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# Asbestos

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Risks of environmental and occupational exposure

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A large, dark gray, stylized letter 'G' logo. The 'G' is bold and features a decorative, curved tail that loops back towards the top of the letter. It is positioned in the lower half of the page, to the right of a horizontal line.





To the Minister of Housing, Spatial Planning and the Environment

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Subject : Presentation of advisory report *Asbestos: Risks of environmental and occupational exposure*  
Your reference : SAS/DBU/200627185  
Our reference : I-637/06/SD/fs/459-F63  
Enclosure(s) : 1  
Date : 3 juni 2010

Dear Minister,

Your ministerial predecessor wrote to me (under reference SAS/DBU/200627185) asking for the Health Council's advice on the risks associated with environmental exposure to asbestos. The then State Secretary for Social Affairs and Employment also sought the Council's advice concerning the risks associated with occupational exposure to asbestos. I accordingly enclose herewith a report compiled by the Dutch Expert Committee on Occupational Safety (DECOS). The report was formulated in consultation with the Standing Committee on Health and Environment and also takes into account input from a number of national and international bodies. The latter feedback was solicited in June 2009, in the context of a public consultation exercise, which involved inviting interested parties to comment on a draft report.

In the report, the Committee puts forward new values corresponding to the risk levels defined in the context of environmental and occupational health policy. The values have been calculated on the basis of a new meta-analysis commissioned by the Committee, for which a selection of epidemiologic studies was made using predefined inclusion criteria. While it has not been possible to exclude all uncertainty from the calculated values, the state-of-the-art analysis undertaken has reduced the element of uncertainty to the minimum.

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Subject : Presentation of advisory report *Asbestos:  
Risks of environmental and occupational exposure*  
Our reference : I-637/06/SD/fs/459-F63  
Page : 2  
Date : 3 juni 2010

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I endorse the conclusions and recommendations that the Committee presents in its report.

Copies of the report are being submitted to the Minister of Social Affairs and Employment and to the Minister of Health, Welfare and Sport.

Yours sincerely,  
(signed)

Prof. D. Kromhout  
Acting President



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# Asbestos

Risks of environmental and occupational exposure

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to:

the Minister of Housing, Spatial Planning and the Environment

the Minister of Social Affairs and Employment

the Minister of Health, Welfare and Sport

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No. 2010/10E The Hague, June 03, 2010

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The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, Agriculture, Nature & Food Quality, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.



The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.



**INAHTA**

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

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This report can be downloaded from [www.healthcouncil.nl](http://www.healthcouncil.nl).

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# Contents

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Executive summary *11*

---

1 Introduction *17*

1.1 Background *17*

1.2 Issues addressed *18*

1.3 Structure of this report *18*

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2 Asbestos and the effects of exposure *21*

2.1 Properties, production and applications of asbestos *21*

2.2 Exposure to asbestos and background concentrations *24*

2.3 Health effects *26*

---

3 Current standards *31*

3.1 Environmental and occupational risk levels *32*

3.2 Asbestos-cancer exposure-response relationship *34*

3.3 Existing environmental standards *38*

3.4 Calculation of occupational exposure limits *45*

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4	Nature and quality of the epidemiological research	47
4.1	Measurement of asbestos exposure in epidemiological studies	47
4.2	Use of conversion factors for the comparison of research results	48
4.3	Lack of detail concerning the quantification of exposure in the occupationally exposed cohorts	49

---

5	Recent risk analyses	51
5.1	Recent meta-analyses	51
5.2	The usefulness of recent analyses for the calculation of new standards for asbestos	52
5.3	The need for a new meta-analysis	55

---

6	Meta-analysis and calculations for lung cancer	57
6.1	Meta-analysis for lung cancer	58
6.2	Calculation of the concentrations that correspond to the reference environmental and workplace risk levels for lung cancer	65

---

7	Meta-analysis and calculations for mesothelioma	71
7.1	Meta-analysis for mesothelioma	72
7.2	Calculation of the concentrations that correspond to the reference environmental and workplace risk levels for mesothelioma	75

---

8	Conclusions: proposed new values for asbestos	81
8.1	New meta-analyses for lung cancer and mesothelioma	81
8.2	Proposed new MPR and NR values for the environment	83
8.3	Proposed new values for the workplace	84

---

	References	85
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	Annexes	93
A	VROM and SZW requests for advice	95
B	The Committee	97
C	Comments on the public draft	101
D	Mortality figures and life table analyses	103
E	Environmental exposure and asbestos-related health risks	105
F	Calculation of $K_L$ values	107
G	Summary of exposure variables for all cohorts	109

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## Executive summary

Health Council of the Netherlands. Asbestos: Risks of environmental and occupational exposure. The Hague: Health Council of the Netherlands, 2010; publication no. 2010/10.

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### Background

Exposure to asbestos can cause cancer in various organs. The conditions most commonly associated with asbestos exposure are cancer of the pleura and peritoneum (known as mesothelioma) and lung cancer. Because these types of cancer often do not develop until years after exposure, environmental and occupational exposure to asbestos in the past continues to cause mortality.

In the Netherlands about eight million tons of asbestos-containing products were produced and consumed, in the previous century – much in the form of asbestos-cement products for use in the building industry, but also in a wide variety of other applications. Two main forms of asbestos are distinguished: serpentine asbestos (also known as chrysotile or white asbestos) and amphibole asbestos (which includes crocidolite, or blue asbestos, and amosite, or brown asbestos). Chrysotile asbestos accounts for more than 90 per cent of asbestos applications. The two most widely used types of amphibole asbestos are amosite and crocidolite.

Although the use of asbestos was prohibited in 1993, people are still being exposed, because asbestos used in the past is still present in many settings. Occupational exposure can still occur when homes and other buildings are demolished, when soil purification activities are undertaken, and when ships, drilling

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platforms and other machines with asbestos insulation are repaired. Incidental exposure may take place in the context of building renovations and if asbestos is present in the environment.

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### Ministerial request for advice

In an advisory letter on asbestos submitted in 2006, the Health Council pointed out that new knowledge was available, which might justify revision of the standards governing exposure to airborne asbestos. The State Secretary for Housing, Spatial Planning and Environmental Management at that time accordingly asked the Council to calculate the asbestos concentrations consistent with the risk levels defined in the context of Dutch environmental policy: the maximum permissible risk level (*maximaal toelaatbaar risiconiveau*, *MTR*) and the negligible risk level (*verwaarloosbaar risiconiveau*, *VR*). The State Secretary for Social Affairs and Employment additionally asked the Health Council to consider whether new occupational exposure limits for asbestos were necessary and, if so, to specify the concentrations corresponding to the risk levels defined by the government.

### The risk analyses underpinning existing policy

The concentrations corresponding to a given risk level\* are calculated by means of risk analysis. Such analysis is based on data concerning groups of people who experienced occupational exposure in the last century. On the basis of the observed associations between asbestos exposure and lung cancer or mesothelioma incidence, so-called  $K_L$  values (for lung cancer) and  $K_M$  values (for mesothelioma) are calculated. These values are expressions of the increase in risk per unit of exposure.

The existing policy is based on reports published by the WHO and the RIVM in 1987. Those reports share two characteristics that are important in this context. First, the various calculations used the average of the  $K_L$  and  $K_M$  values from the individual studies. In other words, no clearly defined allowance was made for the methodological quality of the studies in question. Second, both advisory bodies chose to make recommendations for various concentration intervals, partly because of the uncertainties that existed. However, it was not made clear how the intervals related to the corresponding calculations.

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\* A risk level is an expression of the likelihood of dying of cancer as a result of exposure to a particular carcinogen (in this case, asbestos).

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## The Committee's risk analysis

In this report, the Committee presents detailed arguments for concluding that not all studies are equally suitable as sources of risk analysis data. In many cases, for example, the way the exposure is characterised introduces substantial measurement error. The quality of the available epidemiological data can vary considerably in other respects as well. The Committee therefore considered it essential that meta-analyses are performed for both lung cancer and mesothelioma, using only data from studies selected on the basis of predefined criteria. In this way the best possible point-estimate is obtained, and although the uncertainties are not eliminated, they are reduced as much as possible.

### Lung cancer

For the *lung cancer* meta-analysis, the Committee made a selection from eighteen available cohort studies. On the basis of the Committee's selection criteria, four studies were considered suitable for inclusion. The  $K_L$  values calculated using the data from these studies did not differ with the type of asbestos (chrysotile or amphibole). The weighted average of the  $K_L$  values (resulting in a so-called pooled  $K_L$  value) from the four selected studies has been used as the basis for defining the ultimate values for lung cancer, as associated with all types of asbestos.

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### Mesothelioma

Where *mesothelioma* is concerned, clear differences in carcinogenic potential were discernible between chrysotile asbestos and the amphiboles. Separate  $K_M$  values were therefore calculated for these two general forms of asbestos. For its *mesothelioma* meta-analysis, the Committee made a selection from twelve available cohort studies. Application of the Committee's selection criteria led to just two of these cohort studies being deemed suitable for inclusion: one concerned exclusively with exposure to chrysotile asbestos and one concerned with exposure to a mixture of amosite and chrysotile asbestos, in which the latter was predominant. The Committee used the  $K_M$  values from these studies to calculate a single value for chrysotile asbestos and a single value for exposure to a mixture of chrysotile asbestos and up to 20 per cent amphibole asbestos. However, in the Netherlands, various situations may occur that could result in exposure to amphibole asbestos on its own. The Committee has therefore calculated a  $K_M$  value for amphibole asbestos from the two available studies that looked exclusively at

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amphiboles, even though the studies in question did not satisfy the criteria for inclusion in the meta-analysis. The  $K_M$  values used by the Committee indicate that the carcinogenic potential of amphiboles is fifty times as great as that of chrysotile asbestos.

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### Risk analyses for environmental policy

The following table summarizes the conclusions of the Committee's risk analyses for exposure to asbestos in the environment. Distinction has been made according to the type of fibre to which a person is exposed, and the concentration that corresponds to the risk levels defined by the government is stated in each case. The existing values are also presented for comparison.

Proposed new *MTR* and *VR* values and the existing values for asbestos by type. The values are for lifetime exposure from the general environment, expressed in fibres/m<sup>3</sup> as measured using TEM (Transmission Electron Microscopy). The proposed values are for the two health effects (mesothelioma and lung cancer) combined. The existing *MTR* and *VR* values are for mesothelioma only.

	Proposed new <i>MTR</i> and <i>VR</i> values			Existing <i>MTR</i> and <i>VR</i> values	
	Chrysotile in fibres per m <sup>3</sup>	Mixed exposure to chrysotile and up to 20% amphibole in fibres per m <sup>3</sup>	100% amphibole in fibres per m <sup>3</sup>	Chrysotile in fibres per m <sup>3</sup>	Amphibole in fibres per m <sup>3</sup>
<i>MTR</i>	2,800	1,300	300	100,000	10,000
<i>VR</i>	28	13	3	1,000	100

The Maximum Permissible Risk (*MTR*) values calculated by the Committee for chrysotile asbestos are about forty times lower than the existing *MTR* values; the Committee's *MTR* values for amphibole asbestos are roughly thirty times lower. The discrepancies are attributable not so much to higher  $K_L$  and  $K_M$  values – where the divergence is relatively small – but mainly to methodological differences. Two such differences are of particular significance. First, as indicated above, the current policy is based upon concentration intervals, as opposed to estimates for specific concentrations, which the Committee prefers to work with. Second, the existing *MTR* and *VR* values have been assigned to the upper confidence interval of the calculated concentration; this has a particularly pronounced effect.

On the other hand, the existing environmental quality objective is derived from the *VR* value, whereas, where other substances are concerned, the limit is derived from the *MTR* value. Consequently, although the existing *MTR* value for environmental exposure is considerably higher than the Committee's value, the fact that the existing environmental quality objective for asbestos is based upon

the VR value instead of the MTR value means that it is a hundred times lower than the limit proposed by the Committee.

### *Risk analyses for occupational safety policy*

The proposed occupational exposure limits for chrysotile, for a mixture of chrysotile and up to 20% amphibole asbestos, and for amphibole asbestos on its own are presented in the table below.

Exposure levels by asbestos type for mesothelioma and lung cancer combined, corresponding to risk levels of  $4.10^{-3}$  and  $4.10^{-5}$ . The values are for occupational exposure (eight hours per day, five days per week, for a period of forty years) and are expressed in fibres per  $m^3$  (with fibres/ml between brackets), as measured by TEM.

Risk level	Occupational exposure levels (as measured by TEM) corresponding to the risk level		
	Chrysotile in fibres per $m^3$ (fibres/ml)	Mixed exposure to up to 20% amphibole in fibres per $m^3$ (fibres/ml)	100% amphibole in fibres per $m^3$ (fibres/ml)
$4.10^{-3}$	200,000 (0.2)	130,000 (0.13)	42,000 (0.042)
$4.10^{-5}$	2,000 (0.002)	1,300 (0.0013)	420 (0.00042)

The existing occupational exposure limit is expressed in the form of values as measured by PCM: 10,000 fibres/ $m^3$  or 0.01 fibres/ml; these figures equate to TEM values of 20,000 fibres/ $m^3$  or 0.02 fibres/ml.

NB: the existing Dutch occupational exposure limit is not based on a calculated concentration corresponding to a given risk level.

The existing Dutch occupational exposure limit is 0.01 fibres/ml, as measured by phase contrast microscopy (which equates to a TEM value of 0.02 fibres/ml); this limit applies to all types of asbestos. The existing Dutch occupational exposure limit is not based on a calculated concentration corresponding to a given risk level, but is derived from (and ten times lower than) the current EU standard for chrysotile. The latter standard is based partly on the detection threshold for phase contrast microscopy. The concentrations calculated by the Committee to correspond to a risk level of  $4.10^{-5}$  are substantially lower than the existing Dutch occupational exposure limits.



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# Introduction

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## 1.1 Background

In the twentieth century, roughly eight million tons of asbestos-containing products were produced and used in the Netherlands. These were predominantly asbestos cement products used in the construction industry, but included numerous other items. Although the use of asbestos has been outlawed since 1993, people can still be exposed to asbestos in the everyday environment.

Exposure to asbestos can lead to mesothelioma (cancer of the lining of the lungs and the internal chest wall, known as pleura; and the lining of the abdominal cavities, known as peritoneum) and lung cancer. Because these types of cancer usually do not become manifest until years after exposure, incidental and occupational exposure to asbestos in the last century continues to cause mortality.

In 2007, about four hundred people in the Netherlands died from mesothelioma: a form of cancer for which exposure to asbestos is the only known cause. Modelling indicates that mesothelioma-related mortality in the Netherlands may yet rise to 490 people per year. If so, the total number of deaths due to mesothelioma in the period 2000 to 2028 will be more than 12,400.<sup>1</sup>

Lung cancer mortality attributable to exposure to asbestos is difficult to quantify, since lung cancer can also have other causes. Nevertheless, it is estimated that the annual number of deaths from this form of cancer would be 12% lower without exposure to asbestos.<sup>2</sup>

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Thus, although the use of asbestos is no longer permitted, the health effects of its use will continue for some time to come.

