of data to lower exposure levels.

- Recognition of all types of asbestos exposures, although the originality of Hodgson and Darnton's work is based on recognising the nature of the fibres especially when selecting a model for the slopes. For the authors, it seems clear that the nature of the fibres induces different mesothelioma responses. The results are less convincing for lung cancer, partly due to a lack of corresponding numbers in the cohorts concerned. However, it should be emphasised that taking such data into account is also the source of uncertainty due to nature of the data originating from the cohorts analysed.

- Quantifying the exposures

- Recognising tobacco consumption in excess lung cancer risks. This bias is discussed in the publication. The authors applied a customary weighting factor which took into account the expected number of lung cancer deaths in the general population, that is for 1000 men aged 30, 54 will die of lung cancer between the ages of 40 and 79 (for women the number is 28). The risk of lung cancer for asbestos exposure is expressed as $0.054 P_i$ for men

- Measurement methods

One of the main divergences of this meta-analysis compared with Inserm's analysis was the use of a non-linear relationship for low doses. A linear extrapolation has been validated for concentrations $> 1$ f/ml; however, it remains hypothetical below this level.

The authors decided to design an infra-linear model (even linear in their sensitivity analysis) for lung cancer. No previous epidemiological study had suggested a dose-response relationship of an infra-linear type, although the authors indicated that this hypothesis had been suggested by experimental data on carcinogens (Hoel and Portier 1995). Hodgson and Darnton recognise,
however, that some uncertainty remains with regard to the cohort data used to design the model. The authors therefore decided to include a coefficient equivalent to 1 for the slope (linear model) in the lower limit of their sensitivity analysis.

The approach for mesothelioma is more complex, and the authors used a non-linear model combining two sub-models: one for pleural tumours (supra-linear) and the other for peritoneal tumours (infra-linear). This hypothesis is based on the interpretation of two studies (Berry 1991 and Coggon et al. 1995) and is a debatable point due to a lack of direct scientific information, especially as the quality of the data used to diagnose the cause of death in the different cohorts was sometimes poor. This means that there was a potential bias of misdiagnosing the cause of death (either mesothelioma and lung cancer or the various types of mesothelioma). The authors also debated the possibility of establishing a single threshold for mesothelioma and concluded that if such a threshold existed, its value would be extremely low in view of the various experimental studies published on this subject. Due to the number of problems concerning the existence of a threshold, the authors opted for a non-linear model without a threshold.

It is difficult to judge the quality of a meta-analysis, as the source data is not often described in great detail, meaning it is extremely difficult to make any presumptions about the standard of the studies on which the results are based. A joint analysis should be favoured whenever possible, i.e. it is the data collected from the cohorts that should be applied directly and not the results obtained from such data. Overall, Hodgson and Darnton's article is of high quality even though the approach adopted is a complicated one and the data limited. However, evidence and arguments are lacking for the choice of hypotheses as well as the exposure scenarios.

### 7.3 Excess risk calculations: discussion

#### 7.3.1 Extrapolating data to lower doses

The extrapolation of epidemiological data to low doses (through different excess risk calculation models) has been the subject of many debates. A few recent studies have provided more information on this issue. Firstly, a Swedish case-control study on the general population (Gustavsson et al., 2002) reported 1038 incidents of bronchial cancer and 2359 control cases. Asbestos exposure was assessed in a report based on over 2400 atmospheric samples taken between 1969 and 1973 (PCM measurements, fibres > 5 μm). The bronchial cancer risk model, based on a logistical model and after adjusting several co-factors including tobacco, yielded an OR (Odds Ratio) = 1.5 [1.2 - 1.9] by cumulative exposure unit (expressed as a log (f/ml/year + 1)). Applied to a cumulative asbestos exposure of 4 f/ml/year, the OR calculated for bronchial cancer appears significantly high (OR= 1.90 [1.3 - 2.7]). A second case-control study was carried out on the general population by Pohlabeln et al. (2002) involving 839 cases and 839 control cases. This study assessed occupational exposure by means of an in-depth expert appraisal using a two-phase protocol based on a sample of 164 subjects in each category (exposed and non-exposed) using specialised questionnaires and career information. The cumulative exposure was calculated by estimating the exposure levels and the length of each period of employment. The logistic regression modelling, adjusted to the tobacco consumption, produced an OR of 1.178 [1.052 - 1.318] by exposure unit (Log (cumulative exposure in f/ml/year +1)). A cumulative exposure of 10 f/ml/year was therefore associated with a significantly elevated OR of 1.94 [1.10 - 3.43]. A third study, published in 2006 by Meguellati-Hakkas et al., analysed a cohort of subjects with a low exposure (telephone line maintenance). After carrying out an assessment using an employment-exposure matrix, an exposure of 2 f/ml/year was associated with an OR of 2.1 [1.1 - 4.0] compared to subjects with an exposure below 0.5 f/ml/year. Although yielding markedly different cumulative exposure values (from 2 to 10 f/ml/year) for an OR of 2, all these studies seemed to point to an underestimation of the reference model for low doses.
The data on mesothelioma demonstrated the existence of a significant risk for low cumulative exposure levels. For example, Iwatsubo et al. (1998) produced an OR of 4.0 [1.7 - 9.7] (4.6 [1.4 - 15.4]) for intermittent (sustained) exposures higher than 0.5 f/ml/year. The data collected more recently by the PNSM (French National Mesothelioma Surveillance Programme) confirmed the existence of a significant risk for low cumulative exposures OR 2.6 [1.5 - 4.5] for an exposure of > 0 - 0.06 f/ml/year compared with non-exposed subjects. Following the analysis carried out using Hodgson and Darnton’s model (2000), the experts emphasised the uncertainties and lack of clarification which seemed out of kilter with the detailed calculations set out in the publication. When calculating the excess mortality risks, the authors differentiated the nature of the asbestos fibres (amosite, crocidolite and chrysotile) and the type of disease (lung cancer and mesothelioma). However, the validity of the estimates is limited, contrary to what the detailed results may suggest.

7.3.2 Choice of model: discussion

Despite more recent data and the proposed non-linear curve, Hodgson and Darnton’s model (2000) does not provide any additional details to validate its superiority over the Inserm model due to the issue of the uncertainties it contains.

The Inserm model – some authors have also emphasised its uncertainties and pointed out its primary role as a decision-making tool – is based on French mortality data and uses simple hypotheses, due to the associated limits, especially in terms of the “major” / “unique” exposure to chrysotile (due to a lack of specific data on amphiboles).

The OEL committee has therefore preferred to retain the Inserm model. Moreover, it should be noted that, according to this model, the concentration associated with an individual excess risk of mortality due to mesothelioma (specific health effect of asbestos exposure) of $10^{-4}$ is approximately $1.10^{-2}$ f-pcm/ml. This value, calculated for a "major" or "unique" exposure to chrysotile concords with the estimations contained in Hodgson and Darnton’s model (2000) for an individual excess risk of mortality due to mesothelioma of $10^{-4}$, even if strong hypotheses were retained to calculate these estimations thereby limiting the interpretation of the comparison (see the conversion calculations in Appendix 5).

7.4 Position of the OEL committee

In view of the data available, the OEL committee has retained the following elements:

- all known and commercialised mineral varieties of asbestos are likely to cause cancer in humans by inhalation. The OEL committee recommends establishing a single value to protect against the effects of each mineral variety.

- In light of the data currently available, the OEL committee has indicated that asbestos fibres are considered as a carcinogen without a threshold. As indicated above, the experimental studies have revealed the genotoxic nature of asbestos fibres. After analysing the dose-response relationship for bronchopulmonary cancer and mesothelioma based on cohort studies, models without a threshold were retained on an international level to describe the relationship between cumulative exposure and cancer.

- The OEL committee has suggested, due to the carcinogenic potential of TAFs, to include this dimensional class in the statutory measurement of dust levels for occupational health, which implies changing the analysis method currently used. Although TAFs are not included in the current models used to calculate the potency slope factor (EPA, 1986; Inserm, 1997, Hodgson and Darnton, 2000), the OEL committee wishes, adopting a conservative approach, that the OEL should also include TAFs and all fibres with a length exceeding 5 μm.

- Based on the data available (Afsset, 2008), the OEL committee does not suggest taking SAFs into account for occupational health regulations. Due to the systematic presence of
asbestos fibres with a length above 5 μm in occupational activities linked to asbestos in the workplace, the OEL retained will indirectly cover a possible health risk linked to SAFs.

To conclude, the current asbestos OEL should be reassessed to take into account the carcinogenic effect of TAFs.
8 Conclusions of the OEL committee

According to the methodology of the OEL committee, no 8-hour OEL is proposed for a carcinogenic substance without a threshold. The scientific literature describes several methods for calculating the excess health risks for lung cancers and mesothelioma associated with an occupational exposure to asbestos. The calculations available for occupational exposure scenarios have been described herein; the OEL committee has decided to retain the one used by Inserm due to the fact that it mainly takes into account exposures to the chrysotile variety and estimates the excess mortality risks due to mesothelioma and lung cancer in relation to the population of French workers. The exposure scenario retained is a sustained asbestos exposure (40 h/week and 48 week/year, i.e. 1,920 hours per week) from the age of 20 to 65.

The concentrations associated with different individual excess risks (IER) are the following:

- \(3 \times 10^{-3}\) f-pcm/ml or an IER of \(10^{-4}\)
- \(3 \times 10^{-4}\) f-pcm/ml or an IER of \(10^{-5}\)
- \(3 \times 10^{-5}\) f-pcm/ml or an IER of \(10^{-6}\)

Finally, in the opinion of the committee of specialised experts it is important to remember that:

- the ALARA principle\(^{16}\) must be applied to a carcinogenic substance that does not have a threshold;
- when the available data does not allow or justify the setting of an STEL, it is recommended that a value amounting to five times the 8-hour OEL should not be exceeded over a 15 minute period\(^{17}\).

The assigning of a "skin" notation has not been retained.

\(^{16}\) As Low As Reasonably Achievable

\(^{17}\) For more information, refer to the collective appraisal report on establishing Occupational Exposure Limits for chemicals in the workplace, dated December 2008, detailing the recommendations on Occupational Exposure Limits with a view to limiting the effects and the number of exposure peaks during the working day (section 1)
9 Bibliography


Afsset (French Agency for Environmental and Occupational Health Safety), 2005. Critical review by a group of experts of the article entitled "Asbestos fiber length as related to potential pathogenicity: a critical review" by Dodson et al (2003), 22 pages.


Dodson RF, Shepherd S, Levin J, Hammar SP (2007). Characteristics of asbestos concentration in lung as compared to asbestos concentration in various levels of lymph nodes that collect drainage from the lung. Ultrastruct Pathol 31(2) 95-133.


Gilbert SJ, Stayner LT, Kuempel ED, Dement JD. (2007). Determining an optimal exposure metric from a bivariate distribution of asbestos fiber exposures (length, diameter) in a cohort of textile workers. ASA Section on Statistics in Epidemiology, 2544-2546.


NIOSH (1976). Revised recommended asbestos standard - NIOSH publication No. 77-169, 100 pages.


PART B - Report evaluating the methods of measuring exposure levels in the workplace
1 Introduction

The term 'asbestos' includes the following types and varieties:

<table>
<thead>
<tr>
<th>Types</th>
<th>CAS No.</th>
<th>Variety</th>
<th>Chemical composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysotile</td>
<td>12007-29-5</td>
<td>Serpentine</td>
<td>3MgO.2SiO₂.2H₂O</td>
</tr>
<tr>
<td>Anthophyllite</td>
<td>17068-78-9</td>
<td>Amphibole</td>
<td>7MgO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Amosite</td>
<td>12172-73-5</td>
<td>Amphibole</td>
<td>11FeO.3MgO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Actinolite</td>
<td>13768-00-8</td>
<td>Amphibole</td>
<td>2CaO.4MgO.FeO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Tremolite</td>
<td>14567-73-8</td>
<td>Amphibole</td>
<td>2CaO.5MgO.FeO.8SiO₂.H₂O</td>
</tr>
<tr>
<td>Crocidolite</td>
<td>12001-28-4</td>
<td>Amphibole</td>
<td>Na₂O.Fe₂O₃.FeO.8SiO₂.H₂O</td>
</tr>
</tbody>
</table>

Context:

In France, the current regulations on occupational exposure to asbestos fibres take into account fibres (FRp: fibres measured for industrial health) with the following dimensions: L > 5 μm, D < 3 μm and L/D > 3 where L is the length and D the diameter of the fibre. The limit value is set at 0.1 f/cm³ for 1 hour.

By definition:

**Short asbestos fibres (SAFs):** 0.5 μm < L < 5 μm, d < 3 μm and L/d ≥ 3

**Thin asbestos fibres (TAFs):** L ≥ 5 μm, d < 0.2 μm and L/d ≥ 3

The OEL committee’s report on the health effects of asbestos was based on the conclusions of the Afsset working group, which considered that:

The effects of short asbestos fibres (SAFs) are covered as long as long fibres are taken into account. In fact, any professional activity involving an asbestos-containing material (ACM) necessarily results in the emission of long fibres. It is not necessary therefore to count the SAFs in an occupational environment.

Following the OEL committee’s expert appraisal of the health effects of thin and short asbestos fibres, the metrology section was charged with determining the most suitable method(s) of measuring the airborne concentrations of FRp or TAFs in an occupational environment.
2 Measurement methods (sampling/analysis)

The international measurement methods currently in force are shown in the table below, and are those described in the Afsset report of February 2009: "Taking into account the dimensional criteria for the characterisation of health risks linked to asbestos inhalation"

### Table: Measurement methods (sampling/analysis)

<table>
<thead>
<tr>
<th>Type of microscope</th>
<th>Sampling and analysis protocol</th>
<th>Preparation of sample</th>
<th>Magnification for counting</th>
<th>Fibre-counting criterion (Length, L; diameter, d) (µm)</th>
<th>Minimum measurable diameter (µm)</th>
<th>Fibre-identification method</th>
<th>Type of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCM</td>
<td>XP X 43-269: 2002</td>
<td>Direct</td>
<td>400-500</td>
<td>≥ 3</td>
<td>&gt; 5</td>
<td>0.2</td>
<td>Numerical concentration</td>
</tr>
<tr>
<td></td>
<td>WHO: 1997</td>
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<td></td>
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<td></td>
<td>ISO/DIS 8672: 1993</td>
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<td>NIOSH 7400 method A: 1994 (x)</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>IRSST 243: 1995</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>SEM</td>
<td>ISO 14966: 2002</td>
<td></td>
<td>2000</td>
<td>≥ 3</td>
<td>&lt; 3</td>
<td></td>
<td>Numerical concentration</td>
</tr>
<tr>
<td></td>
<td>VDI - 3492: 1994</td>
<td></td>
<td>2000 - 2500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEM</td>
<td>ISO 10312: 1995</td>
<td></td>
<td>20000</td>
<td>≥ 5</td>
<td>&gt; 0.5</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5000</td>
<td>≥ 3</td>
<td>&gt; 5</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISO 13794: 1999</td>
<td>Indirect</td>
<td>20000</td>
<td>≥ 5</td>
<td>&gt; 0.5</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5000</td>
<td>≥ 3</td>
<td>&gt; 5</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISO 13794: 1999</td>
<td></td>
<td>10000</td>
<td>≥ 3</td>
<td>&gt; 5</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20000- 30000</td>
<td></td>
<td></td>
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</tbody>
</table>