Research by the Erasmus Medical Center Rotterdam, the Comprehensive Cancer Centre for the Twente Urban Triangle and the Twente hospitals has indicated that ongoing exposure to asbestos-containing waste (the so-called asbestos roads) in the area around Goor is the main reason for substantially above-average incidence of mesothelioma in local women.<sup>3</sup> The research prompted the State Secretary for Housing, Spatial Planning and the Environment (VROM) to ask the Health Council of The Netherlands for advice on the situation in 2006.<sup>4</sup>

The Health Council's resulting 2006 advisory letter addressed the question of whether further knowledge had become available since 1987 – when the existing environmental quality requirements regarding asbestos were proposed – which would warrant the review of those requirements. The Council concluded that that was indeed the case, and the consensus was that the existing environmental quality requirements should be reassessed.

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## **1.2 Issues addressed**

Following the advisory letter, the State Secretary for VROM asked the Health Council to re-evaluate the existing environmental quality requirements relating to asbestos exposure, and to propose revisions where appropriate. In addition, the State Secretary for Social Affairs and Employment (SZW) asked the Council to indicate the asbestos concentrations corresponding to the risk levels relevant in the context of occupational health and safety policy. Finally, the State Secretary for SZW requested that, in its report, the Council address certain matters relating to exposure and the methods used for its measurement in the workplace. The letters from the two State Secretaries seeking the Council's advice are reproduced in Annex A.

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## **1.3 Structure of this report**

In section 2, the Dutch Expert Committee on Occupational Safety (*Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen*, whose members are listed in Annex B) considers the general characteristics of asbestos and asbestos exposure, and the health effects associated with exposure to asbestos, in particular the prevalence of mesothelioma. Section 3 describes the risk analyses which form the basis of existing Dutch and other standards; the extent to which the epidemiological research data used for such risk analyses vary in nature and quality

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is highlighted in section 4. In section 5, having reviewed the recent asbestos risk analyses, the Committee presents its conclusion that none of the analyses take (adequate) account of the variation in quality of the epidemiological studies; the Committee has accordingly commissioned new meta-analyses as a basis for calculating afresh the concentrations that correspond to defined environmental and workplace risk levels for both lung cancer and mesothelioma, in the context of which distinction is made between the better-quality studies and those that do not stand up to critical examination (subsections 6.1 and 7.1). On the basis of the better-quality studies, the Committee calculated the concentrations that correspond to the defined environmental and occupational risk levels for lung cancer (subsection 6.2) and mesothelioma (subsection 7.2). The concentrations that the committee ultimately presents in section 8 as corresponding to the risk levels recognised in the context of environmental and occupational health and safety policy take account of both lung cancer-related and mesothelioma-related mortality.



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## **Asbestos and the effects of exposure**

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In this section, the Committee presents background information on the properties, production and applications of asbestos (subsection 2.1), exposure to asbestos and background concentrations (subsection 2.2), and health effects of exposure to asbestos (subsection 2.3).

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### **2.1 Properties, production and applications of asbestos**

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#### *2.1.1 Properties of asbestos*

Asbestos is a mineral that is used mainly for its reinforcing, resilient and heat-resistant properties; it is the generic name for a group of naturally occurring fine inorganic fibres (mineral, inorganic metal silicates prone to longitudinal separation). The length and shape of the fibres vary considerably, depending on factors such as the way the material is processed, its precise origin and the type of asbestos concerned. The properties of the fibres – and hence the potential applications of the various types of asbestos – are defined by the material’s chemical composition and crystalline structure. Two main forms of asbestos are distinguished: serpentine or chrysotile asbestos, and amphibole asbestos:

- Chrysotile (also referred to as white asbestos) is a magnesium-containing sheet silicate whose flat structure is ‘rolled’ around a virtual axis to form a tube known as a fibril. A fibre normally contains several fibrils and is often inclined to curl. The fibrils give the fibre its strength and flexibility. Chrys-

otile asbestos has a silky structure and its microfibrils can have a diameter of less than 0.03  $\mu\text{m}$ .

- Amphiboles contain less magnesium, but include iron, calcium and manganese and typically have a more glassy structure, making them less flexible, more brittle and more rough-textured than white asbestos. The diameter of the fibrils is never less than 0.1  $\mu\text{m}$ , with the exception of crocidolite (approx. 0.05  $\mu\text{m}$ ). The two most widely used amphiboles are crocidolite (blue asbestos) and amosite (brown asbestos).
- The physical and chemical properties of the various types of asbestos are summarised in Table 1.

*Table 1* Physical and chemical properties of the various types of asbestos.

	Serpentines		Amphiboles			
	Chrysotile (white asbestos)	Amosite (brown asbestos)	Tremolite	Actinolite	Anthophyllite	Crocidolite (blue asbestos)
Mineral	Chrysotile (white asbestos)	Amosite (brown asbestos)	Tremolite	Actinolite	Anthophyllite	Crocidolite (blue asbestos)
Colour	White, grey, green, yellowish	Brown, grey, greenish	White to pale green	Green	Grey, white, brownish-grey, green	Lavender, blue, green
Flexibility	Good	Intermediate	Brittle	Intermediate to brittle	Intermediate to brittle	Good
Melting point, decomposition temperature $^{\circ}\text{C}$	800-850	600-900	1,040	Unknown	950	800
Specific mass ( $\text{g}/\text{cm}^3$ )	2.55	3.43	2.9-3.2	3.0-3.2	2.85-3.1	3.37

Amphibole asbestos fibres are to a very large extent chemically inert. Chrysotile fibres are also almost fully inert, but the magnesium in the outer layer of the fibre will dissolve in an acidic solution. The length and diameter of the fibres have a major influence on the health effects associated with each type of asbestos. In practice, asbestos fibres are usually a few tens of micrometers in length. The typical diameters of chrysotile and amphiboles are summarised in Table 2. The diameters of glass, mineral wool and ceramic fibres are also given, by way of comparison.

Table 2 Typical fibre diameters of the various types of asbestos and other fibres.

Fibre type	Diameter in micrometers
Chrysotile fibril	0.02-0.04
Chrysotile fibre	0.75-1.5
Amphibole fibril, type crocidolite	0.05-0.07
Amphibole 'fibril', other types	0.1-0.2
Amphibole fibre	1.5-4.0
Ceramic fibre	0.5-4
Glass fibre	1-5
Mineral wool fibre	4-7

### 2.1.2 Production and applications of asbestos

In antiquity, asbestos was used in earthenware, shrouds and lamp wicks. Modern industrial use began in about 1880, with the boom in extraction and use getting underway around 1910. At the start of the twentieth century, global production was roughly 30,000 tonnes a year; its peak was in 1975, when five million tonnes were produced (see Figure 1).

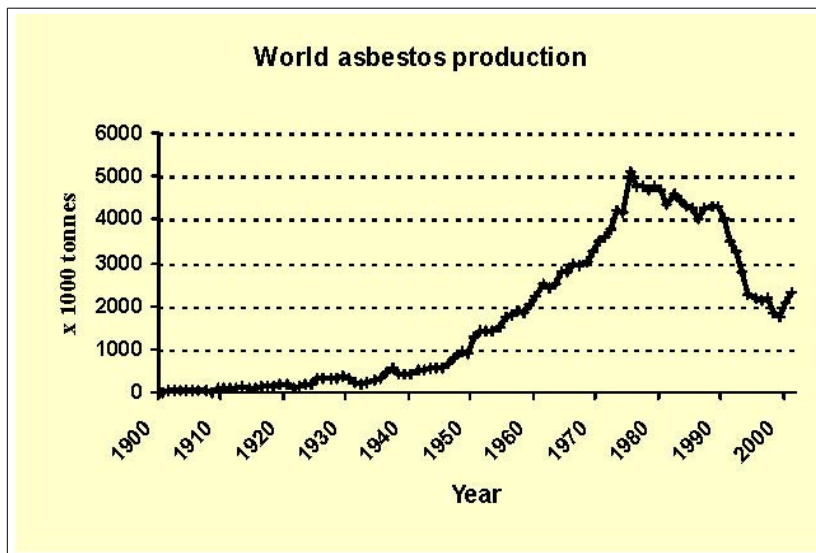


Figure 1 Global asbestos production from 1900 to the present day.<sup>5</sup>

The use of asbestos is now prohibited in the European Union; it has been illegal in the Netherlands since 1993 and throughout the EU since 2005. In the USA and Canada, there is no such complete ban, but it is nevertheless barely used any more. It is estimated that nearly eight million tons of asbestos-containing products were used in the Netherlands prior to its prohibition, mainly asbestos cement products.

Despite the ban that exists in a significant part of the Western world, global asbestos production is still approximately two million tons a year. Indeed, global production has actually started to rise again in recent years. The principal producers are South Africa, Canada and Russia.

More than 90% of asbestos applications involve chrysotile (white) asbestos: a relatively cheap form of asbestos, which is also the most flexible. Amosite (brown asbestos) is used primarily for insulation and fire retardation, while crocidolite (blue asbestos) is found mainly in insulation and asbestos cement products. Table 3 summarises the historical applications of asbestos. As well as being incorporated into asbestos cement, plastics and resins, asbestos fibres were sometimes used in woven textiles.

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## 2.2 Exposure to asbestos and background concentrations

Most occupational exposure to asbestos in the Netherlands occurred after the 1930s. The country had a sizeable asbestos-processing sector, in which insulation companies, shipyards and the asbestos cement industry were predominant. At least 330,000 workers experienced significant exposure to asbestos in the past; in the shipbuilding and ship repair industries, almost all workers were exposed to asbestos insulation in various forms.

*Table 3* Common applications of asbestos.

Corrugated roofing material	Brake linings
Exterior cladding	Clutch plates
Underlay for vinyl floor coverings	Partitions and ceilings
Plant containers	Central heating boiler insulation
Windowsills	Fireproof board
Spray-on coatings for steel structures	Asbestos textiles (fire blankets, welding blankets, gloves, etc)
Insulation material in old electrical appliances, such as toasters, hair dryers, irons	

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Asbestos insulation was used on a large scale not only in shipbuilding, but also by installation contractors and in the chemicals industry, the rubber and plastics industries, mechanical engineering, the metal products industry and the electro-technical industry. Asbestos cement was used extensively in construction and in the agriculture industry; this typically involved the sawing of asbestos cement slabs, often with an angle grinder. Until 1990, it was also standard practice to clean asbestos-containing brake linings, clutch plates and vibrating conveyor systems with compressed air.

Moreover, people working at asbestos-processing firms would often get asbestos fibres on their clothes and thus take them home, resulting in significant continued exposure outside the workplace. In the domestic environment, exposure could arise from the use of asbestos-containing products such as certain floor coverings, asbestos cement sheeting, insulation materials in electrical equipment and heating systems, and construction fillers.

Increasing concern regarding the health hazards led to a rapid decline in the use of asbestos and asbestos products after 1980. In 1993, all occupational handling and processing of asbestos was prohibited in the Netherlands, as a result of which its importation stopped.

Nevertheless, people are still being exposed to asbestos because it is still present in many settings. Occupational exposure can occur when homes and other buildings are demolished, when soil purification activities are undertaken, and when items such as ships, drilling platforms and machines that have asbestos insulation are repaired. Incidental exposure may take place in the context of building renovations and if asbestos is present in the environment. In the area around the former (Eternit) asbestos cement factories in the towns of Goor and Harderwijk for example, asbestos cement waste was used extensively for paving roads and yards up until the 1970s.

The RIVM\* Guidance Document on Asbestos published in 1987 reported background asbestos concentrations measured by TNO\*\* in the preceding years by means of transmission electron microscopy (TEM).<sup>6</sup> In *rural areas*, the background concentrations were close to the detection limit of the TEM method then in use, i.e. 500 fibres/m<sup>3</sup>. In the Goor and Harderwijk areas, where asbestos was previously used for road paving, higher asbestos fibre concentrations were reported, but the exposure level was generally much lower than that associated with occupational exposure in that era. In *urban areas* the outdoor atmospheric background concentrations were between 1,000 and 16,000 fibres/m<sup>3</sup> (0.001-0.016 fibres/ml), but up to 80,000 fibres/m<sup>3</sup> (0.08 fibres/ml) near to busy roads and tunnels; this compared with 100 to 1,000 fibres/m<sup>3</sup> (0.0001-0.001 fibres/ml) in rural areas.\*\*\* Strictly speaking, the higher concentrations should not have been described as background concentrations, since they were in fact the concentrations in the vicinity of sources, such as road junctions (at a time when almost all vehicles had asbestos-containing brake linings).

In the past, workplace concentrations of between a few million and 200 million fibres/m<sup>3</sup> (200 fibres/ml) were measured. The data reported in the RIVM Guidance Document on Asbestos were measured before 1981 (when asbestos use was at its peak, well before the ban introduced in 1993).<sup>6</sup>

With a few exceptions, such as people living in certain locations near to Goor, most people nowadays experience very little exposure to asbestos fibres. Since the late 1970s, there has been no systematic measurement of background asbestos concentrations. However, when investigating workplace concentrations more recently, TNO has often performed reference measurements in uncontaminated urban and non-urban areas. These unpublished measurements indicate that the existing background concentration is roughly 10-20 fibres/m<sup>3</sup> (personal correspondence, J. Tempelman, TNO).

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## 2.3 Health effects

### 2.3.1 Toxicity and carcinogenicity

Inhaled asbestos fibres can enter the smallest parts of the respiratory tract and the alveoli. Those that are not too large are then engulfed by macrophages; larger fibres can migrate into the tissue.

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\* The National Institute for Public Health and the Environment.

\*\* Netherlands Organisation for Applied Scientific Research

\*\*\* The convention is that a fibre is counted if it is longer than 5 µm and its length:diameter ratio is at least 3:1. The quoted values obtained by electron microscopy therefore relate to fibres of at least the specified dimensions.

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Fibres that are coughed up are liable to be swallowed, and then leave the body after passing through the digestive tract. However, they can also enter the lymphatic system and thus be transported to parts of the body far from the lungs.

Over time, macrophages deposit iron-containing proteins (ferritins) on the larger fibres in the lungs. This coating leads to the formation of characteristic asbestos bodies in the pulmonary tissue. The number of such asbestos bodies is therefore broadly indicative of the level of asbestos exposure that a person has suffered. In response to the accumulation of asbestos fibres in the lung, fibrous tissue formation (pulmonary fibrosis) occurs; the particular form of diffuse pulmonary fibrosis caused by exposure to asbestos is referred to as asbestosis. It is believed that the presence of reactive oxygen species and direct contact between asbestos and adjacent cells contribute to the further development of asbestosis.<sup>7</sup> In the surrounding tissue, asbestos can subsequently trigger the development of malignant growths.

The most common forms of malignant growth attributable to asbestos exposure are lung cancer and (pleural) mesothelioma (cancer of the membrane lining of the lungs, or pleura). Numerous possible mechanisms of disease have been investigated, including direct interaction with macro-molecules (proteins, RNA, DNA, membrane lipids), production of oxygen radicals by macrophages, and cell-mediated processes. However, no compelling evidence has been found that any of these mechanisms is responsible for the occurrence of lung cancer or mesothelioma.<sup>7-9</sup>

In the literature, it is generally assumed that asbestos fibres less than 5 µm in length have considerably less carcinogenic potential than longer fibres.<sup>7</sup> The greater carcinogenic potential of longer fibres may be related to the inability of macrophages to engulf such fibres (in humans, macrophages are between 14 and 21 µm).

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### 2.3.2 *Diagnosis and prognosis of mesothelioma and lung cancer*

Mesothelioma is a malignant disease that usually results in death within one or two years of diagnosis. It normally affects the pleura (lining of the lungs and internal chest wall), but can also occur in the peritoneum (lining of the abdominal cavity). In the Netherlands, exposure to asbestos was first linked to the occurrence of mesothelioma by the occupational doctor, Stumphius, who studied people working at a shipyard in Zeeland,<sup>10</sup> and by Zielhuis *et al.*, who conducted a patient-control study.<sup>11</sup> In South Africa, Wagner *et al.* had previously demonstrated a correlation between mesothelioma incidence and occupational exposure to crocidolite.<sup>12</sup>

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Mesothelioma is diagnosed on the basis of a tissue sample (biopsy) taken from the suspect growth. If there is doubt as to how the biopsy observations should be interpreted, the case can be referred to the Netherlands Mesothelioma Panel (Nederlandse Mesotheliomen Panel, NMP), which reassesses a large proportion of biopsies in cases of suspected mesothelioma in the Netherlands. If the disease has progressed to the point where a biopsy of the affected pleura is not considered to be in the patient's interest, a probable diagnosis can be made on the basis of the condition's presentation and clinical progression. It is very unusual for treatment to lead to remission.

In about 80% of cases, it is possible to identify potentially causal exposure to asbestos in the patient's past. In the other cases, such exposure cannot be confirmed. Although other causes cannot be excluded in such cases, it is likely that, in the Netherlands, almost all mesotheliomas are attributable to asbestos.\*.14

Since the 1950s, it has been known that lung cancer is also more prevalent in people who have worked with asbestos. However, in contrast to the situation with mesothelioma, there is a high background incidence of lung cancer in the non-exposed population (the general population). In the general population, lung cancer causes more deaths in men than any other type of cancer. The annual incidence in the Netherlands is seventy cases per 100,000 men and thirty per 100,000 women. Heavy smokers are at least fifteen times more likely to develop lung cancer than non-smokers.

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### 2.3.3 *Incidence of mesothelioma and lung cancer attributable to asbestos exposure*

Rates of mesothelioma-related mortality in the years ahead can be forecast from mortality data for various birth cohorts. Using recent data, the most reliable model predicts 490 male pleural mesothelioma deaths per year in the Netherlands, and a total of approximately 12,400 deaths between 2000 and 2028. Pleural mesothelioma mortality in women is forecast to total about 800 cases between 2000 and 2028.<sup>1</sup> Figure 2 shows the actual number of mesothelioma deaths in men from 1969 to 1999. The Committee has added data on deaths between 2000 and 2007 to the original graph produced by Segura *et al.* (2003).<sup>1</sup>

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\* Other potential causes reported in the literature are radiotherapy, the SV40 virus and genetic predisposition.<sup>7,13</sup>

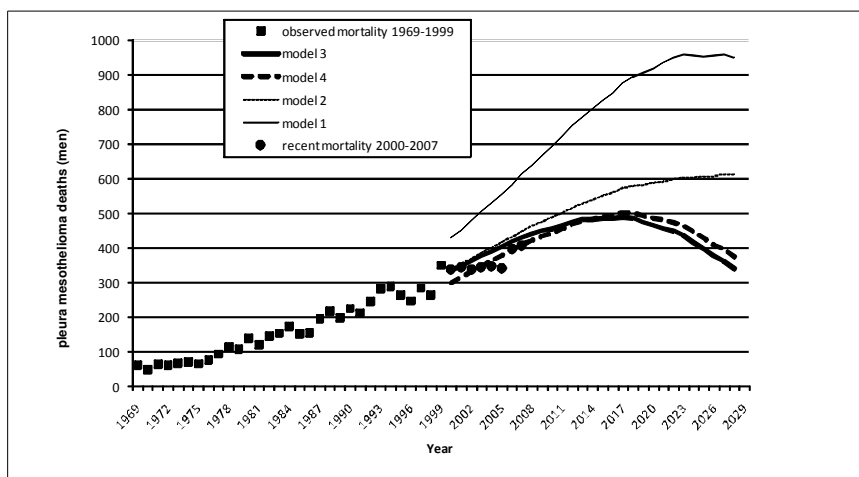


Figure 2 Male mesothelioma mortality in the Netherlands. The estimates for the period after 1999 were obtained by modelling on the basis of various assumptions\*.<sup>1</sup> Data on deaths between 2000 and 2007 have been added to the original graph (black circles).

A recent international comparative study has revealed that the current level of mesothelioma-related mortality in the Netherlands is relatively high, even though asbestos was estimated not to have been more extensively used in the past in the Netherlands than elsewhere.<sup>15</sup> The reason is not apparent. Figure 2 shows mortality from 2007 onwards, forecast on the basis of several modelling exercises, with different assumptions made in each case.<sup>1</sup> The estimates involve some uncertainty, however. The inclusion of data for the period 1994 to 1999 led to a 44% reduction in forecast mesothelioma mortality, compared with the figure produced by Burdorf and Swuste on the basis of data for the period up to 1993.<sup>16</sup> The authors indicate that the assumptions made for model 3 produce the most plausible forecast.<sup>1</sup> The mortality data for the period 2000 to 2007 added by the Committee confirm the reliability of the latter forecast.

The number of people who develop lung cancer as a result of asbestos exposure is harder to ascertain than the number of people who develop mesothelioma.

\* Model 1 uses age and year-specific mortality data for the period 1969 to 1993 and assumes that there will be no mesothelioma in workers born in or after 1962. Model 2 additionally makes use of mortality data for the period up to and including 1998 (an extra five years' data) and assumes that all workers born in or after 1962 have the same (small) risk of developing mesothelioma as those born in the period 1957 to 1961. Model 3 is an extension of model 2, in which the mesothelioma risk for all workers born in or after 1962 is deemed to be zero. Model 4 is an extension of model 3, which additionally makes allowance for a gradual reduction in the total population exposed to asbestos, estimated on the basis of the risk of mesothelioma in each five-year period, after correction for age and birth year.

It is often assumed that the trend in asbestos-related lung cancer mortality should be consistent with the malignant mesothelioma trend. While this may be true in workers who experience relatively low levels of exposure, in those who experience high asbestos exposure, asbestos-related lung cancer mortality is several times higher than malignant mesothelioma mortality.<sup>17</sup>

A comprehensive Dutch epidemiological study suggested that 12% of all lung cancer cases in men could have been prevented by the avoidance of occupational exposure to asbestos.<sup>2</sup> The study subjects were men between fifty-five and sixty-nine years old, who had been recruited in 1986 and who had been exposed to asbestos in the period around World War II and particularly in the postwar period. This estimate of the proportion of lung cancer mortality attributable to asbestos exposure is broadly consistent with figures from other countries: 6% in Scotland,<sup>18</sup> 14% in northern Italy,<sup>19</sup> 16% in Gothenburg (Sweden),<sup>20</sup> and 19% in Helsinki (Finland).<sup>21</sup>

Assuming that the Dutch estimate is valid, this equates to roughly 900 avoidable cases a year in the Netherlands. Given that the relevant research used a cohort of older workers who had been exposed to high concentrations of asbestos, it may reasonably be assumed that asbestos exposure's contribution to lung cancer mortality will decline in the future. However, as with mesothelioma, such a decline is unlikely to begin for some years, due to the length of the latency period.

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## Current standards

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The International Agency for Research on Cancer (IARC) has recently reaffirmed its conclusion that asbestos is a human carcinogen and that all types of asbestos are causally associated with mesothelioma and lung cancer.<sup>22</sup> Furthermore, the IARC<sup>22</sup> asserts that there is now also adequate evidence that asbestos causes ovarian and laryngeal cancer. However, the asbestos-related risk is much higher for lung cancer and mesothelioma than for the other cancers.<sup>7,23-25</sup> Lung cancer and mesothelioma risks were therefore used to define standards. Asbestosis occurs only in association with exposure to concentrations (more than 10 fibre-years, measured using TEM<sup>14,24</sup>) that are generally a lot higher than the concentrations associated with lung cancer and mesothelioma in a regulatory context. Therefore asbestosis was also ignored in this standard setting process.

In subsection 3.1, the Committee begins by considering the risk levels used for carcinogens in the context of environmental and occupational health and safety policy. In subsection 3.2, the Committee examines the exposure-response relationship between asbestos and cancer, and the principles and assumptions used to calculate cancer risk. The existing environmental standards are described in subsection 3.3, and the existing workplace standards in subsection 3.4.

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## 3.1 Environmental and occupational risk levels

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### 3.1.1 Environmental risk levels

In the context of policies for the management of risk associated with substances in the environment, two risk concepts play important roles: the ‘maximum permissible risk (MPR) level’ and the ‘negligible risk (NR) level’. It is assumed that any exposure to a genotoxic carcinogen entails some risk of cancer; in other words, there is no safe level of exposure, (also known as a ‘threshold’ in the scientific literature). Policy concerned with such substances is therefore aligned with what is deemed to be a permissible level of risk that a given form of cancer will occur following exposure\*. A year of exposure to the concentration corresponding to the MPR should result in a risk of cancer mortality not exceeding one in a million ( $10^{-6}$ )\*\*. The cancer mortality risk associated with year-long exposure to the concentration corresponding to the NR should not exceed one in a hundred million ( $10^{-8}$ ).

However, risk analyses for asbestos (including the risk analysis presented in this report) involve the calculation of a concentration corresponding to a given risk of developing mesothelioma or lung cancer later in life, as a result of one’s total lifetime exposure (cumulative exposure). From the policy document ‘Premises for risk management’, it may be deduced that a cancer mortality risk of one in ten thousand ( $10^{-4}$ ) associated with lifetime exposure is equivalent to the MPR.<sup>26</sup> Since the negligible risk (NR) level is defined as a level of risk a hundred times lower than the MPR, the NR (in policy terms) is equivalent to a risk of one in a million ( $10^{-6}$ ) associated with lifetime exposure.

In other words, the Committee calculated concentrations (or exposure limits) that correspond to:

- A cancer mortality risk of one in ten thousand *associated with lifetime exposure*. In this report, this risk is referred to as the  $10^{-4}$  risk (for lifetime exposure). For policy purposes, this value equates to the MPR value.

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\* The precise effect mechanism of asbestos is not known; on precautionary grounds, it is therefore assumed that there is no safe level of exposure to asbestos.

\*\* The policy document in which the MPR is defined states that all induced cancers are assumed to result in death.<sup>26</sup> In this report, the Committee calculates values for lung cancer and mesothelioma, which may indeed be expected to lead to death.

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- A cancer mortality risk of one in a million *associated with lifetime exposure*. In this report, this risk is referred to as the  $10^{-6}$  risk (for lifetime exposure). For policy purposes, this value equates to the NR value.

The concentrations stated in this report as corresponding to the above-mentioned environmental risk levels ( $10^{-4}$  and  $10^{-6}$  lifetime exposure) have been calculated on the assumption that exposure is measured by means of transmission electron microscopy (TEM)\*.

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### 3.1.2 Risk levels and occupational exposure limits

Under the current procedure, the Minister of Social Affairs and Employment asked the Health Council to calculate the airborne asbestos concentrations corresponding to the following risks:

- 1 extra cancer death for every 250 deaths from all causes, given forty years of occupational exposure. This equates to a risk of  $4 \cdot 10^{-3}$  associated with exposure throughout a person's working life. The *annualised* equivalent is a risk of one in ten thousand deaths ( $1 \cdot 10^{-4}$  per year)
- 1 extra cancer death per 25,000 deaths from all causes, given forty years of occupational exposure. This equates to a risk of  $4 \cdot 10^{-5}$  associated with exposure throughout a person's working life. The *annualised* equivalent is a risk of one in a million deaths ( $1 \cdot 10^{-6}$  per year)\*\*.

Where asbestos is concerned, the values relate to the extra mesothelioma-related mortality or asbestos-related lung cancer (exposure measured using phase contrast microscopy (PCM)).

The standard procedure is for the Social and Economic Council (SER) to then be asked to report on the technical and economic feasibility of realising the concentrations corresponding to the two risk levels. Finally, the Minister of Social Affairs and Employment sets an exposure limit.

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\* There is a strong possibility that non-asbestos fibres (e.g. paper, cotton, mineral wool and glass fibres) will be present in the environment. It is therefore advisable to use TEM or Scanning Electron Microscopy (SEM), in order to differentiate adequately. In a workplace setting where it is considered less likely that other fibres will be encountered, phase contrast microscopy (PCM) may be used. The conversion of values obtained by PCM analysis to be equivalent to TEM-based values is considered in section 4.

\*\* This risk level equates to the environmental MPR value associated with exposure for one year.

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## 3.2 Asbestos-cancer exposure-response relationship

Epidemiological research data have been used to specify the associations (and exposure-response relationships) between (the level of) exposure to the various types of asbestos and the occurrence of lung cancer and mesothelioma. By making assumptions regarding matters such as the duration/length of the latency period, interaction (joint effect, or effect modification) between asbestos exposure and smoking (where lung cancer is concerned), and average life expectancy, it is possible to perform a risk analysis using the exposure-response relationship data, and thus to calculate the risk of mesothelioma or lung cancer associated with a given level of exposure.

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### 3.2.1 Exposure-response relationships: fibre exposure and lung cancer

Epidemiological research has shown that the risk of lung cancer increases as the total amount of inhaled asbestos (usually expressed as the cumulative exposure) increases. The cumulative exposure – usually quantified in ‘fibre-years’, i.e. (fibres/ml) × years – is the product of the exposure concentration in fibres/ml air and the exposure duration in (working) years\*. A meta-analysis by Hodgson and Darnton (2000) identified a relationship between cumulative exposure and lung cancer mortality, which took a form that was between a linear association and a quadratic association, based on a regression analysis across all studies included.<sup>27</sup> However, in one study using relatively high quality exposure information, a linear relationship between exposure and lung cancer risk was observed.<sup>28</sup> In view of the aforementioned research results, analyses of lung cancer risk have assumed a linear increase in the effect of asbestos exposure on lung cancer incidence with increasing exposure. This linearity is represented by  $K_L$ : the gradient of the exposure-response relationship, normally expressed as the increase in lung cancer risk per fibre-year of exposure.

So, for example, given a cumulative exposure of 100 fibre-years, a  $K_L$  value of 0.01 will result in a doubling of the relative risk of lung cancer\*\*.

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\* The fibre-year ‘unit’ is therefore an expression of fibres/ml of air times years. Since this is the standard unit used in the literature, values expressed in this way have, in the context of this report, not been converted into fibres/m<sup>3</sup> times years.

\*\* The lung cancer risk, as established in cohort studies, is usually expressed as relative risk (RR). This is risk in the exposed population divided by the risk in the non-exposed population (the general population or a control group). RR and  $K_L$  are related according to the formula:  $RR=1+K_L \times f \times d$ , where  $f \times d$  = cumulative exposure in fibres/ml x years and  $K_L$  is the carcinogenic potential in (fibres/ml x years)<sup>-1</sup>.