(x): the NIOSH 7400 method does not impose any counting criteria on the diameter

Four main methods were identified:

- **Method 1:** Phase Contrast Microscopy (PCM)

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18 EDXA: Energy Dispersive X-ray Analysis
19 SAED: Selected Area Electron Diffraction
Method 2: Analytical Transmission Electron Microscopy which observes fibres after completely destroying the sampling filter (indirect TEM)

Method 3: Analytical Transmission Electron Microscopy which observes the fibres directly (direct TEM)

Method 4: Analytical Scanning Electron Microscopy (SEM)

The criteria set out in Standard EN 482:2006, which classifies the methods used to sample/analyse compounds belonging to categories 1 (recognised and validated) or 2 (indicative methods) are not generally suitable for fibres. For this reason this classification method will not be used in this document. However, the expert's decision will be used to compare the efficacy of the various methods used to assess occupational exposure to asbestos fibres.

2.1 Presentation of measurement methods

2.1.1 Method 1: Phase Contrast Microscopy (PCM)

The PCM method, corresponding to Standard XP X 43-269 : 2002, is the statutory method for measuring occupational exposure to asbestos fibres. Its main characteristics are:

→ Sampling on a squared cellulose ester membrane (diameter: 25 mm)
→ Flow: 1 to 6 l/min
→ Sampling time depends on the expected concentration of fibres
→ The membrane is rendered transparent after sampling, then observed using a phase contrast microscope (PCM). The magnification is 400 to 500
→ The dimension of the fibres counted is > 5 μm, D < 3 μm and L/D > 3 where L is the length and D the diameter of the fibre. The sensitivity of the method does not allow fibres of a diameter superior to 0.4 μm to be taken into account, or 0.25 μm if additional equipment such as a CCD digital sensor is available.
→ The method does not identify the nature of the fibres
→ The results are expressed in terms of numbers of fibres/cm³ of air sampled

2.1.2 Method 2: Analytical Transmission Electron Microscopy - indirect method

The indirect TEM method, corresponding to French Standard NFX 43-050 : 1996, is the statutory method used to determine the concentration of asbestos fibres in the overall environment (measurement of dust levels in buildings). Its main characteristics are:

→ Sampling on cellulose ester membrane (diameter: 37 or 47 mm) with a sampling head to allow, as a minimum, the sampling of the thoracic fraction
• Flow depends on the sampling head: 5 l/min if a support system for standard aerosol filter is used, with a 7 mm diameter orifice or 7 l/min, if a selector system for the aerosol thoracic fraction is used (CATHIA system)

• Sampling time: 8 hours/day for 5 days

• The membrane, or part of the membrane, is burned after sampling in an oxygen plasma oven. The particles are then recovered from the water then, after manual agitation, filtered through a polycarbonate filter previously coated with a layer of carbon. After filtration, the recovered particles are then covered by a second layer of carbon. The polycarbonate filter is dissolved using a solvent. The fibres and particles are collected on grids for observation using a transmission electron microscope.

• The dimension of the fibres counted is L > 5 μm, D < 3 μm and L/D > 3 where L is the length and D the diameter of the fibre. It should be noted that TEM is a much more sensitive method than PCM as its high resolution allows objects with a diameter smaller than 0.01 μm to be observed; it also allows fibres with a length exceeding 0.5 μm to be counted.

• The method allows fibres belonging to different classes to be distributed based on morphological observations, electronic diffraction diagrams and energy dispersive x-ray analysis spectra.

• However, this method does not distinguish individual asbestiform amphibole fibres from those originating from other amphibole facies of the same mineral (cleavage fragments).

• The results are expressed as the number of fibres per litre of sampled air

2.1.3 Method 3: Analytical transmission electron microscopy - direct method

This is the same method as method 2 but using a direct method:

• The sampling membrane is treated directly after spending a brief period in the plasma oven

• The fibres are observed on a carbon replica on the surface of the filter. This requires that an optimum load is deposited on the filter. ISO Standard 10312 determines that the dust deposited on the observation grid should not cover more than 10% of its surface, as overloading means that the fibres cannot be easily observed. This drawback is even greater when short fibres are involved.

2.1.4 Method 4: Analytical scanning electron microscopy

Scanning Electron Microscopy (SEM) coupled with Energy Dispersive X-ray Analysis (EDXA) analyses fibres on the basis of their morphological appearance and elementary chemical composition.

• Sampling on a cellulose ester membrane or a gold pre-coated polycarbonate membrane

• The filter is read directly

• The analysis does not specifically identify the nature of the fibres
• The dimension of the fibres counted is \( L > 5 \mu m \), \( D < 3 \mu m \) and \( L/D > 3 \) where \( L \) is the length and \( D \) the diameter of the fibre. It should be noted that the observation, analysis and counting requires a magnification of at least \( x \) 2000. At a magnification of \( x \) 2000, the minimum detectable diameter of fibres is around 0.2 \( \mu m \). There are resolution problems with this technique when the diameter is smaller than this size.
2.2 Discussion of the methods

The following table compares the performances of each of the methods (PCM, indirect TEM, direct TEM and SEM) currently used to measure fibres for occupational health (FRp: \(L>5\,\mu m\), \(D<3\,\mu m\) and \(L/D>3\)), and thin asbestos fibres (TAF: \(L>5\,\mu m\), \(D<0.2\,\mu m\) and \(L/D>3\)); it emphasises the strengths and weaknesses of each of the techniques.

It also takes into account the feasibility of the method in terms of the fibre concentrations associated with the various estimated risk levels. In fact, the OEL committee decided not to retain an OEL for asbestos but to report the following excess risks:

\(10^{-4}\) for a "lifetime occupational exposure" of 0.003 f/ml (i.e. 3 f/l)

\(10^{-5}\) for a "lifetime occupational exposure" of 0.0003 f/ml (i.e. 0.3 f/l)

\(10^{-6}\) for a "lifetime occupational exposure" of 0.00003 f/ml (i.e. 0.03 f/l)
<table>
<thead>
<tr>
<th>Method</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Application in relation to the concentration levels used to calculate the excess risks and TAFs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method 1</strong>&lt;br&gt;PCM</td>
<td>The standard method use to evaluate occupational exposure to fibres (WHO) with the following dimensions:&lt;br&gt;L&gt;5 μm, D&lt;3 μm and L/D&gt;3</td>
<td>Does not specify which type of asbestos (no identification of fibres)</td>
<td>TAFs cannot be observed with PCM, nor can it identify the nature of the fibres.</td>
</tr>
<tr>
<td></td>
<td>Easy method to use and low cost</td>
<td>Not possible to observe fibres with a diameter &lt; 0.25 μm</td>
<td>The limit of analytical quantification is 0.01 f/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This counting method takes into account cleavage fragments, if they have the required dimensions</td>
<td>Conclusion: Method not applicable to TAFs</td>
</tr>
<tr>
<td><strong>Method 2</strong>&lt;br&gt;Indirect TEM</td>
<td>Identifies (elementary chemical composition and crystalline structure) and counts the fibres.</td>
<td>It is possible to lose fibres or change their dimension distribution during the preparation process</td>
<td>Indirect or direct TEM allows the observation and identification of TAFs.</td>
</tr>
<tr>
<td></td>
<td>It is possible to examine objects with a diameter of &lt; 0.01 μm</td>
<td>Complex and extremely costly method (both as an investment and for operating)</td>
<td>With the current atmospheric measurement conditions (8-hour individual sampling at a maximum flow of 4 l/min), the limit of the analytical quantification is 0.0025 f/ml</td>
</tr>
<tr>
<td></td>
<td>It can also count fibres with a length &gt; 0.5 μm</td>
<td></td>
<td>Conclusion: Method can be applied to TAFs</td>
</tr>
<tr>
<td></td>
<td>The sampling may take a long time (if the filter is overloaded, it will only be possible to analyse one section)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Method 3</strong>&lt;br&gt;Direct TEM</td>
<td>Identifies (elementary chemical composition and crystalline structure) and counts the fibres.</td>
<td>The preparation is tricky to perform</td>
<td></td>
</tr>
<tr>
<td></td>
<td>It is possible to examine objects with a diameter &lt; 0.01 μm</td>
<td>Requires an optimal load of the deposit on the filter, especially for SAFs</td>
<td>SEM does not observe TAFs or identify the nature of the fibres.</td>
</tr>
<tr>
<td></td>
<td>It also counts fibres &gt; 0.5 μm in length</td>
<td>Complex and extremely costly method (both as an investment and for operating)</td>
<td>The limit of analytical quantification is higher than for TEM.</td>
</tr>
<tr>
<td></td>
<td>The aerosol is not disturbed during the observation</td>
<td></td>
<td>Conclusion: Method not applicable to TAFs</td>
</tr>
<tr>
<td><strong>Method 4</strong>&lt;br&gt;SEM</td>
<td>Counts the fibres and determines the elementary chemical composition.</td>
<td>The chemical analysis alone does not specifically identify the fibres</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The preparation is less restrictive than with TEM</td>
<td>Resolution problems for asbestos fibres with a diameter &lt; 0.2 μm (same resolution as PCM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The filter is read directly</td>
<td>Less sensitive than TEM</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3 Conclusions and recommendations of the group

In view of the previous findings, the group has noted that:

- The PCM and SEM methods do not specifically identify the fibres observed or take TAFs into account
- The direct or indirect TEM method specifically identifies the fibres observed and counts the TAFs
- The direct TEM method requires an optimal loading of the deposit on the filter, which is tricky in an occupational environment
- During the analysis phase, the indirect TEM method may result in a loss of fibres; there is also a risk of modifying the particle size distribution during the preparation process.

The group considers that none of the methods (PCM, SEM, and indirect TEM and direct TEM) is entirely suited to measuring occupational exposure to asbestos fibres (FRp and TAFs) for the purpose of comparing them to the OELs.

Adaptation of the TEM methods, using the indirect route (in order to alleviate the risk of fibre loss and changes in their particle size distribution during the preparation phase) or direct TEM (to obtain optimal distribution of the deposit on the filter during sampling), should eventually allow these methods to become valid for use in the occupational environment so that the exposure of operators to asbestos fibres (FRp and TAFs) can be assessed.
4 Bibliography

Afsset (2009). Short and thin asbestos fibres - Taking into account the dimensional criteria for the characterisation of health risks linked to asbestos inhalation, Reassessment of toxicological, metrological and epidemiological data, to assess the health risks for the general and occupational population.

Standards and methods:


NF EN 482 (2006) Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents. AFNOR.

NF X 43-050 (1996) Air quality - Determination of the concentration of asbestos fibres using transmission electron microscopy - Indirect method. AFNOR.


5 List of the main sources consulted for the identification of the sampling/analysis methods for the assessment of occupational exposure

- France: INRS (French National Research and Safety Institute - MetroPol database)
  http://www.inrs.fr/metropol/sommet.htm
- Europe: Gestis database: groups together the validated centralized European methods in the BGIA (Berufsgenossenschaftliche Institut für Arbeitsschutz) Germany
  http://www.hvbg.de/e/bia/gestis/analytical_methods/index.html
- Spain: INSHT (Instituto Nacional de Seguridad e Higiene en el Trabajo)
- UK: HSE (Health and Safety Executive)
  http://www.hse.gov.uk/pubns/mdhs/index.htm
- Canada: IRSST (Canadian Robert-Sauvé Research Institute for Occupational Health and Safety)
  http://www.irsst.qc.ca/fr/_listersst.html#B
- USA: NIOSH (National Institute for Occupational Safety and Health)
  http://www.cdc.gov/niosh/nmam/default.html
- USA: OSHA (Occupational Safety and Health Administration)

Standards applicable to the evaluation of occupational exposure

- INRS (MétroPol database)
  http://www.inrs.fr/metropol/sommet.htm list of standards applicable for the evaluation of occupational exposure (in the "general" sheets: standardisation). The list is updated at least once a year:
APPENDICES
## Appendix 1: Monitoring of report updates

<table>
<thead>
<tr>
<th>Date</th>
<th>Version</th>
<th>Page</th>
<th>Description of change</th>
</tr>
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<tr>
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<td>01</td>
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<td>First version</td>
</tr>
</tbody>
</table>
Appendix 2: Summary of public declarations of interest from experts in relation to the field of the solicited request

A - Summary of public declarations of interest from members of the OEL Committee in relation to the field of the solicited request

SUMMARY OF PUBLIC DECLARATION OF INTEREST HEADINGS

<table>
<thead>
<tr>
<th>IP-A</th>
<th>One-off interventions: other</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP-AC</td>
<td>One-off interventions: consultancy</td>
</tr>
<tr>
<td>IP-CC</td>
<td>One-off interventions: conferences, symposia, training</td>
</tr>
<tr>
<td>IP-RE</td>
<td>One-off interventions: expert appraisal reports</td>
</tr>
<tr>
<td>IP-SC</td>
<td>One-off interventions: scientific works, trials, etc.</td>
</tr>
<tr>
<td>LD</td>
<td>Long-term or permanent links (employment contract, regular payment, etc.)</td>
</tr>
<tr>
<td>PF</td>
<td>Financial holdings in a company's capital</td>
</tr>
<tr>
<td>SR</td>
<td>Other links without one-off payment (family employed in the companies outlined above)</td>
</tr>
<tr>
<td>SR-A</td>
<td>Other links without one-off payment (member of the board of administration or scientific board of a firm, company or professional organisation)</td>
</tr>
<tr>
<td>VB</td>
<td>Activities giving rise to the payment of a budget to an organisation</td>
</tr>
</tbody>
</table>

SUMMARY OF PUBLIC DECLARATIONS OF INTEREST (DPI) FROM CES (COMMITTEE OF SPECIALISED EXPERTS) MEMBERS IN RELATION TO THE FIELD OF THE SOLICITED REQUEST