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$K_L$  values are often reported as  $100 \times K_L$ , because the actual value of  $K_L$  is low.

In order to analyse the lung cancer risk associated with asbestos, it is important to take account of the interaction between asbestos exposure and smoking. A study published in 1968 demonstrated that the combination of asbestos exposure and smoking resulted in a risk of lung cancer that exceeded the sum of the separate risks.<sup>29</sup> On the basis of a recent meta-analysis, it is now believed that the combined risk is between the sum of the separate risks (additive interaction) and the multiple of the separate risks (multiplicative interaction), making it difficult to define using a simple function.<sup>27,30</sup> A recent study, in which a large cohort of people exposed to chrysotile asbestos were followed for a long period, provided further evidence that the combined effect of smoking and asbestos exposure is less than a multiple of the separate effects.<sup>31</sup> Nevertheless, for practical reasons, smoking and asbestos exposure are usually assumed to have a multiplicative effect.

### 3.2.2 Exposure-response relationships: fibre exposure and mesothelioma

Cancer risk is determined by the cumulative exposure; a function of concentration and duration. However, with mesothelioma there is a very long latency period of about thirty to forty years. This is probably due to the length of time needed for the fibres to migrate through the lung tissue to the pulmonary membrane (pleura). Figure 3 shows how time since first exposure, age and mesothelioma risk are associated.

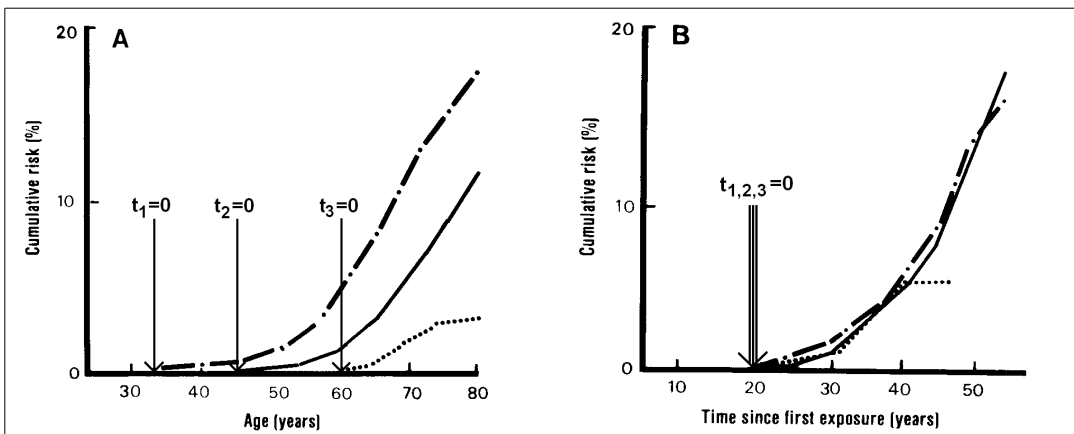


Figure 3 Association between time since first exposure, age and risk of mesothelioma. Diagram A shows three (part) cohorts (from the same study), with first exposure occurring at various ages (indicated as  $t_1=0$ ,  $t_2=0$  and  $t_3=0$ ). In diagram B, the curves have been shifted so that the age of first exposure is the same ( $t_1, t_2, t_3=0$ ); it will be seen that the curves then coincide (adopted from <sup>32</sup>).

The incidence density of mesothelioma-related mortality ( $K_M$ ) can adequately be defined by the following formula (EPA 1986)<sup>24</sup>

$$\begin{aligned}
 I(t,f,d) &= K_M \times f \times [(t-10)^3 - (t-10-d)^3] && \text{if } t > 10+d \\
 &= K_M \times f \times (t-10)^3 && \text{if } 10+d > t > 10 \\
 &= 0 && \text{if } 10 > t
 \end{aligned}$$

Where:  $I(t,f,d)$  equals the mortality density (expressed in the mesothelioma-related mortality in year  $t$ ), depending on  $t$  (the number of years since first exposure),  $f$  (the exposure level in fibres/ml),  $d$  (the exposure duration in years); 10 is the minimum latency period required between exposure and effect (in years). This formula gives the expected likelihood of mesothelioma in a given year, e.g. the seventieth life-year of someone who was exposed to asbestos at work between the ages of twenty and forty. A person's cumulative lifetime risk is calculated by summation of the risks calculated for each year since first exposure. However, this will result in a significant overestimate, since it is necessary to take account of the lifetime risk of mesothelioma-related mortality and mortality from other causes. This formula cannot therefore serve as direct input for risk analysis, but needs to be used in combination with life tables (see Annex D).

The background incidence of mesothelioma in the general population is very low. The exposure-response relationship between asbestos and mesothelioma can therefore most easily be defined in terms of absolute risk.\*

In the formula above, the incidence density of mesothelioma is expressed as the number of cases per 100 000 person-years; hence, the value of  $K_M$  is very low.  $K_M$  is consequently often expressed as a number times  $10^8$ .\*\*The relationship between incidence density and exposure duration is not linear but exponential, as may be deduced from figure 3.  $K_M$  values and the time factor exponent have been estimated using various models and data from various cohorts.

In a model, the values of  $K_M$ , the exponent of the time factor and the assumed latency period are interrelated. The most widely used model is the EPA model, in

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\* Where lung cancer is concerned, the relationship is defined in terms of a relative risk (RR), a risk relative to the background incidence of lung cancer; see subsection 3.2.1.

\*\* The formula presented above defines the mesothelioma incidence (density), which the committee has used in combination with so-called 'life tables' (see Annex D) to calculate lifetime risk. To calculate lifetime risk or the cumulative incidence, the formula has to be integrated; the dimension associated with the  $K_M$  value is then: (fibres/ml x years<sup>4</sup>)<sup>-1</sup>.

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which an exponent value of 3 and a minimum latency period of ten years provide the 'best fit' with the data.<sup>24</sup> Berman and Crump (2008) recently tested the most up-to-date data for the cohorts against this model and again observed a good fit.<sup>33</sup> The Committee has therefore used the EPA model for the calculations presented in this report (with a value of 3 assigned to the time factor exponent and assuming the minimum latency period to be ten years). The combination of the exponent and the modelled latency period of ten years approximates the 'actual latency period', which is generally thought to be about thirty to forty years.

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### 3.2.3 *Principles and assumptions for the calculation of cancer risk*

Given the defined exposure-response relationships for lung cancer and mesothelioma, it is possible to calculate the concentrations that correspond to the specified environmental and occupational risk levels. All the information necessary to make the calculations is extracted from epidemiological literature. Various assumptions then need to be made, such as the following:

- The duration of occupational exposure is usually assumed to be forty years at 1920 hours per year. The duration of environmental exposure is assumed to be life-long.
- Calculations can be made using assumed average or maximum human life expectancy figures. However, it is better to work from the life expectancies defined in 'life tables', which take account of the risk of dying from some other cause ('competing risks'). Hence, the likelihood of dying from asbestos-related mesothelioma or lung cancer is calculated for each life year (allowing for the likelihood of dying from another cause).
- The calculations are normally made using a minimum latency period of ten years.
- Where lung cancer is concerned, assumptions need to be made regarding interaction between the effects of smoking and those of exposure to asbestos.
- The levels of exposure observed in less recent epidemiological studies are generally significantly higher than those experienced by modern-day workers. Extrapolation to a much lower exposure level corresponding to the risk level used for regulatory purposes is usually required. In the context of such extrapolation, a linear relationship is normally assumed to exist between exposure and effect.
- The principles and assumptions adopted by the Committee are set out in subsections 6.2 and 7.2.

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### 3.3 Existing environmental standards

The calculation of the existing Dutch MPR and NR values for asbestos is described in the RIVM Guidance Document (1987);<sup>6</sup> this document and the calculation method were the subject of a 1988 Health Council report.<sup>34</sup> The RIVM Guidance Document follows the WHO's guidelines<sup>25</sup> (published in 1987), except in relation to chrysotile asbestos.

On the following pages, the Committee summarises first the WHO guidelines<sup>25</sup> and then the proposals set out in the RIVM Guidance Document on Asbestos, concerning MPR and NR values for the Netherlands.<sup>6</sup>

In relation to mesothelioma, the WHO's advice draws upon the risk analyses performed by two USA bodies: the National Research Council (NRC, 1984) and the Environmental Protection Agency (EPA, 1986).<sup>24,35</sup> Where lung cancer was concerned, the WHO made its own calculations.

The WHO, the US Academy of Sciences and the US EPA all indicate that findings of any separate risk analyses for lung cancer and mesothelioma will be divergent.<sup>24,35,36</sup> The calculation is based on epidemiological data regarding the working population. In order to enable comparison between, on the one hand, the WHO guidance and the analyses presented by the WHO and, on the other hand, the concentrations that correspond to the relevant environmental risk level, all values quoted in this subsection have been converted to concentrations corresponding to a risk level  $10^{-4}$  (for lifetime exposure), as measured by means of TEM\*.

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#### 3.3.1 WHO risk analysis for lung cancer

##### Availability of analytical data at the time of the WHO risk analysis

Table 4 presents the  $K_L$  values used in risk analyses performed by the US EPA, the US Consumer Product Safety Commission (CPSC), the NRC, Canada's Ontario Royal Commission (ORC) and the UK Health and Safety Executive (HSE)<sup>17,24,35-37</sup> prior to formulation of the WHO report.<sup>25</sup> It will be apparent that the studies differ particularly in terms of the estimated risk per unit exposure (vertical). Differences in  $K_L$  value were also observed within individual studies.

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\* The Committee assumes that the values obtained by means of TEM were twice as high as those obtained by PCM; see subsection 6.2.1.

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The latter differences were due to variation in the selected conversion factors and statistical analysis (and, in some cases, in the cohort re-analysis method).

*Table 4* Comparison of lung cancer risk estimates from earlier risk analyses (adopted from <sup>17</sup>) that were based on cohort studies of exposed workers. The reported figures are 100×K<sub>L</sub> values: the increase in lung cancer risk per unit of asbestos exposure (fibre-years).

Auteur	100×K <sub>L</sub> -value in (fibres/ml×year) <sup>-1</sup>				
	EPA	CPSC	NRC	ORC	HSC
Dement <i>et al.</i> <sup>38</sup>	2.8	2.3	5.3	4.2	
McDonald <i>et al.</i> <sup>39</sup>	2.5				1.25
Peto <i>et al.</i> <sup>40</sup>	1.1	1.0	0.8	1.0	0.54
McDonald <i>et al.</i> <sup>41</sup>	1.4				
Berry & Newhouse <sup>42</sup>	0.058	0.06		0.058	
McDonald <i>et al.</i> <sup>43</sup>	0.010				
McDonald <i>et al.</i> <sup>44</sup>	0.06	0.06	0.06	0.02-0.046	
Nicholson <i>et al.</i> <sup>45</sup>	0.17	0.12	0.15		
Rubino <i>et al.</i> <sup>46</sup>	0.075	0.17			
Seidman <sup>47</sup>	4.3	6.8	9.1		
Selikof <i>et al.</i> <sup>48</sup>	0.75	1.0	1.7	1.0	
Henderson & Enterline <sup>49</sup>	0.49	0.50	0.3	0.069	
Weill <i>et al.</i> <sup>50</sup>	0.53	0.31			
Finkelstein <sup>51</sup>	6.7	4.8		4.2	
Newhouse & Berry <sup>52</sup> , (Men)			1.3		
(Women)			8.4		
(Geometrical average) value used for the risk analysis (100×K <sub>L</sub> )	1.0	0.3-3	2.0	0.02-4.2	1.0

EPA (1986): Environmental Protection Agency (US); CPSC (1983): Consumer Product Safety Commission (US); NRC (1984): National Research Council (US); ORC (1984): Ontario Royal Commission (Canada); HSC (1979): Health and Safety Executive (UK) <sup>17,24,35-37</sup>

In 1987, on the basis of a review of K<sub>L</sub> values by Liddell (1985),<sup>53</sup> the WHO<sup>25</sup> estimated that the average 100×K<sub>L</sub> value was 1. The 1986 EPA risk analysis is often cited in the literature, because of the extensive K<sub>L</sub> value calculations it involved<sup>24</sup>; for lung cancer, the average 100×K<sub>L</sub> value was put at 1. This figure was obtained by working out the average of the K<sub>L</sub> values from all the available epidemiological studies (except for those concerning mine workers), in some cases after making certain corrections (e.g. for differences in the background lung cancer mortality levels assumed in the context of a cohort study and the national or regional mortality figures). Studies of mine workers<sup>44-46</sup> generally indicate a lower risk; it has been suggested that this may be due to the fibres encountered during extraction having a different length:diameter ratio from those encountered during processing.

All the studies used by the EPA involved workers with relatively high levels of cumulative exposure. The average exposure varied between 31 and 400 fibre-years. For lung cancer, for example, the NRC initially calculated  $100 \times K_L$  values for nine studies, which varied from 0.06 to 9.1.<sup>35</sup> The median value of  $100 \times K_L$  was 1.1, but for its risk analysis the NRC decided to adopt a  $100 \times K_L$  value of 2. The EPA, HSC and WHO all used 1 as the value of  $100 \times K_L$ .<sup>17,24,36</sup>

#### WHO lung cancer calculation

The assumptions and principles adopted by the WHO<sup>25</sup> for its calculation of lung cancer risk included the following:

- Smokers are ten times more likely to develop lung cancer than non-smokers. The joint effect of asbestos exposure and smoking (interaction) is assumed to be multiplicative.
- The value of  $100 \times K_L$  is put at 1, which implies that a cumulative exposure of 100 fibre-years would double the risk of lung cancer.
- Lifetime exposure implies exposure over a period of seventy years; smokers are assumed not to have smoked for the first twenty years of life.
- The estimated concentrations are as measured using PCM; TEM-measured values will be twice as high (conversion factor = 2).

As well as providing its own risk analysis, the WHO presents the findings of three other risk analyses, including those by the EPA and the NRC.<sup>24,35,36</sup> The figures calculated for male smokers by the WHO, NRC and EPA are between 260 and 1,000 fibres/m<sup>3</sup><sup>24,35,36</sup> (These figures are converted\* into TEM-measured\*\* exposures corresponding to a risk level of  $10^{-4}$  (for lifetime exposure) – i.e. the reference level of risk used in this report and the Guidance Document). It is not surprising that the various risk analyses yielded quite similar results, since all used almost the same  $100 \times K_L$  value: 1 (EPA and WHO) or 2 (NRC). According to the WHO, the risk to non-smokers is ten times lower than the risk to smokers.

On the basis of its own analysis (in which the value of  $K_L$  is 1) and those performed by others, the WHO puts the exposure concentration at 10,000 to 100,000

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\* Such conversions are easy to make, since all the models concerned assume a linear relationship between exposure and risk.

\*\* The WHO works on the basis of an PCM-TEM conversion factor of 2.

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fibres/m<sup>3</sup> for an exposure corresponding to a risk level of 10<sup>-4</sup> (for TEM-measured lifetime exposure) and assuming that 30% of the population smokes.

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### 3.3.2 WHO risk analysis for mesothelioma

The WHO<sup>25</sup> guidelines on mesothelioma drew upon, among other sources, the risk analyses performed by the National Research Council (NRC, 1984) and the Environmental Protection Agency (EPA, 1986).<sup>24,35</sup> These risk analyses were in turn based on a relatively small number of cohort studies, since the available studies did not encompass a sufficiently high number of deaths to support the calculation of reliable exposure-response relationships. Only in cohorts exposed to both chrysotile and amphiboles, or to amphiboles only, was mesothelioma-related mortality sufficiently high to permit the calculation of an exposure-response relationship.

Converted into TEM-measured concentrations that correspond to a risk level of 10<sup>-4</sup> (for lifetime exposure), the findings of the four mesothelioma risk analyses referred to in the WHO report vary between 500 and 2,000 fibres/m<sup>3</sup>. The WHO quotes a guideline range of 1,000 to 10,000 fibres/m<sup>3</sup> (converted into a concentration) corresponding to a risk level of 10<sup>-4</sup> (for TEM-measured lifetime exposure).<sup>25</sup>

#### WHO conclusions on mesothelioma and lung cancer

To summarize, the WHO<sup>25</sup> gives the following values – converted to concentrations corresponding to the risk level of 10<sup>-4</sup> (for TEM-measured lifetime exposure) – for lung cancer and mesothelioma:

Table 5 WHO guidelines (1987)<sup>25</sup> converted to concentrations corresponding to the risk level 10<sup>-4</sup> (for TEM-measured lifetime exposure).

	WHO guidelines, <sup>25</sup> converted to concentrations corresponding to a risk level of 10 <sup>-4</sup>
Lung cancer	10,000 to 100,000 fibres/m <sup>3</sup>
Mesothelioma	1,000 to 10,000 fibres/m <sup>3</sup>

Although the WHO states that amphiboles have greater mesothelioma-inducing potential, for precautionary reasons it is assumed that chrysotile carries the same risk as amphiboles. In calculating the risk of lung cancer, too, the WHO makes no distinction between different types of asbestos.

### 3.3.3 Comments on the WHO report

Shortly before the WHO report was published, it became clear that the analysis performed by the National Research Council (NRC)<sup>35</sup> contained a number of errors, which were published and corrected in the journal *Science*<sup>54</sup> and duly incorporated into the WHO report. The NRC had underestimated the risk of mesothelioma because their study had calculated lifetime risk not on the basis of its cumulative incidence but on the basis of its incidence in a given year. This led to underestimation by a factor of 17.4. In a response also published in *Science*, the NRC admitted that the risk of lung cancer had also been underestimated because in examining exposure they had calculated environmental exposure, not on the basis of a total annual exposure duration of 8,760 hours, but on the basis of an occupationally exposed worker's annual working hours (then estimated to average 1,920 hours).<sup>55</sup> The table below shows the corrected values for mesothelioma and lung cancer as given by the NRC.<sup>55</sup>

*Table 6* Estimated risk after lifelong exposure to median (400 fibres/m<sup>3</sup>; 0.0004 fibres/ml) and high (2000 fibres/m<sup>3</sup>; 0.002 fibre/ml) concentrations of airborne asbestos fibres. (Corrected values from NRC, 1984;<sup>54</sup>). (Calculated using:  $100 \times K_L = 2$ ;  $K_M = 2.53 \times 10^{-8}$ ).

Type of effect	Exposure group	Estimated mortality per 10 <sup>6</sup> deaths	
		Median exposure 400 fibres/m <sup>3</sup> (0.0004 fibres/ml)	High exposure 2,000 fibres/m <sup>3</sup> (0.002 fibres/ml)
Lung cancer	Male smoker	292	1,459
Lung cancer	Female smoker	105	524
Lung cancer	Male non-smoker	27	132
Lung cancer	Female non-smoker	14	60
Mesothelioma	All groups	156	780

Notes on Table 6: The table presents the estimated additional number of deaths per million deaths associated with a lifetime environmental exposure to 400 fibres/m<sup>3</sup> and 2,000 fibres/m<sup>3</sup>. Thus, in a group of one million male smokers who experience lifelong exposure to 400 fibres/m<sup>3</sup>, it is estimated that there will be 292 additional asbestos-related lung cancer deaths. It should be considered that in such a group, there will ultimately be about 70,000 lung cancer deaths (estimate based on<sup>56</sup>). In a group of one million male non-smokers, the number expected to die from lung cancer is of course much smaller, approximately 9,000.

In its response in *Science*, the NRC also pointed out that the table showed that the risks of lung cancer and mesothelioma were broadly comparable.<sup>54</sup> The outcomes of the risk analyses cited in the WHO report<sup>25</sup> also show no clear differences between the lung cancer risk and the mesothelioma risk. Nevertheless, for lung cancer, the WHO report ultimately opted for a range of 10,000 to 100,000

fibres/m<sup>3</sup>.<sup>\*</sup> A higher guideline value than that calculated by the WHO itself was considered preferable at the time of the report, because it was felt that the wide range of  $K_L$  values precluded reliable estimation (the WHO mentioned an extremely large margin of uncertainty) and because earlier estimates were consistent with a range of 10,000 to 100,000 fibres/m<sup>3</sup>.

The WHO guidelines based on mesothelioma risk cite a range (converted to concentrations corresponding to the environmental risk level) of 1,000 to 10,000 fibres/m<sup>3</sup> (measured by TEM).<sup>25</sup> However, the findings of the risk analyses cited in the WHO report had suggested a figure (converted to a concentration that corresponds to the environmental risk level) of between 500 and 2,000 fibres/m<sup>3</sup> (measured by TEM); see also table 18. It is not clear why the range of 1,000 to 10,000 fibres/m<sup>3</sup> was chosen instead; possibly the NRC's corrected risk analysis<sup>54</sup>, which appeared immediately before the WHO report, was not taken into account. The above-mentioned lower limit of 500 fibres/m<sup>3</sup> is the corrected outcome of the NRC risk analysis<sup>54</sup>; prior to correction, the NRC analysis indicated a figure of 8,700 fibres/m<sup>3</sup>.<sup>35</sup> If the NRC correction is not taken into account, the range of the exposures associated with risk level  $10^{-4}$  (for TEM-measured lifetime exposure cited by the WHO is 833 to 8,700 fibres/m<sup>3</sup> (see also table 18), which roughly corresponds to the range put forward by the WHO (1,000 to 10,000 fibres/m<sup>3</sup>).

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### 3.3.4 Calculation of the current Dutch MPR and NR

The current Dutch MPR and NR are derived from the values in the 1987 RIVM Guidance Document<sup>6</sup>; this document and the calculation method used were discussed in a 1988 Health Council report.<sup>34</sup> The RIVM Guidance Document is based upon the WHO guidelines discussed above (WHO, 1987)\*\*.<sup>25</sup>

The RIVM Guidance Document adopts the values given in the WHO report (see Table 5), except that the RIVM assumes that the mesothelioma-inducing potential of chrysotile asbestos is ten times lower than that of amphibole asbestos. This is justified by reference to the working hypothesis suggesting that the two types of asbestos differ by a factor of twenty in terms of their mesothelioma-inducing potential.<sup>57</sup>

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\* As previously indicated, the values quoted and discussed by the WHO have been converted by the Committee into concentrations corresponding to an environmental risk level of  $1 \times 10^{-4}$  for lifetime exposure.

\*\* According to the document's Annex, the authors of the Guidance Document<sup>6</sup> were working from a draft version of the WHO report, which took no account of the correction referred to in subsection 3.3.3; prior to correction, the findings of the analyses considered in the WHO report varied from 833 to 8,700 fibres/m<sup>3</sup>.

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The concentrations from the Guidance Document that correspond to the risk levels  $10^{-4}$  and  $10^{-6}$  (for lifetime exposure) are given in Table 7 (values based on TEM measurements; for the conversion of PCM values to TEM values, the RIVM follows the WHO in applying a factor of 2).

Table 7 Proposed exposure concentrations corresponding to the reference environmental risk levels ( $10^{-4}$  and  $10^{-6}$  for lifetime exposure), as cited for mesothelioma and lung cancer in the RIVM Guidance Document on Asbestos (in fibres/m<sup>3</sup>, measured by TEM).<sup>6</sup>

Risk after lifetime exposure	Mesothelioma fibres/m <sup>3</sup>	Lung cancer fibres/m <sup>3</sup>
$10^{-4}$ for chrysotile (white)	10,000-100,000	
$10^{-4}$ for amphiboles (blue and brown)	1,000-10,000	10,000-100,000
$10^{-6}$ for chrysotile (white)	100-1,000	
$10^{-6}$ for amphiboles (blue and brown)	10-100	100-1,000

The concentrations from the Guidance Document that correspond to the risk levels  $10^{-4}$  and  $10^{-6}$  (for lifetime exposure) are given in Table 7 (values based on TEM measurements; for the conversion of PCM values to TEM values, the RIVM follows the WHO in applying a factor of 2).

The Health Council committee that reviewed the Guidance Document on Asbestos supported the values put forward in the Guidance Document, which are valid for fibres longer than 5 µm.<sup>34</sup> The Committee did, however, add that it could not necessarily be assumed that fibres of less than 5 µm presented no carcinogenic risk. In the policy document *Asbestos in the environment*,<sup>58</sup> the MPR and NR values were calculated from the concentrations put forward by the RIVM. As previously indicated, the MPR and NR formally correspond to risk levels of  $10^{-4}$  and  $10^{-6}$  for lifetime exposure. In addition, the decision was made to express not only the difference in potential between chrysotile and amphiboles but also between different fibre lengths by means of a weighting factor. This system assumes an MPR of 100,000 fibres/m<sup>3</sup> (the upper limit of the range of chrysotile concentrations associated with the  $10^{-4}$  risk) and a concentration corresponding with the NR of 1,000 fibres/m<sup>3</sup> (the upper limit of the range of chrysotile concentrations associated with the  $10^{-6}$  risk) and the following weighting factors:

1 chrysotile fibre with a length >5 µm	equivalence factor 1
1 chrysotile fibre with a length <5 µm	equivalence factor 0.1
1 amphibole fibre with a length >5 µm	equivalence factor 10
1 amphibole fibre with a length <5 µm	equivalence factor 1

Dividing the MPR by a given equivalence factor yields a specific MPR for a given fibre type of a given length.

In the policy document *Asbestos in the environment*, the limit set for outdoor environments is that corresponding to the NR level.<sup>58</sup> This limit is a specification of the quality level that must be attained; higher concentrations are not permitted.

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### 3.4 Calculation of occupational exposure limits

Workplace environments in the Netherlands are currently subject to an exposure limit of 0.01 fibres/ml (10,000 fibres/m<sup>3</sup>) for all types of asbestos and for an average exposure duration of eight hours per day. The fibre concentration must be established with phase contrast microscopy and in accordance with the methods described by the WHO or an equivalent method.<sup>59</sup> The limit set by the Dutch Minister of Social Affairs and Employment is therefore ten times lower than the EU threshold, i.e. 0.1 fibres/ml (100,000 fibres/m<sup>3</sup>), as specified in Directive 2003/18/EC of the European Parliament and of the Council. In the draft of this Directive (EU 2001/0165), two reasons were given for adopting this value. First, it was assumed that exposure would normally involve chrysotile asbestos, since amphiboles had already been kept off the market for some considerable time. Second, the measurement method proposed by the WHO makes it hard to measure concentrations below 0.1 fibres/ml (100,000 fibres/m<sup>3</sup>). Thus, the current exposure limit in the Netherlands is not based on a risk analysis, in the context of which the concentrations that correspond to certain risk levels have been calculated.

The American Conference of Governmental Industrial Hygienists (ACGIH) advocates the same limit of 0.1 fibres/ml (100,000 fibres/m<sup>3</sup>) for asbestos fibres.<sup>60</sup> According to the ACGIH, application of this limit protects against the development of asbestosis (asbestos-induced 'dust lung'). The ACGIH's argument for basing a limit on asbestosis is that no adequate dose-response data are available for mesothelioma that could be used to set an exposure standard. The ACGIH also contends that application of its asbestosis-based limit will minimise the risk of both lung cancer and mesothelioma. The US Occupational Safety and Health Administration has also defined a Permissible Exposure Limit (PEL) at the same level. Stayner calculated that lung cancer mortality through forty-five years of exposure to the above-mentioned concentration of 0.1 fibres/ml (100,000 fibres/m<sup>3</sup>) would amount to five additional deaths per thousand exposed people.<sup>28</sup> This is roughly equivalent to an occupational risk level of 4.10<sup>-3</sup>.



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## Nature and quality of the epidemiological research

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Analyses of the risk posed by asbestos draw on data concerning occupationally exposed cohorts, gathered in the context of studies that have been described and discussed in the published literature since 1960. The studies in question are not all equally suitable for use as basis for risk analysis. In some of the studies, the characterisation of exposure in particular is neither complete nor optimal.

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### 4.1 Measurement of asbestos exposure in epidemiological studies

Over the years, the various cohort studies have made use of a variety of measurement techniques for fibres. In the first of these studies, carried out before the Second World War, exposure to asbestos was measured by capturing fibres in wash bottles (impingers) filled with a liquid (usually alcohol) and counting the particles. The measuring period was generally shorter than half an hour. Fibres were not distinguished from particles, and more detailed identification of the fibres was technically impossible. The concentration was expressed in millions of particles per cubic foot (mppcf). Filter methods were also used in order to establish substance concentrations gravimetrically (by weighing).

Shortly thereafter, methods were introduced which made use of microscopic counting techniques. Phase contrast microscopy (PCM) has long been the most

widely used microscope technology in such counting methods\*; it allows the measurement of fibres thicker than approximately 0.25 µm. With transmission electron microscopy (TEM) or scanning electron microscopy (SEM)\*\* , it is possible to also count fibres thinner than those observable using PCM; these techniques allow for the detection of fibres with a diameter of as little as 0.01 µm. However, the use of electron microscopy is more expensive than the use of PCM and requires the involvement of specially trained personnel. Initially, measurements were based on the use of static equipment. Later on, personal sampling became more widely applied.

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#### 4.2 Use of conversion factors for the comparison of research results

Because the numerous studies of asbestos risk have made use of a variety of measurement techniques, their results are expressed in different units of exposure. Conversion factors are therefore needed if the results are to be compared and expressed in one unit of exposure.

A report of the US National Research Council provides an overview of widely used conversion factors.<sup>35</sup> Table 8 (adopted from<sup>35</sup>) shows, for instance, that where measurement by impinger would yield a value of 1 particle per m<sup>3</sup>, a phase contrast microscope would have detected on average 6 fibres/m<sup>3</sup>. The use of standard conversion factors results in a simplification of reality, however, because an accurate conversion factor is strongly dependent on the specifics of the environment, and should ideally be determined on a case-by-case basis for each environment. In practice, true conversion factors have been found to vary considerably\*\*\*.