<table>
<thead>
<tr>
<th>SURNAME</th>
<th>First Name</th>
<th>Dates of the declaration of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>BINET</td>
<td>Stéphane</td>
<td>16 November 2006 14 September 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afsset Analysis: /</td>
</tr>
<tr>
<td>BISSON</td>
<td>Michèle</td>
<td>18 October 2007 17 March 2008 17 April 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afsset Analysis: /</td>
</tr>
<tr>
<td>Name</td>
<td>Function</td>
<td>Dates</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>DIERS Brigitte</td>
<td>Training for Chemistry and Pharmacy companies giving rise to payment to an affiliated body (CNRS - French National Centre for Scientific Research)</td>
<td>14 December 2006, 9 July 2007</td>
</tr>
<tr>
<td>VB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DONNADIEU-CLARAZ Marie</td>
<td></td>
<td>16 November 2006, 14 September 2007</td>
</tr>
<tr>
<td>FASTIER Antony</td>
<td></td>
<td>14 December 2006, 11 July 2007, 4 March 2008</td>
</tr>
<tr>
<td>GRIMBUHLER Sonia</td>
<td></td>
<td>18 October 2007</td>
</tr>
<tr>
<td>HAGUENOER Jean-Marie</td>
<td></td>
<td>29 October 2007, 14 December 2007</td>
</tr>
<tr>
<td>HERVÉ-BAZIN Benoît</td>
<td></td>
<td>16 October 2007, 17 March 2008</td>
</tr>
<tr>
<td>IWATSUBO Yuriko</td>
<td></td>
<td>18 January 2007, 11 July 2007</td>
</tr>
<tr>
<td>KERDINE-ROEMER Saadia</td>
<td></td>
<td>3 January 2007, 11 July 2007</td>
</tr>
<tr>
<td>Name</td>
<td>Role</td>
<td>Percentage</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>LECARPENTIER</td>
<td>Christian</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACÉ</td>
<td>Tatiana</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>MATRAT</td>
<td>Mireille</td>
<td></td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>NISSE</td>
<td>Catherine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAQUET</td>
<td>François</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PILLIÈRE</td>
<td>Florence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAMBOURG</td>
<td>Marie-Odile</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SANDINO</td>
<td>Jean-Paul</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLOIM</td>
<td>Michel</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOYEZ</td>
<td>Alain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOKLOV</td>
<td>Muriel</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### B - Summary of public declarations of interest from expert rapporteurs external to the CES (Committee of Specialised Experts) in relation to the field of the solicited request

<table>
<thead>
<tr>
<th>Expert Name</th>
<th>Declared Date</th>
<th>Analysis Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TELLE-LAMBERTON</td>
<td>15 October 2007, 17 March 2008</td>
<td>No declared link</td>
</tr>
<tr>
<td>VIAU</td>
<td>8 November 2006, 11 July 2007</td>
<td>No declared link</td>
</tr>
<tr>
<td>VINCENT</td>
<td>15 November 2006, 14 September 2007</td>
<td>No declared link</td>
</tr>
</tbody>
</table>
| BROCHARD          | 21 November 2005, 4 April 2008 | Study financed by Saint-Gobain Isover on the "Morbidity of artificial mineral fibres (AMFs) in a production environment" giving rise to a payment to an affiliated organisation (French Institute for Public Health, Epidemiology and Development - ISPED, University of Bordeaux 2)  
No risk of conflict of interest in relation to the subject of the solicited request. |
**Appendix 3: Summary of changes to the occupational exposure limits for asbestos fibres.**

Mppcf = million particles per cubic foot (1 cubic foot = 0.028317 m³)

<table>
<thead>
<tr>
<th>Year</th>
<th>Source</th>
<th>Value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>Public Health Services (USA)</td>
<td>5 mppcf (approximately 176,600 particles per litre)</td>
<td>Asbestosis detected (x-ray of lungs) in 4 factories. Recommendation adopted by the ACGIH (in 1946) and by many countries. Sample taken using a bubbler.</td>
</tr>
<tr>
<td>1968</td>
<td>ACGIH</td>
<td>2 mppcf &quot;or&quot; 12 f/ml</td>
<td>New proposal to provide protection against asbestosis.</td>
</tr>
<tr>
<td>1968</td>
<td>BOHS</td>
<td>2 f/ml</td>
<td>Exposure at 100 f/ml for 50 years would reduce by 1% the maximum risk of asbestosis. Sampling via thermal precipitator.</td>
</tr>
<tr>
<td>1971</td>
<td>OSHA</td>
<td>2 mppcf &quot;or&quot; 12 f/ml</td>
<td>Following the ACGIH proposal (1968).</td>
</tr>
<tr>
<td>1971</td>
<td>OSHA</td>
<td>5 f/ml 10 f/ml (peak)</td>
<td>Emergency proposals due to asbestosis in two textile factories in Pennsylvania, exposure generally &lt; 2 mppcf.</td>
</tr>
<tr>
<td>1972</td>
<td>OSHA</td>
<td>5 f/ml 10 f/ml (peak)</td>
<td>Confirmation of the previous proposal. Average value over 8 hours and with a ceiling of 10 f/ml.</td>
</tr>
<tr>
<td>1972</td>
<td>NIOSH</td>
<td>2 f/ml</td>
<td>Recommendation to adopt the BOHS proposal for the prevention of asbestosis and also probably cancers.</td>
</tr>
<tr>
<td>1975</td>
<td>OSHA</td>
<td>0.5 f/ml (8H) 5 f/ml (&lt; 15 min)</td>
<td>Proposal following abnormal x-rays at &lt; 2 f/ml, reporting of mesothelioma, pulmonary cancers suspected. Never applied.</td>
</tr>
<tr>
<td>1976</td>
<td>OSHA</td>
<td>2 f/ml</td>
<td>Regulatory value.</td>
</tr>
<tr>
<td>1976</td>
<td>NIOSH</td>
<td>0.1 f/ml</td>
<td>Value considered as the lowest level detectable analytically but not necessarily providing protection.</td>
</tr>
<tr>
<td>1979</td>
<td>NIOSH/OSHA</td>
<td>0.1 f/ml</td>
<td>Recommendation based on the &quot;lowest level measurable reliably&quot;, estimated still to be at risk.</td>
</tr>
<tr>
<td>1979</td>
<td>GT (UK)</td>
<td>1 f/ml (chrysotile) 0.5 f/ml (amosite)</td>
<td>Crocidolite prohibited. The analytical advances imply an actual reduction by a factor of 2 to 5 compared with 1968. The limit is not based on an evaluation of the risk of cancer.</td>
</tr>
</tbody>
</table>
### Table: Asbestos Fibre Standards

<table>
<thead>
<tr>
<th>Year</th>
<th>Region</th>
<th>Standard</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>EC</td>
<td>1 f/ml</td>
<td>Average value over 8 hours (83/477/EEC).</td>
</tr>
<tr>
<td>1987</td>
<td>UK</td>
<td>0.5 f/ml</td>
<td>Average value over 4 hours.</td>
</tr>
<tr>
<td>1988</td>
<td>OSHA</td>
<td>0.2 f/ml</td>
<td>1 f/ml (peak)</td>
</tr>
<tr>
<td>1994</td>
<td>OSHA</td>
<td>0.1 f/ml</td>
<td></td>
</tr>
</tbody>
</table>

For this table, see in particular:

### Appendix 4: Review of current OELs for asbestos fibres with a length over or equal to 5 μm


<table>
<thead>
<tr>
<th>Country</th>
<th>Long-term OEL (f/cm³)</th>
<th>Short-term OEL (f/cm³)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>0.25</td>
<td>1</td>
<td>TRK value (based on technical feasibility)</td>
</tr>
<tr>
<td>Canada - Quebec</td>
<td>1 (actinolite, anthophyllite, chrysotile)</td>
<td>5 (actinolite, anthophyllite, chrysotile)</td>
<td>0.2 (amosite, crocidolite) 1 (amosite, crocidolite)</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Germany (AGS)</td>
<td>0.01</td>
<td></td>
<td>Binding OEL</td>
</tr>
<tr>
<td></td>
<td>0.015</td>
<td></td>
<td>Reference value / individual measurement associated with the OEL</td>
</tr>
<tr>
<td>Hungary</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>2</td>
<td></td>
<td>Apart from amosite and crocidolite</td>
</tr>
<tr>
<td>Spain</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (OSHA)</td>
<td>0.1</td>
<td>1 (30 minutes)</td>
<td>For information, ACGIH TLV-TWA (2000), NIOSH (REL over 100 minutes for a 400-litre sample: 2001): 0.1 fibre/ml</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>0.1</td>
<td>0.6 (10 minutes)</td>
<td>All fibrous forms. Limit value of 0.1 f/cm³ for a 4-hour period (PCM counting method, WHO 1997). An &quot;approved code of practice&quot; (L143, ISBN 0717662063) requires action when the short-term value exceeds 0.6 f/cm³ (period of 10 min). The regulations and practical guides are summarised at <a href="http://www.hse.gov.uk/asbestos/regulations.htm">http://www.hse.gov.uk/asbestos/regulations.htm</a></td>
</tr>
</tbody>
</table>
Appendix 5: Estimation of individual excess risks (IERs) for mesothelioma and lung cancer based on Hodgson et al. (2000)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of fibre</th>
<th>Final cumulative level (f/ml/5 years)</th>
<th>No. of deaths (10^{-4})</th>
<th>f/ml (1 year) for IER 10^{-4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>mesothelioma</td>
<td>crocidolite</td>
<td>1</td>
<td>65</td>
<td>0.0003846</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>crocidolite</td>
<td>0.1</td>
<td>10</td>
<td>0.0002500</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>crocidolite</td>
<td>0.01</td>
<td>2</td>
<td>0.0001250</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>chrysotile</td>
<td>1</td>
<td>0.5</td>
<td>0.0500000</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>chrysotile</td>
<td>0.1</td>
<td>0</td>
<td>insignificant</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>chrysotile</td>
<td>0.01</td>
<td>0</td>
<td>insignificant</td>
</tr>
<tr>
<td>lung</td>
<td>crocidolite</td>
<td>1</td>
<td>8.5</td>
<td>0.0029412</td>
</tr>
<tr>
<td>lung</td>
<td>crocidolite</td>
<td>0.1</td>
<td>0.4</td>
<td>0.0062500</td>
</tr>
<tr>
<td>lung</td>
<td>crocidolite</td>
<td>0.01</td>
<td>0</td>
<td>insignificant</td>
</tr>
<tr>
<td>lung</td>
<td>chrysotile</td>
<td>1</td>
<td>0.2</td>
<td>0.1250000</td>
</tr>
<tr>
<td>lung</td>
<td>chrysotile</td>
<td>0.1</td>
<td>0</td>
<td>insignificant</td>
</tr>
<tr>
<td>lung</td>
<td>chrysotile</td>
<td>0.01</td>
<td>0</td>
<td>insignificant</td>
</tr>
</tbody>
</table>

The work of Hodgson & Darnton is based on a non-linear model. The choice of the cumulative exposure level is therefore conveyed by a different estimation of the individual excess risk. Moreover, the estimated additional number of deaths was assessed based on an exposure starting at the age of 30 and lasting for a maximum period of 5 years. The estimations should therefore be added together to obtain the lifetime occupational estimation. To obtain a figure for 40 years, the individual excess risk estimates were multiplied by 8, as the figures supplied by Hodgson et al. corresponded to a 5-year exposure period. Three cumulative levels were retained for these estimates, due to the model's non-linear nature: 0.01, 0.1 and 1 f/ml/year.

To provide an example, details are supplied below of an annual estimated concentration (f/ml) with an individual excess risk of mortality due to mesothelioma of 10^{-4}. The final cumulative level corresponding to a 5-year exposure is 1 f/ml, i.e. 0.2 f/ml per year (1 f/ml divided by 5 years). The individual excess risk associated with this concentration for a 5-year exposure is 6.5 \times 10^{-3}, i.e. 5.2 \times 10^{-2} for a 40-year exposure period (6.5 \times 10^{-3} multiplied by 8). In order to calculate the estimated annual concentration (f/ml) for an individual excess risk of mortality due to mesothelioma of 10^{-4} (following a 40-year exposure period), a simple cross-multiplication is required: 0.2 \times 10^{-4} / 5.2 \times 10^{-2} i.e. 3.85 \times 10^{-4}.

According to the Inserm model, the concentration associated with an individual excess risk of mortality due to mesothelioma (specific health effect of asbestos exposure) of 10^{-4} is approximately 1.10^{-2} f-pcm/ml. This value, calculated for a "major" or "unique" exposure to chrysotile, confirms the estimations obtained using Hodgson & Darnton's model (2000). In fact, for an individual excess risk of mortality due to mesothelioma of 10^{-4}, the concentration associated with a single exposure to chrysotile is 5.10^{-2} f-pcm/ml; for crocidolite it is 4.10^{-4} f-pcm/ml. Therefore, the estimation of the Inserm model, involving exposure to chrysotile alone or combined with amphiboles, is based on the time period proposed in Hodgson & Darnton's model (2000) associated with either a single exposure to chrysotile (asbestos fibres considered to be the least carcinogenic in the publication) or a single exposure to crocidolite (asbestos fibres considered to be the most carcinogenic in the publication).

However, high ranging hypotheses were used to calculate these estimates therefore limiting the interpretation and validity of the values presented in the table. In fact, the model proposed
by Hodgson & Darnton's model is not linear. In order to convert the annual concentration values to a 40-year exposure period, the originally extrapolated linear model was retained using several points of the curve produced by Hodgson & Darnton's model. Consequently, the proposed estimations can never be used to estimate the excess mortality rates; they were, however, calculated to illustrate the qualitative differences compared to the estimations supplied by the Inserm model.
Appendix 6: Solicited request letters

MINISTERE DES SOLIDARITES, DE LA SANTE ET DE LA FAMILLE
MINISTERE DE L’ECOLOGIE ET DU DEVELOPPEMENT DURABLE
MINISTERE DE L’EMPLOI, DU TRAVAIL ET DE LA COHESION SOCIALE

Direction générale de la santé
Direction des études économiques et de l’évaluation environnementale

COURRIER RECELE

- 8 FEB 2005
92288

Paris le 07 février 2005

Le Directeur général de la santé
Le Directeur des relations du travail
Le Directeur des études économiques et de l’évaluation environnementale

à

Madame la Directrice générale de l’Agence Française de Sécurité Sanitaire Environmentale
27-31 Avenue du Général Leclerc
94701 Maisons-Alfort

Objet: Fibres « courtes » d’amiante

Madame la Directrice générale,

Les dispositions réglementaires relatives à la protection de la population contre l’exposition passive (environnementale) à l’amiante dans les immeubles bâties (code de la santé publique, article R.1334-14 et suivants) ainsi que celles relatives à la protection des travailleurs contre les risques liés à l’inhalation de poussières d’amiante (décret n°96-98 du 7 février 1996 modifié) prévoient, chacune en ce qui la concerne, des mesures de niveau d’empoussièrement en fibres d’amiante. Dans tous les cas, seules sont prises en compte les fibres dont la longueur est supérieure à 5 microns, la largeur inférieure à 3 microns et le rapport longueur sur largeur supérieur à 3. Ce choix résulte d’un consensus scientifique international adopté à la fin des années 1980, le risque cancérogène mis en évidence étant alors beaucoup plus caractérisé pour les fibres longues et fines que pour les fibres courtes. Ce choix harmonisé permettait, au niveau international, la comparaison et l’exploitation, en particulier épidémiologique, des mesures effectuées par différentes laboratoires.

Or, notre attention vient d’être attirée par une publication relative à la pathogénicité des fibres courtes d’amiante, intitulée « Asbestos fiber length as related to potential pathogenicity: a critical review » parue dans « American journal of industrial medicine ».« X = 1.25 ».