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\* Workplace measurements using PCM usually provide a good insight into the prevailing atmospheric asbestos concentration. However, PCM does not allow for asbestos fibres to be distinguished from other fibres, such as cotton, paper, mineral wool and glass fibres. When indoor measurements are made in a setting where non-asbestos fibres are likely to be present, there is a significant risk of overestimation; yet the inability to detect fibres with a diameter of < about 0.25 µm is liable to lead to underestimation. Consequently, if non-asbestos fibres are likely to be present, environmental concentrations are often measured by means of transmission electron microscopy (TEM) or scanning electron microscopy (SEM), possibly in combination with detection techniques such as XRMA or SAED, which allow for distinction to be made between different fibre types.

\*\* In Europe, most laboratories (except those in France) use SEM, rather than TEM. The current generation of SEM equipment is at least as good as – and in some ways superior to – modern TEM equipment. SEM is better in terms of minimum detection limit, measurement uncertainty and the likelihood of contamination.

\*\*\* Comparative research has previously shown that the factor for the conversion of 'light-microscope to electron-microscope chrysotile measurements' varies from 19 to 76 for all airborne asbestos fibres, depending on the type of working environment (<sup>61</sup>, in ATSDR, 20017).

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*Table 8* Factors for the conversion of atmospheric fibre concentrations obtained by means of the various measurement methods used to measure workplace asbestos levels (adopted from <sup>35</sup>). Bracketing of a conversion factor indicates that the quoted figure is an estimate obtained by the combination of other conversion factors.

Original measurement obtained using:	Equivalent value for alternative method			
	Impinger (particles)	PCM (fibrres/ml, fibrres >5µm)	TEM (fibrres/ml)	Gravimetric (mass) mg/m <sup>3</sup>
Impinger (particles)	1	6	360	0.2
PCM (fibrres/ml, fibrres >5µm)	0.17	1	60	0.03
TEM (fibrres/ml)	0.0028	0.017	1	0.0005
Gravimetric (mass) measurement mg/m <sup>3</sup>	5	30	2,000	1

Fibres shorter than 5 µm are considered to make little contribution to the carcinogenic potency of asbestos (see subsection 2.2.1). These small fibres cannot be measured using PCM in a way that complies with the applicable counting convention. For regulatory purposes, the most important conversion factors are those used to convert PCM-based fibre concentrations into TEM figures for fibres longer than 5 µm. Verma and Clark’s comparative research established a PCM to TEM conversion factor for fibres longer than 5 µm (with a diameter greater than 0.3 µm) of between 1.2 and 10.4, but usually between 1.4 and 3.2.<sup>61</sup> A report published by the Health Effects Institute suggested that a conversion factor range from one order of magnitude below to one order of magnitude above would probably cover all workplace settings.<sup>17</sup> The EPA concluded that the PCM-to-TEM conversion factor (for fibres more than 5 µm long with a diameter greater than 0.4 µm) was between 2 and 4 (EPA, 1986).<sup>24</sup>

### 4.3 Lack of detail concerning the quantification of exposure in the occupationally exposed cohorts

The usefulness of earlier studies is limited not only by differences in measurement methods but also by the differences in the nature of the available data; for instance, data are incomplete, or have not been collected in accordance with current standards.

In some studies, for example, the measurement strategy used to characterise the exposure – i.e. to assign exposure levels to samples of workers and in time based on measurements of airborne asbestos or external data – was not consistent with modern principles, resulting in the misclassification of exposure and potential attenuation or more generally bias of the exposure-response relationship. For some cohort studies, the researchers did not know exactly how long workplace

exposure had lasted and they therefore simply made crude estimates regarding duration of exposure.

In many of the studies, subjects were exposed to various types of asbestos. Moreover, the distribution of fibre lengths differed very likely from one study to the next or was not known; the asbestos that mine workers are exposed to will not exhibit the same fibre length distribution as the asbestos that people working in an asbestos textile factory are exposed to. Yet fibre length distribution data are available only for a few of the studied cohorts.

There are also gaps in the information available regarding the asbestos-cancer exposure-response relationship. The relationship between fibre length (and diameter) and the carcinogenic potency of asbestos is not clear from the published research. Some data are available from animal research, but not readily transferrable to humans. Moreover, while recent epidemiological analyses suggest that longer and thinner fibres may play a more important role, the precise relationship between fibre dimensions and health effects cannot reliably be determined, because most of the studies provide too little information about fibre length and diameter distributions.

Another shortcoming is that information about smoking patterns is available only for a few of the cohorts, meaning that the association between asbestos exposure and lung cancer often could not be adjusted for smoking.

Finally, in several studies the information provided on the cause of death is not completely accurate (particularly with regard to diagnosis of mesothelioma cases in the decades before and immediately after the Second World War)

The shortcomings in the nature and quality of the epidemiological research described above are expected to lead to misclassification and bias the apparent association between asbestos exposure and the occurrence of lung cancer or mesothelioma. The degree of bias is difficult to estimate in most cases, being possible only where validation studies were performed. Any interpretation of the entire body of evidence regarding health effects resulting from asbestos exposure data needs to take account of the considerations set out above.

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## Recent risk analyses

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More scientific data on occupational exposure to asbestos have become available since the risk analyses of the 1980s were carried out. Monitoring of the existing study cohorts has continued – so that the studies now cover longer follow-up periods and include more cancer cases – and new studies have been published. Research has also been performed on the prevalence of mesothelioma in the general population living near to (former) asbestos plants in the Netherlands (for a discussion of these studies, see Annex E). The latter studies cannot be used for quantitative risk analysis, however, because the available exposure data are at best merely indicative.

Over the last ten years, several re-analyses and meta-analyses have been published. In this section, the Committee considers the most recent of these analyses and their usefulness for the calculation of standards.

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### 5.1 Recent meta-analyses

The research results from a large series of studies of cohorts that were occupationally exposed to asbestos have been described and analysed in two recent meta-analyses by Hodgson and Darnton (2000)<sup>27</sup> and Berman and Crump<sup>23,33</sup> (2003, 2008). Hodgson and Darnton's study was commissioned by the British Health and Safety Executive, while Berman and Crump's evaluation (2003)<sup>23</sup> was commissioned by the US Environmental Protection Agency (EPA). Berman

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and Crump's 2008 analysis<sup>33</sup> was a follow-up to their 2003 analysis. The two teams made use of different analytical techniques.

Hodgson and Darnton calculated the average asbestos exposure for each cohort and the additional mortality attributable to lung cancer and mesothelioma per cohort.<sup>27</sup> The exposure-response relationship over all cohorts collectively was based on the point estimates for each of the individual cohorts. Because this approach required information only about the average exposure in a cohort (the point estimate), it allowed for the inclusion of cohorts for which only an average exposure estimate was available. Hodgson and Darnton also investigated which model best fitted the observed relationship between exposure and response;<sup>27</sup> Berman and Crump analysed the exposure-response relationship for each cohort separately, and then performed a meta-analysis to derive various  $K_L$ s. Berman and Crump considered only linear exposure-response relationships.<sup>23</sup>

As part of their evaluation of the different cohorts, Berman and Crump sought to establish the degree of uncertainty deriving from a number of factors, including a) the measurement of static exposure, as opposed to personal exposure; b) the conversion of impinger measurements to phase contrast microscopy measurements; c) the level of detail of the exposure assignment based on linkage of department or job title specific measurements with the workers' employment history established on the level of department, job title or taks.<sup>23</sup> Where possible, these uncertainty factors were incorporated into the analysis, and this yielded adjusted and generally wider confidence intervals (termed 'uncertainty interval' by Berman and Crump) around the  $K_L$  and  $K_M$  values.

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## 5.2 The usefulness of recent analyses for the calculation of new standards for asbestos

The Committee observes that few of the meta-analyses performed so far selected studies for inclusion on the basis of their quality. In the analysis by the Health Effects Institute (HEI) (1991), it is reported that, of the fourteen cohort studies considered, only four yielded exposure data of sufficient quality to be considered for use in quantitative exposure-response analysis.<sup>17</sup> However, in its final analysis, the HEI makes use of the average exposure-response data for *all* the cohorts. In the context of their risk evaluation for the British HSE, Doll and Peto<sup>57</sup> judged only two studies to be of sufficient quality, but they did not specify the quality criteria applied.

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In the evaluation carried out for the EPA (2003), Berman and Crump<sup>23</sup> attempted to take the quality of the analysed studies into account. This was done by evaluating the quality of the exposure data and the diagnostic information concerning lung cancer and mesothelioma. However, not all aspects of an exposure assessment strategy were taken into consideration. No attempt was made to assess the measurement strategy uncertainties deriving from the measurement effort (e.g. number of measurements, their distribution across the population, number of person-years in the cohort, and the attribution of exposure to individuals). Moreover, Berman and Crump did not exclude any studies on grounds of study quality.

In the past, it was unusual to make an explicit selection of studies on the basis of measurement strategy quality criteria. However, it is notable that, even in the context of the more recent studies by Hodgson and Darnton<sup>27</sup> (2000) and by Berman and Crump<sup>23,33</sup> (2003, 2008), recent insights into the evaluation of ‘weight of evidence’ have not been applied, despite the fact that asbestos is an extensively evaluated substance. This is all the more surprising given the comprehensive evaluation in both analyses of the (carcinogenic) potential of the various types of asbestos in relation to both lung cancer and mesothelioma.

As indicated in Section 4, the characterisation of exposure constitutes an important source of uncertainty in the epidemiological studies. If the exposure is not properly characterised, exposure might be affected by misclassification leading to underestimation of the exposure-response relationships. Misclassification also affects the power of the study to detect associations between exposure and disease.

Where the exposure-response relationships involving asbestos, lung cancer and mesothelioma are concerned, one would expect the gradients of the exposure-response relationships (the  $K_L$  and the  $K_M$  values) to be underestimated and to have wider confidence intervals than those found in the studies, as a consequence of various measurement and misclassification errors (for a thorough exposition of the relevant epidemiological theory, see<sup>62</sup>). The following considerations are also relevant:

- Lung cancer is a common form of cancer whose main cause is tobacco smoking. In order to establish an association with exposure to asbestos against the background of the effects of a strong determinant like smoking, the measurement strategy has to yield sufficient contrast in exposure. A measurement strategy that is flawed – because, for instance, too few measurements are carried out, or there is insufficient distinction between exposure groups – easily

leads to erroneous characterisation of the relationship between lung cancer and asbestos.

- All the meta-analyses assume that other risk factors for cancer will have had no disruptive effect. Where mesothelioma is concerned, such an assumption is more likely to be valid, since exposure to asbestos is the only known cause of pleural mesothelioma. With lung cancer, however, interference from other factors cannot be ruled out, since smoking is the main cause of lung cancer. Even a small degree of interference can lead to erroneous characterisation of the relationship between asbestos and lung cancer. The analysis performed by Hodgson and Darnton<sup>27</sup> would appear to be all the more sensitive to such interference because it compares mortality between different cohorts which have different average exposures; the cohort studies were carried out at different times and in different countries. There is no reason to assume that the relative contributions of a variety of causes of lung cancer (asbestos, smoking, occupational exposure to other carcinogens, food consumption patterns) were the same across all these countries throughout the twentieth century. Hodgson and Darnton's analysis has elements of what is commonly described as an 'ecological analysis'. In such analyses, it is not possible to adjust for interference from other factors on the level of an individual. An analysis in which the asbestos exposure-response relationship is studied within each cohort is therefore to be preferred when examining lung cancer (so, in this case, the analysis performed by Berman and Crump is preferable to the one performed by Hodgson and Darnton).

For mesothelioma, on the other hand, the approach employed by Hodgson and Darnton<sup>27</sup> is considered relatively robust. The advantage of this design is that it allows the inclusion of studies with a relatively simple exposure component, which would not be suited to more sophisticated internal analysis. As a result, Hodgson and Darnton were able to include studies on mesothelioma in their meta-analysis which others had not included because of insufficient information about differences in exposure within the cohort, which were sufficient for an internal analysis. They were also able to include studies that involved relatively low absolute levels of mesothelioma mortality (these were mostly studies of exposure to chrysotile), even though the absolute number of mesothelioma cases in these studies was generally too low to warrant their use for (internal) exposure-response analysis. In Berman and Crump's analysis<sup>33</sup> (2008), a number of such studies were included, but this yielded relatively uncertain  $K_M$  values (values with a wide confidence intervals). One last advantage of Hodgson and Darnton's approach is that misclassification of exposure plays potentially a smaller

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role than it does in an internal analysis; this is because only an average cumulative exposure has to be estimated, as opposed to an estimate for the exposure of each individual in the cohort. Such an estimate is acceptable in many cases; for instance, the HEI panel members held that such an average can be estimated to within half an order of magnitude.<sup>17</sup> However, this characteristic becomes a disadvantage if cohorts are included which display an extremely skewed exposure distribution, since this can lead to underestimation of the associations.

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### 5.3 The need for a new meta-analysis

Where lung cancer is concerned, the Committee sees limitations in the analyses performed by Hodgson and Darnton<sup>27</sup> and by Berman and Crump<sup>23</sup> (2003). Neither analysis involved the selection of studies on the basis of their quality, and for the reasons explained earlier, the method employed by Hodgson and Darnton is not considered ideal. The analysis performed by Berman and Crump (2003) was based on an EPA update of the  $K_L$  values available at that time.

In their recent re-analysis, Berman and Crump (2008)<sup>33</sup> elected not to anchor the dose-effect line at an intercept of 1 (as is usual in risk assessment)\*; in other words, they do not make the regression line pass through a relative risk of 1 (which reflects the background incidence of lung cancer in the general population) in the absence of exposure to asbestos. For a number of studies this has led to very high intercepts of more than 2 (RR) or 200 (standardised mortality rate, SMR), which implies that, at zero exposure, the mortality from lung cancer in the occupational population is more than double that seen in the general population\*\*. The Committee is of the opinion that the intercepts used by Berman and Crump for a very common form of cancer (and therefore one with a high level of background incidence) are improbable, even if smoking levels amongst cohort members were strongly deviating, relative to the control group. It would therefore seem more likely that exposure misclassification is responsible for these high intercept values.

In risk analysis, it is normal to extrapolate to low exposure levels, close to the point where the cumulative exposure is zero and the relative risk is 1 (or the SMR = 100). The Committee has accordingly recalculated the  $K_L$  based on a linear regression with fixed intercept ( $\alpha = 1$ ) values for all cohorts.

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\* Or, if the risk is expressed as an SMR, at a background value (no exposure to asbestos) of 100.

\*\* It is not unusual for a mortality pattern in a working population to deviate from that in the general population, but in most such cases the working population displays a lower mortality which is the result of selection processes and referred to as the so-called 'healthy worker effect'.

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Hodgson and Darnton's meta-analysis<sup>27</sup> is in principle usable in relation to mesothelioma; however, the authors use so-called  $R_M$  values, which are calculated differently and therefore vary from the  $K_M$  values more commonly employed. Although there is close correlation between the two indicators, direct comparison is not possible. Where mesothelioma is concerned, the Committee has therefore recalculated  $K_M$  values and choose not to use  $R_M$  values calculated by Hodgson and Darnton.

In view of the above-mentioned reservations, especially concerning not selecting studies for inclusion on the basis of exposure data quality, the Committee decided that new meta-analyses should be performed, both of the data linking asbestos with lung cancer and those linking it with mesothelioma. At the Committee's request, the meta-analyses were carried out by D Heederik, A Burdorf (both members of the Committee), V Lenters, L Portengen and R Vermeulen (Institute for Risk Assessment Sciences, Utrecht University). The results are generated by the panel and agreed on by the committee. The two meta-analyses are considered in the following two sections of the report.