Nous vous demandons, en conséquence, d’expertiser le contenu et l’impact potentiel de cette publication et de bien vouloir :
évaluer la toxicité des fibres d’amiante dont la longueur est inférieure à 5 microns, au regard des différentes études réalisées et plus particulièrement de celles postérieures à 1996, date de mise en place des dispositifs réglementaires relatifs à la protection de la population dans les immeubles bâtis et des travailleurs ;

déterminer s’il est possible de caractériser la répartition granulométrique des fibres selon les circonstances d’exposition de la population générale et des travailleurs (environnement intérieur ou extérieur, nature des matériaux en présence, nature des travaux effectués...) et selon la nature de l’amiante (chrysotile, Amphiboïles). Vous examinerez notamment le cas des fibres dégagées par les affleurements naturels de roches amiantifères ;

évaluer les risques pour la santé humaine liés à une exposition aux fibres courtes d’amiante non prises en compte dans la réglementation actuelle, puis, le cas échéant, procéder à une évaluation comparative des risques en considérant différents scénarios d’exposition, notamment au regard de la répartition granulométrique des fibres.

Cette évaluation devra nous permettre d’apprécier si les dispositions réglementaires actuellement applicables conservent leur pertinence, à savoir :

- la non prise en compte des fibres de longueur inférieure à 5 microns lors de la mesure des niveaux d’empoussièrement, décidée à l’issue d’un consensus scientifique international ;
- les seuils actuels fixés à 5 fibres par litre dans la réglementation relative à la protection de la population et à 0,1 fibre par millilitre dans celle relative à la protection des travailleurs.

Nous vous saurions gré de nous faire parvenir le rapport final pour la fin du premier semestre 2005.

Nous vous prions d’agréer, Madame la Directrice générale, l’expression de notre considération distinguée.
MINISTÈRE DE LA SANTÉ ET DES SOLIDARITÉS
MINISTÈRE DE L’ÉCOLOGIE ET DU DÉVELOPPEMENT DURABLE
MINISTÈRE DE L’EMPLOI, DE LA COHESION SOCIALE ET DU LOGEMENT

Direction générale de la santé
Direction de la prévention des pollutions et des risques
Direction générale du travail

Paris le 16 mai 2007

Le directeur général du travail
Le directeur général de la santé
Le directeur de la prévention de la pollution et des risques

à

Madame la directrice générale de l’Agence française de sécurité sanitaire de l’environnement et du travail (AFSSET)
253 Avenue du Général Leclerc
94701 Maisons-Alfort

Objet : Saisine relative aux fibres courtes d’amiante du 7 février 2005 et saisine complémentaire relative aux fibres fines d’amiante.

Par courrier du 23 février 2007, vous nous informez, et nous vous en remercions, de l’état d’avancement de la saisine relative aux fibres courtes d’amiante du 7 février 2005. Nous avons pris note de la constitution d’un groupe de travail dont la composition a été validée en juillet 2005 et qui associe les experts de l’INRS. Nous avons également noté que les travaux de ce groupe de travail se poursuivent sur :

- la métrologie - afin de réunir un plus grand nombre d’échantillons pour être en mesure de caractériser la granulométrie notamment en milieu professionnel ;
- la toxicité des fibres courtes - les seuls critères dimensionnels n’étant pas suffisants, d’autres critères tels que la reactivité de surface et la biopersistence devront aussi probablement être pris en compte ;
- l’analyse des données épidémologiques et d’évaluation des risques afin de déterminer si une évaluation des risques complémentaire est nécessaire.

Nous avons également relevé qu’un rapport intermédiaire récapitulant les premiers éléments issus des travaux du groupe de travail est prévu pour la fin de second trimestre 2007.

Par ailleurs, les discussions engagées par la DGT (bureau CT2) avec les laboratoires accrédités (ULSB : Union des Laboratoires de Santé du Bâtiment, LEPI, ITGA, LHCF Environnement) et l’INRS dans le cadre de l’élaboration du projet d’arrêté relatif à la mesure de la concentration en fibres d’amiante sur les lieux de travail et aux conditions d’accréditation des laboratoires ont conduit à aborder le sujet de l’évolution des techniques d’analyses, point sur lequel nous souhaitons que l’Agence apporte son éclairage.
En effet, la microscopie optique en contraste de phase (MOCP) est la technique de référence actuelle pour le contrôle de l'exposition professionnelle à l'amiante.

La valeur obtenue est comparée à la valeur limite d'exposition professionnelle (0,1 fibre par centimètre cube d'air en moyenne sur 1 heure - article R. 231-59-7 du code du travail - ). Cette valeur limite a été fixée grâce, notamment, aux études épidémiologiques réalisées dans l'industrie de l'amiante qui ont permis d'établir une relation entre le niveau d'exposition aux fibres d'amiante et les effets sur la santé. Les mesures de niveaux d'exposition pour ces études ont été établies sur la base d'analyses réalisées avec la MOCP.

Cependant, selon l'expérience des laboratoires précités et de l'INRS, les performances du microscope optique sont telles que seules les fibres dont la largeur est supérieure à quelques dixièmes de microns sont observées. Ainsi, les fibres fines, c'est-à-dire les fibres dont la largeur est inférieure à 0,2 μm, ne sont pas prises en compte par l'analyse en MOCP.

Or, certains travaux sur l'amiante en place peuvent apparemment produire des fibres fines d'amiante, pratiquement exclusivement. Il existe une autre technique la MET (microscopie électronique à transmission) qui permettrait de comptabiliser ces fibres fines. C'est cette technique qui est d'ailleurs référencée dans les textes du code de la santé publique.

En conséquence, nous souhaiterions que l'AFSSET puisse de manière complémentaire et concomitante à la salamine relative aux fibres courtes d'amiante :

- Évaluer, au regard des publications disponibles, la toxicité des fibres fines d'amiante et leurs risques pour la santé humaine. Par fibres fines, on entend ici les fibres d'un diamètre inférieur à 0,2 μm, dont la longueur est supérieure ou égale à 5 μm et dont le rapport L/D est supérieur ou égal à 3 ;
- Déterminer les types de matériaux contenant de l'amiante et les types de techniques d'intervention sur ces matériaux susceptibles de produire des fibres fines, afin d'identifier les types de travaux et de chantiers les plus concernés ;
- Dans le cas d'un chantier avec une production importante de fibres fines, déterminer les possibilités techniques pour réduire la production de ces fibres et prévenir les risques liés à l'exposition (adaptation des modes opératoires et des équipements de protection individuelle, ...). 

Par ailleurs, et plus globalement, des questions se posent spécifiquement en milieu de travail en matière de métrologie des fibres d'amiante (caractère opérationnel de la technique et interprétation de la mesure) et de VLEP associée. Nous vous demandons d'indiquer les possibilités offertes par la technique MET pour mieux comptabiliser l'ensemble des fibres d'amiante, dont les fibres fines, pendant la période de référence de la valeur limite, par rapport à la technique MOCP, ainsi que ses limites. Plus largement, il conviendrait d'étudier également, en examinant notamment la situation internationale, l'existence d'autres techniques d'identification des fibres d'amiante qui pourraient être mieux adaptées pour cette comptabilisation. De plus, en cas d'utilisation de la technique MET, nous souhaiterions que l'AFSSET puisse préciser, avec l'appui du CES VLEP, l'interprétation qui pourrait être faite des résultats des mesures d'empoussièrement et les conséquences qui pourraient en être tirées en termes de mesure de protection des travailleurs, la pertinence d'une comparaison avec la valeur limite de 0,1 fibre par cm² sur 1 heure destinée à la protection des travailleurs alors que cette valeur a été fixée à partir de la technique MOCP, ainsi que la nécessité d'établir une autre VLEP en indiquant alors le ou les niveaux et la ou les périodes de référence recommandées.

1 Selon les prescriptions de la norme AFNOR XP X 43-259 « Qualité de l'air – Air des lieux de travail – Détermination de la concentration en nombre de fibres par microscopie optique en contraste de phase – Méthode du filtre à membrane» de mars 2002.

2 Guide INRS « Travaux de retrait ou de confinement d'amiante ou de matériaux en contenant – Guide prévention ».

3 Norme NF X 43-050 « Qualité de l'air – Détermination de la concentration en fibres d'amiante par microscopie électronique à transmission - Méthode indirecte » de janvier 1996.
Subject: "Short" asbestos fibres

Dear Madam,

The statutory provisions relating to protecting the population from passive exposure (environmental) to asbestos in buildings (French Public Health Code, Article R.1334-14 and subsequent) and those relating to protecting workers from risks associated with the inhalation of asbestos dust (French Decree no. 96-98 of 7 February 1996, amended) all provide measurements for determining the asbestos fibre dust levels. In all cases, only fibres with a length exceeding 5 microns, with a width under 3 microns and a length/width ratio of over 3, were taken into account. These fibres were selected on the basis of the international scientific consensus adopted at the end of the 1960s, when the proven carcinogenic risk was perceived to be much higher for long and thin fibres than for short ones. This standardised selection has meant, on an international level, that the measurements obtained by the various laboratories could be used and compared – especially on an epidemiological level.

However, we have recently been advised of a publication relating to the pathogenicity of short asbestos fibres entitled "Asbestos fiber length as related to potential pathogenicity: a critical review" which appeared in the "American Journal of Industrial Medicine" in 2003.

We would like you to review its contents and potential impact and:

- evaluate the toxicity of asbestos fibres with a length under 5 microns, in view of the studies carried out - especially those carried out after 1996, the date when the statutory provisions relating to the protection of the population in buildings and also workers were established;
establish whether it is possible to determine the particle size distribution of fibres according to the type of exposure of the general population and workers (indoor and outdoor environment, nature of the materials present, nature of the work carried out, etc.) and according to the nature of the asbestos (chrysotile or amphibole). You should also examine the case of fibres released by natural outcrops of asbestos-bearing rocks;

assess any risks for human health of exposures to short asbestos fibres which are not taken into account by the current regulations, then, if necessary, carry out a comparative assessment of these risks using different exposure scenarios, especially in terms of the particle size distribution of the fibres.

This assessment will allow us to determine whether or not the statutory provisions currently applicable are still relevant, that is:

fibres with a length inferior to 5 microns are not taken into account when measuring dust levels, in accordance with the international scientific consensus;

the current thresholds set at 5 fibres/litre in the regulations for the protection of the general population and set at 0.1 fibres/millilitre for the protection of workers.

We would like to receive your final report by the middle of 2005.

Yours faithfully,

DIRECTOR GENERAL OF HEALTH

HEAD OF DEPARTMENT
[Signature]
Dr Yves COQUIN

DIRECTOR OF ECONOMIC STUDIES AND ENVIRONMENTAL EVALUATIONS
[Signature]
Dominique BUREAU

DIRECTOR OF INDUSTRIAL RELATIONS
[Signature]
Jean-Denis COMBREXELLE
Paris, 16 May 2007

Director General of Work
Director General of Health
Director for pollution and risk prevention

To

The Director General of the French Agency for Environmental and Occupational Health Safety (AFSSET)
253 Avenue du Général Leclerc
94701 Maisons-Alfort

New solicited request DESET treatment

Subject: Solicited request relating to short asbestos fibres of 7 February 2005 and additional solicited request relating to thin asbestos fibres.

In a letter of 23 February 2007, you informed us about the progress of your work on the solicited request relating to short asbestos fibres of 7 February 2005. We thank you for this information. We duly noted that a working group had been set up and validated in July 2006, in conjunction with experts from the National Research and Safety Institute (INRS). We also noted that this working group was concentrating on:

• metrology - in order to obtain the largest number of samples possible to be able to characterise particle sizes, especially in occupational environments;
• the toxicity of short fibres – the use of dimensional criteria alone seems insufficient, therefore, other criteria such as surface reactivity and biopersistence should also probably be taken into account;
• analysing the epidemiological data and evaluating risks in order to determine if an additional risk assessment is necessary.

We have also noted that the interim report summarising the initial findings of the working group is due at the end of the second quarter of 2007.
Furthermore, the discussions carried out by the DGT (Directorate General of Work) (office CT2) and the accredited laboratories (USLB: French Union of Laboratories for Buildings and Health, LEPI, ITGA, LHCF Environment) and the INRS for the purpose of establishing a draft order relating to measuring the concentration of asbestos fibres in the workplace and the conditions for accrediting laboratories, have tackled the subject of advances in the analytical techniques, which is an issue we would like the agency to clarify.

In fact, phase contrast microscopy (PCM) is currently the standard technique used to check occupational exposure to asbestos\(^{20}\)

The value obtained was compared to the occupational exposure limit value (0.1 fibres per cubic centimetre of air over one hour (mean) - Article R.231-59-7 of the French Labour Code). This limit value has been determined based on the epidemiological studies carried out in the asbestos industry, which established a relationship between the asbestos fibre exposure levels and certain effects on health. The exposure level measurements in these studies were established using a PCM analysis.

However, based on the experience of the aforementioned laboratories and the INRS\(^{21}\), the performance of optical microscopes is such that only fibres with a width over a few tenths of a micron are visible. For this reason, thin fibres - that is fibres with a width less than 0.2 \(\mu\)m - are not taken into account with PCM.

Seemingly, certain types of work carried out on asbestos in situ can almost exclusively produce thin asbestos fibres. Another technique, TEM (transmission electron microscopy)\(^{22}\) allows these thin fibres to be counted. This is the technique mentioned in the text of the French Public Health Code.

Consequently, we would like AFSSET, in addition and concomitantly to the solicited request relating to short asbestos fibres:

- to assess, using the publications available, the toxicity of thin asbestos fibres and their risk to human health. A thin fibre is defined as a fibre with a diameter under 0.2 \(\mu\)m, with a length over or equal to 5 \(\mu\)m and whose length/diameter ratio is more than or equivalent to 3.

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\(^{21}\) INRS (French National Research and Safety Institute) Guide "Asbestos or asbestos-containing material, removal or containment work - Prevention Guide".

• to determine the types of material that contain asbestos and the type of work on such materials that could potentially release thin fibres, for the purpose of identifying the types of work and the sites most concerned
• to determine, for sites likely to release large quantities of thin fibres, the possible techniques to adopt to limit the release of such fibres and prevent the risks associated with exposure (adaptation of operating methods and personal protection equipment, etc.).

Furthermore, and on a wider basis, there are also issues specifically concerning the workplace in relation to measuring asbestos fibres (operational nature of the technique and interpretation of the measurements) and the associated OEL. We would also like you to outline the options offered by the TEM technique in terms of counting the overall number of asbestos fibres, including thin fibres, during the reference period set out in the limit value, to provide a comparison with the PCM technique and outlining any limitations of the TEM technique. More broadly, the international situation should be analysed as well as other techniques used to identify asbestos fibres which would be more suited to counting the fibres. If a PCM technique is used, we would like Afsset to determine, with the support of the OEL committee, how the dust measurement results could be interpreted and what would be the consequences in terms of protecting workers, as well as the relevance of a comparison with the limit value of 0.1 fibre/cm³ over 1 hour for the protection of workers when this value is determined using a PCM technique, and the need to determine another OEL to indicate the recommended level(s) and reference periods.