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## Meta-analysis and calculations for lung cancer

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With the goal of characterising the relationship between exposure to asbestos and lung cancer, the Committee has performed a meta-analysis, which will also be published separately (Lenters *et al.*, submitted). The meta-analysis was performed in accordance with a recently developed protocol, modified to take account of certain considerations specific to asbestos.<sup>94</sup> The studies were assessed on the basis of the quality of various aspects of the exposure assessment strategy by which measurement data were obtained ('exposure assessment') and the way that exposure data were linked to the subjects' occupational histories ('exposure assignment'). More specifically, account was taken of: measurement strategy documentation (number of measurements, expression of average exposure in arithmetic or geometric average exposures, etc.); the use of estimates when data was absent; the use of conversion factors to convert concentrations into other units measured by other methods (impinger values to PCM values); the availability of measurements from subjects' entire occupational histories; and the completeness of the occupational history data.

Each study was scored on each variable by a panel of three independent experts (Heederik, Burdorf and Lenters). First, each panel member assessed each study without conferring with the other members. Next, these assessments were compared and consensus reached regarding the definitive assessment. The studies were selected for inclusion in the meta-analysis on a step-by-step basis, with the application of each successive criterion resulting in the exclusion of one or more studies. The end result was a selection of better-quality studies, which were

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used to calculate a pooled  $K_L$  value. In subsection 6.2, calculations are presented of the concentrations that correspond to the reference environmental and occupational risk levels; these calculations make use of the pooled  $K_L$  value yielded by the Committee's analysis and a number of assumptions. Details of the calculations are given in Annex F.

See section 3 for background information about the use of  $K_L$  values (the gradients of the exposure-response relationships determined in the cohort studies) in the definition of exposure standards for lung cancer.

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## 6.1 Meta-analysis for lung cancer

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### 6.1.1 *Included studies and the $K_L$ values used\**

Table 9 and Annex G detail twenty-one studies, of which eighteen were included in the meta-analysis for lung cancer. The studies were identified by literature searches in PUBMED; most had already been included in the analyses carried out by Hodgson and Darnton (2000)<sup>27</sup> and Berman and Crump (2008)<sup>33</sup>. A number of the studies considered were excluded from the new meta-analysis (63-65) because the exposure information did not permit quantitative exposure-response analysis, or because the study did not involve an occupational setting, or – in the case of a study of textile workers in South Carolina<sup>41</sup> (study 6 in Annex G) – because the study examined the same population as the study by Hein *et al.*<sup>66</sup> In addition, only one study of the Libby Cohort<sup>67</sup> (the most recently published study of the cohort, study 11 in Annex G) was included in the analysis.

In total, eighteen lung cancer studies were selected: seventeen cohort studies and one population-based case-referent study (Gustavsson *et al.*<sup>68</sup>). The Table 9 gives the Committee's  $100 \times K_L$  values and the associated standard error (SE) for each of the studies. The  $K_L$  values for each study were recalculated on the basis of the information extracted for that study. The  $K_L$  values from Berman *et al.* (2008)<sup>33</sup> were not used, because in that study the regression lines were not forced through  $RR=1$  (or  $SMR = 100$ ), as is normal in risk analyses of this type (see also subsection 5.3).

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\* The  $K_L$  value is the gradient of the exposure-response relationship.

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Table 9 Fibre type, production method,  $100 \times K_L$  value and standard error (SE) for each of the studies considered for the meta-analysis (of which eighteen were ultimately included). The  $100 \times K_L$  values marked\* with an asterisk were obtained using weighted linear regression; the others using Poisson.

	Author	Fibre type	Production method	Cohort	$100 \times K_L$ in (fibres/ml year) <sup>-1</sup>	SE
1	Liddell <i>et al.</i> <sup>69</sup>	Chrysotile	Mining and milling	Quebec mines and mills	0.0412	0.006
2	Piolatto <i>et al.</i> <sup>70</sup>	Chrysotile	Mining and milling	Italian mine and mill	0.0348	0.0588
3	McDonald <i>et al.</i> <sup>43</sup>	Chrysotile	Friction products	Connecticut plant	0.1904	0.2234
5	Hein <i>et al.</i> <sup>66</sup>	Chrysotile	Textiles	South Carolina plant	2.9734	0.4355
7	Berry <i>et al.</i> <sup>71</sup>	Crocidolite	Mining and milling	Wittenoom, Australia mine	4.1546	0.5361
8	Seidman <i>et al.</i> <sup>72</sup>	Amosite	Insulation manufacture	Patterson, NJ factory	6.3238	0.8294
9	Levin <i>et al.</i> <sup>73</sup>	Amosite	Insulation manufacture	Tyler, Texas factory	1.2513	0.506
10	Sullivan <sup>74</sup>	Tremolite	Vermiculite mines and mills	Libby, Montana	0.878	0.2639
12	Berry and Newhouse <sup>42</sup>	Mixed	Friction products	British factory	-0.1284	0.1246
13	Finkelstein <sup>75</sup>	Mixed	Cement manufacture	Ontario factory	4.8572	1.3855
14	Hughes <i>et al.</i> <sup>76</sup>	Mixed	Cement manufacture	New Orleans plants	0.3975	0.1684
15	Albin <i>et al.</i> <sup>77</sup>	Mixed	Cement manufacture	Swedish plant	1.405*	1.134
16	Laquet <i>et al.</i> <sup>78</sup>	Mixed	Cement manufacture	Belgium factory	-0.083*	0.045
17	Enterline <i>et al.</i> <sup>79</sup>	Mixed	Factory workers	U.S. retirees	0.2066	0.0383
18	Selikoff and Seidman <sup>80</sup>	Mixed	Insulation application	U.S. insulation workers	0.8222	0.0294
19	McDonald <i>et al.</i> <sup>41</sup>	Mixed	Textiles	Pennsylvania plant	0.5692	0.205
20	Peto <i>et al.</i> <sup>40</sup>	Mixed	Textiles	Rochdale, UK plant	0.5185	0.1551
21	Gustavsson <i>et al.</i> <sup>68</sup>	Mixed	Multiple (population- based)	Stockholm, Sweden	20.983*	5.917

### 6.1.2 Assessment of the studies

In line with the assessment protocol<sup>94</sup>, the studies were scored on variables indicative of study quality. The relevant characteristics of the various studies are listed in Annex G. With a view to avoiding the subjective assessment of study quality as far as possible, the assessors focused on the following: sufficient documentation of the exposure assessment approach followed; the information available and transparent use of the available information. The studies were assessed by three panel members, each of whom first made an independent assessment, before the independent assessments were jointly reviewed and, where necessary, revised on the basis of consensus. The results of their assessment can be found in Annex G. The panel considered the following four criteria: the documentation of exposure (number of measurements, measurement techniques, arithmetic or geo-

metric averages); the use of factors for the conversion of concentrations into other units measured by other methods; the availability of measurements from subjects' entire occupational histories; and the completeness of the occupational history data.

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### 6.1.3 Results of the meta-analysis

When performing a meta-analysis, before the results of the data are pooled, the usual procedure is to examine the heterogeneity of the studies under consideration. Studies are considered homogeneous if they are similar in terms of study population, research design and methodology. Cochran's Q test\* and the I<sup>2</sup> statistic \*\* indicate that the studies under consideration here are significantly heterogeneous in statistical terms. The presence of heterogeneity is a strong indication that numerous factors influence the slope of the exposure-response relationship. This implies a wider range of outcomes than might be expected to occur by chance, and that numerous variables could explain the differences between the K<sub>L</sub> values yielded by the studies. The relative contribution of a given study to the pooled K<sub>L</sub> value has been calculated on the basis of a random effects meta-analysis model\*\*\*.

Studies were selected for inclusion in the meta-analysis on the basis of the following four criteria:

- 1 The documentation of exposure in the study is sufficiently informative and clear to allow proper comparison with other studies.

For the calculation of a limit value on the basis of a meta-analysis of published studies, it is vital that only those studies are included which provide adequate information about exposure to asbestos in the cohort under study. This implies documentation of the number of measurements, variation in exposure within and between different categories of exposed worker, and the quality and comprehensiveness of the occupational histories of the workers. In many cases, only average concentrations are documented, the number of measurements on which these averages is based is unknown, and details of the measurement methods and strategies are described only in summary or not at all. In seven of the studies consid-

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\* The Q test is a Chi<sup>2</sup> test that is used to assess heterogeneity in meta-analyses.

\*\* The I<sup>2</sup> value is an expression of the percentage of the total variation in the meta-analysis that is attributable to heterogeneity.

\*\*\* The random effects meta-analysis is applied because there was evidence of heterogeneity; I<sup>2</sup> exceeded 50%.

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ered (studies 2, 3, 12, 13, 14, 16, 17 in Table 9), the information provided regarding exposure was minimal, precluding interpretation in terms of the common index of exposure. In one study, exposure was estimated on an ordinal scale, after which regression analysis was used to interpolate quantitative estimates. This analysis is not sufficiently precise and the study in question (study 7) was therefore excluded from the meta-analysis. Two other studies (studies 8 and 18) were excluded because they based cumulative exposure on data that did not involve the study population; this approach entails unacceptable potential for the misclassification of exposure, because exposure patterns can differ widely from one workplace to another. *After assessment against this criterion, ten studies remained under consideration (studies 1, 5, 9, 10, 14, 15, 17, 19, 20, 21 in Table 9).*

2 Internal (study-specific) conversion factors for data obtained using different measurement methods have been used to convert concentrations expressed in particles/volume into concentrations expressed in fibres/ml.

Before the mid-1960s, the measurement of asbestos concentrations generally meant counting airborne particles. Phase contrast microscopy (PCM) was then introduced, and used to measure and assess exposure to airborne asbestos. In the great majority of studies, the study population had been exposed since before 1964; so for accurate estimates, earlier particle measurements expressed in millions of parts per cubic foot (mppcf) needed to be converted into estimated fibre concentrations expressed in fibres/ml of air. Research into such conversion factors has shown that the conversion factor is not a constant, but is strongly influenced by the nature of the production process concerned, and can therefore vary widely between departments of one and the same company. To be able to arrive at a good estimate of exposure it is therefore important that the conversion factors used are derived from paired, or side-by-side measurements (using different measurement techniques) within the same study, in other words using 'internal' conversion factors. Some studies made use of 'external' conversion factors taken from other studies; exclusive reliance on external conversion factors introduces considerable room for exposure misclassification.

Three of the studies considered (numbers 9, 17, 19 in Table 9) either used an external conversion factor or did not specify the conversion factor used. *After assessment against this criterion, seven studies remained under consideration (studies 1, 5, 10, 14, 15, 20, 21 in Table 9).*

- 3 The measured data are sufficiently representative of the subjects' occupational history.

This criterion was applied to ascertain whether sufficient information was recorded regarding changes in workers' jobs or duties over the course of their careers (whether within one company, or as they moved from company to company) to enable workers to be allocated to particular exposure groups. Satisfaction of this criterion also required that measurements had been taken in an appropriate place. Studies in which measurements were carried out at other companies, at other times, or under other conditions were therefore rejected on the basis of this criterion.

In studies 1, 14 and 15, work histories were incomplete, subjects had worked at a variety of locations, or very different groups of workers had been combined in a single category. These shortcomings could easily have led to misclassification. *After assessment against this criterion, four studies remained under consideration (studies 5, 10, 20, 21).*

- 4 Exposure measurements have been collected over a period of more than half the follow-up period.

In a cohort study of the effects of exposure, the follow-up period is the entire period from the first moment of exposure. If the available data relate to only part(s) of this period, the ability to accurately quantify cumulative exposure will be hindered. The more measurements are available and the longer the period they cover, the better changes over time can be assessed and can be taken into account. Any study in which the exposure measurement period was less than 50 % of the follow-up period was therefore excluded from the meta-analysis. The rationale being that asbestos exposure levels are known to have changed considerably over the years as employers took steps to reduce them. The application of this criterion was intended primarily to draw a distinction between cohorts for which only one measurement was made, and cohorts for which measurements were carried out over a lengthy time period.

Application of this criterion ruled out studies 1, 2, 8, 9, 15, 16, 17, 18, but there was no change with regard to the result of step 3. *Hence, studies 5, 10, 20, 21 remained under consideration.*

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Of the four studies remaining after this selection process, the exposure component is best described in Hein (study number 5: the follow-up to the study by Dement); this study also exhibits the most sophisticated design and analysis, and may safely be regarded as a study which meets today's criteria for the accurate characterisation of exposure best. The most recent update of this study shows an equally steep exposure-response curve with a  $100 \times K_L$  value of 3.<sup>66</sup> The data from the Hein study<sup>66</sup> have been analysed by Stayner *et al.*, who examined the exposure-response relationships on the basis of both the TEM technique and the PCM technique.<sup>81</sup> This involved re-examining stored dust samples by means of TEM and calculating new conversion factors. Particular attention was paid to exposure to long, thin fibres, which are not easily detected by PCM. The TEM-based exposure estimates exhibited a stronger correlation with the risk of lung cancer than the PCM-based estimates had, suggesting that the  $K_L$  value calculated in the context of this high-quality study may nevertheless have underestimated the true  $K_L$ .

The  $K_L$  value from the study by the case-control Gustavsson<sup>68</sup> (*study 21*) is much higher (a  $100 \times K_L$  value of 21) than that calculated in the cohort studies. This may be (at least partly) because Gustavsson's research population, unlike those in the cohort studies, was born much later (it was a postwar population). Hence, smoking habits and other confounding factors may have played a less prominent role than in the cohort studies. Gustavsson's study also concerned workers with a relatively recent and low level of cumulative exposure. Nevertheless, account must also be taken of the fact that this strong association might be a chance finding. A possible limitation of this study (and one that is inherent to case-control research) is that the characterisation of exposure took place after the event, although it was carried out independently of the epidemiological study. The large standard error for Gustavsson's results means that the study has relatively little influence (low relative weighting) on the outcome of the Committee's meta-analysis.<sup>68</sup>

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#### 6.1.4 Discussion and choice of $K_L$ values

The variation in the  $K_L$  values from the various studies is assumed to be a consequence of differences in the quality of the exposure data, the fibre type and size distribution of the fibres involved.

The process of selecting studies by the successive application of quality criteria showed that there were indeed major differences in study quality. Most studies did not adequately and transparently describe the exposure component, and many

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studies lacked simple descriptive information or failed to make clear how their exposure information was linked to the epidemiological data. This is not surprising: after all, exposure characterisation is a field that has developed considerably in recent decades and has only recently been integrated into epidemiology.

From the data presented in Table 10, it will be apparent that the  $K_L$  value increases as more quality criteria are applied (and fewer studies are included in the analysis); this is consistent with epidemiological theory. Most shortcomings in the characterisation of exposure lead to measurement errors which increase the inaccuracy of exposure estimates, resulting in underestimation of the exposure-response relationship. In the absence of quality selection, the pooled  $100 \times K_L$  value for all cohorts\* together is 0.7 (confidence interval 0.48-0.96). If quality criteria are applied, the pooled  $100 \times K_L$  value rises to 1.64 (0.34-2.95) for studies that meet the minimum exposure component transparency criterion, use study-specific conversion factors, have no job history documentation shortcomings, and have exposure data covering at least 50% of the follow-up period. On the basis of its own meta-analysis, the Committee has chosen a pooled (weighted average)  $100 \times K_L$  value of 1.64. Previous analyses have indicated that the uncertainty can be several orders of magnitude. Moreover, before the application of the first quality criterion in the Committee's meta-analysis, the inter-cohort variation in  $K_L$  values was great: more than a factor of 200.

*Table 10* Calculated pooled  $K_L$  values ( $\times 100$ ) for all eighteen studies considered, and for the studies that passed each successive step of the selection procedure, pooled by random effects meta-analysis method. The 95% confidence interval is given between brackets.

Inclusion	Weighted average $100 \times K_L$ in (fibres/ml $\times$ year) <sup>-1</sup>	Studies
All 18 studies (excluding the duplicates, i.e. 4, 6 and 11)	0.72 (0.48-0.96)	1-3, 5, 7-10, 12-21
Step 1. Only studies with acceptable documentation	0.56 (0.34-0.78)	1, 5, 9, 10, 14, 15, 17, 19, 20, 21
Step 2. Only studies that used internal conversion factors	0.91 (0.34-1.48)	1, 5, 10, 14, 15, 20, 21
Step 3. Only studies with accurate job histories	} 1.64 (0.34-2.95)	5, 10, 20, 21
Step 4. Only studies with data covering >50% of the follow-up period		5, 10, 20, 21

\* The study by Loomis (2009)<sup>82</sup> was not included in the meta-analysis because it did not appear until after completion of the the meta analysis. This was not significant in relation to the selection process, however, since the study did not meet the quality criteria of the committee and would not therefore have been included.

It is apparent that greater selectivity on the basis of study quality is associated with reduced  $K_L$  value variation. This is indicative of a significantly lower uncertainty in the  $K_L$  value; the  $K_L$ -value variation across the three cohorts\* retained for the meta-analysis is less than a factor of 6. The Committee therefore concludes that the uncertainty associated with the adopted  $K_L$  value is within a single order of magnitude.

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## 6.2 Calculation of the concentrations that correspond to the reference environmental and workplace risk levels for lung cancer

The Committee has calculated the concentrations that correspond to the reference environmental and workplace risk levels using the formula presented in subsection 3.2.1, a  $100 \times K_L$  value of 1.64 and a number of other principles and assumptions.

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### 6.2.1 Principles and assumptions

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#### Lung cancer and mesothelioma

The exposure levels corresponding to the relevant environmental and occupational health and safety standards were calculated using life tables derived from Dutch mortality data (see Annex D). The following assumptions were also made:

- The concentrations corresponding to the reference environmental risk levels were calculated on the basis of lifetime exposure since birth. The concentrations corresponding to the reference workplace risk levels were calculated on the basis of exposure for a significant part of a person's working hours over a period of forty years.
- In line with standard practice, the exposure concentrations that correspond to the MPR and NR levels are expressed in fibres/m<sup>3</sup> measured by TEM. Values for workplace settings are stated both in fibres/ml and in fibres/m<sup>3</sup> measured by TEM.
- Following the lead of the WHO and the RIVM, the Committee decided to use a PCM-to-TEM conversion factor of 2 to calculate the exposure concentrations corresponding to the reference environmental and occupational risk levels. The Committee recognises that true conversion factors will vary, depending on fibre diameter distribution and the fibre type. However, when

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\* The case-control study by Gustavsson<sup>82</sup> is disregarded in this context, since its sizeable SE means it has little influence on the outcome of the meta-analysis.

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defining standards, the use of a single conversion factor is unavoidable. Of the cohorts considered by the Committee when making its calculation, internal conversion factors had been established<sup>84</sup> only for the asbestos textile worker cohort documented by Dement<sup>83</sup> (and updated by Hein<sup>66</sup>); this was done as part of a follow-up study by Dement *et al.* Although it was concluded in the context of that study that true PCM-to-TEM conversion factors were subject to considerable variation, the average conversion factors for the various occupational groups were found to vary between 1 and 2.

- As reported in subsection 2.2.1, it is generally assumed in the literature that the carcinogenic potency of asbestos fibres shorter than 5 µm is much less than that of longer fibres. The discrepancy in potency has been observed in toxicological research with laboratory animals. Hence, predominantly potent asbestos fibres are defined as fibres at least 5 µm in length. It is worth noting that much of the exposure documented in the cohort studies that the Committee has used to calculate the ultimate values involved fibres shorter than 5 µm. This implies that any effects of such shorter fibres have been included in the risk analysis. Nevertheless, the ultimate environmental and workplace values relate to fibres at least 5 µm in length.

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### **Lung cancer**

- The calculations for lung cancer have been made assuming a minimum latency period of ten years.
  - On the basis of a recent meta-analysis, it is now believed that the combined effect of smoking and asbestos exposure is between an additive and a multiplicative interaction (:the sum of the separate effects and the multiple of the separate effects) making it difficult to define using a simple function.<sup>27,30</sup> A recent study, in which a large cohort of people exposed to chrysotile asbestos were followed for a lengthy period, provided further evidence that the combined effect of smoking and asbestos exposure is less than a multiple of the separate effects.<sup>31</sup> Nevertheless, for practical reasons, the interaction of smoking and asbestos exposure is usually assumed to have a multiplicative effect.
  - The calculations assume a linear relationship between exposure and effects.
  - No distinction is made on the basis of fibre type: the calculations apply to both chrysotile asbestos and amphiboles. Distinction between chrysotile and amphiboles (or between different amphiboles) cannot be made on the basis of the available data on lung cancer. The application of one or more quality criteria reduces the number of studies included in the analysis to the point where it is not possible to discern any statistically valid difference in potential
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between the different types of asbestos. It is worth noting that the analysis performed by Berman and Crump (2003), which did not involve the selection of studies on the basis of inclusion criteria, found no statistically significant difference between chrysotile and amphiboles in terms of average lung cancer risk.<sup>23</sup>

### 6.2.2 *Exposure concentrations corresponding to the reference environmental and workplace risk levels for lung cancer*

The calculated exposure concentrations corresponding to the reference environmental and workplace risk levels for lifetime exposure (as measured by electron microscopy and expressed in fibres/m<sup>3</sup>) are presented in the tables below. Where lung cancer is concerned, no distinction is made between chrysotile asbestos and amphiboles.

*Table 11* Environment. Exposure concentrations corresponding to the reference environmental risk levels for lung cancer. The values relate to lifetime exposure, expressed in fibres/m<sup>3</sup>, as measured by TEM.

Risk level	Exposure concentration in fibres/m <sup>3</sup>
Risk 10 <sup>-4</sup>	3,200
Risk 10 <sup>-6</sup>	32

*Table 12* Workplace. Exposure concentrations corresponding to the reference workplace risk levels for lung cancer. The values relate to occupational exposure (eight hours per day, five days per week, for forty years), expressed in fibres/m<sup>3</sup> (with fibres/ml in brackets), as measured by TEM.

Risk level	Exposure concentration in fibres/m <sup>3</sup> (fibres/ml)
Risk 4.10 <sup>-3</sup>	220,000 (0.22)
Risk 4.10 <sup>-5</sup>	2,000 (0.0022)

Like the environmental values, the workplace values are TEM-based values. They can be converted to PCM-based values by applying the conversion factor of 2 referred to above (values obtained by TEM are twice as high as values obtained by PCM).

### 6.2.3 *Notes regarding the proposed values*

#### Uncertainties associated with the use of epidemiological data

One source of uncertainty, which is difficult to quantify, is the length and diameter distribution of the fibres to which the subjects of the various studies were

exposed. The relationship between fibre length (and diameter) and the effects of asbestos is not sufficiently well documented for inclusion in risk analysis. Some data are available from animal research, but not readily transferrable to humans. Moreover, while recent epidemiological analyses suggest that longer and thinner fibres may play a more important role, the precise relationship between fibre dimensions and health effects cannot reliably be determined, because most of the studies provide too little information about fibre length and diameter distributions.

The distribution of the fibre lengths and diameters is also significant in relation to the factor used for the conversion of PCM-based exposure data from the cohort studies into TEM-based field study values. The Committee recognises that, for the reasons explained elsewhere in this report, true conversion factors will vary, depending on fibre diameter distribution and the fibre type. However, when defining standards, the use of a single conversion factor is unavoidable. The Committee sees no reason to depart from the factor of 2, as used in previous risk analyses by the WHO and others.

#### Uncertainty arising from linear extrapolation

The calculations assume a linear relationship between exposure and effects. Previous analyses – including those by Hodgson and Darnton (2000)<sup>27</sup> and Berman and Crump (2003)<sup>23</sup> – have yielded evidence of supra-linearity. However, the researchers in question did not select studies for inclusion on the basis of quality, so the (in any case weak) evidence cannot be considered reliable. Another study, which utilised only good-quality exposure information, confirmed the existence of a linear relationship between exposure and lung cancer risk.<sup>28</sup>

#### Uncertainty arising from the pooled $K_L$ value used

As indicated earlier in this report, the pooled  $100 \times K_L$  value of 1.64 ultimately adopted by the Committee does not differ greatly from the values obtained in previous analyses. However, the value calculated by the Committee for lung cancer is significantly more certain than the values presented in the 1987 Guidance Document, since the Committee's calculation draws on considerably more cohort studies of exposed workers, some of them more recent; a total of eighteen studies were used in the meta-analysis for lung cancer.

In the cohort studies used by the Committee, the inter-cohort variation in  $K_L$  values was great: more than a factor of 200. However, it was apparent that the variation in the pooled  $K_L$  values fell as more quality-based study selection crite-

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ria were applied. Because a relatively small number of studies were ultimately included, it was not possible to distinguish between types of asbestos in terms of the associated  $K_L$  value. Nevertheless, since the pooled  $K_L$  value in this report is based on the best available studies, it may be assumed that the uncertainty associated with this value is significantly smaller; the Committee estimates that it is within a single order of magnitude.

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#### 6.2.4 *Comparison with previous risk analyses*

Where lung cancer is concerned, no direct comparison can be made between the outcomes of previous risk analyses and the Committee's calculations, due to presentational differences (separate values for smokers and non-smokers; differences in lung cancer mortality figures) and differences in the calculation method.

However, it is possible to compare the  $K_L$  values used in the various analyses. The  $100 \times K_L$  values used in the previous analyses were fairly similar to one another: the WHO report<sup>25</sup> used a value of 1; the EPA analysis (1986)<sup>24</sup> and the NRC analysis (1984)<sup>35</sup> (both cited in the WHO report) used  $K_L$  values of 1 and 2, respectively. It is worth noting that, due to the life tables used by the Committee and the assumption made regarding the lung cancer latency period, it is not the case that using a  $K_L$  value that is twice as high will result in the concentration attributed to a given risk level being exactly twice as low.

It is not surprising that the  $K_L$  values used in the previous analyses were similar to one another, since the analyses were based on (broadly) the same cohort studies, and the researchers generally based their calculations on averages from the cohort studies. The pooled (weighted average)  $100 \times K_L$  value of 1.64 ultimately adopted by the Committee is also quite similar to the values used in the previous analyses. On the basis of this pooled  $K_L$  value, the Committee has calculated that the concentration corresponding to one in  $10^4$  risk from lifetime exposure is 3,200 fibres/ $m^3$ . It is important to note, however, that the Committee's meta-analysis provides no evidence of any difference between the various asbestos types in terms of carcinogenic potential.

Making reference to previous risk analyses (neither described nor cited by the WHO), the WHO put forward a guideline value for lung cancer of 10,000-100,000 fibres/ $m^3$  (as measured by TEM, after conversion to a concentration corresponding to the Committee's reference risk level). That value is significantly higher than the Committee's value of 3,200 fibres/ $m^3$ . The Committee has not been able to ascertain why the WHO value is so much higher.

The WHO guidelines<sup>25</sup> were adopted by the Guidance Document on Asbestos,<sup>6</sup> which is the basis of the current (environmental) Dutch MPR and NR values. Because the guideline value for mesothelioma was lower than that for lung cancer, the mesothelioma risk is used as the basis for regulation. The current Dutch occupational exposure limit is not therefore based on the calculation of concentrations corresponding to certain risk levels.

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## Meta-analysis and calculations for mesothelioma

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In contrast to the situation with lung cancer, for mesothelioma there are strong indications of a clear difference in carcinogenic potential between chrysotile and amphibole asbestos. This is apparent first from the differences between the raw mortality figures for chrysotile-exposed cohorts and those for amphibole-exposed cohorts: there are fewer mesothelioma cases in chrysotile-exposed cohorts than in amphibole-exposed cohorts. The meta-analysis by Hodgson and Darnton<sup>27</sup> and the evaluation by Berman and Crump<sup>23,33</sup> also found major differences in potency between the different types of asbestos with respect to mesothelioma.

The methodology employed by the Committee for its mesothelioma meta-analysis was identical to that used for its lung cancer meta-analysis (subsection 6.1). In subsection 7.2, calculations are presented of the concentrations that correspond to the reference environmental and occupational risk levels; these calculations make use of the pooled  $K_M$  value yielded by the Committee's analysis and a number of assumptions.

See section 3 for background information about the use of  $K_M$  values (the gradients of the exposure-response relationships determined in the cohort studies) in the definition of exposure standards for mesothelioma.

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## 7.1 Meta-analysis for mesothelioma

### 7.1.1 Included studies and $K_M$ values used

Table 13 details fourteen studies (with associated  $K_M$  values), of which twelve were included in the meta-analysis for mesothelioma.

Table 13 Fibre type, production method,  $K_M$  value ( $\times 10^{-8}$ , in (fibres/ml  $\times$  years<sup>4</sup>)<sup>-1</sup>) and SE for each of the cohort studies considered

	Author	Fibre type	Production methode	Cohort	$K_M \times 10^8$	SE
1a	Liddell <i>et al.</i> <sup>69</sup> and raw data.	Chrysotile	Mining and milling	Asbestos, Quebec	0.012	0.0043
1b	Liddell <i>et al.</i> <sup>69</sup> and raw data.	Chrysotile	Mining and milling	Thetford Mines	0.021	0.0045
1c	Liddell <i>et al.</i> <sup>69</sup> and raw data	Mixed	Factory workers	Asbestos, Quebec	0.095	0.0417
3	McDonald <i>et al.</i> <sup>43</sup>	Chrysotile	Friction products	Connecticut plant	0	0.0357
4	Hughes <i>et al.</i> <sup>a,76</sup>	Chrysotile	Cement manufacture	New Orleans plants	0.2	0.1146
5	Hein <i>et al.</i> <sup>66</sup> , and raw data	Chrysotile	Textiles	South Carolina plant	0.15	0.0842
7	Berry <i>et al.</i> <sup>71</sup> , and raw data	Crocidolite	Mining and milling	Wittenoom, Australia mine	12	0.8929
8	Seidman <sup>72</sup>	Amosite	Insulation manufacture	Patterson, NJ factory	3.9	0.9226
13	Finkelstein <sup>75</sup>	Mixed	Cement manufacture	Ontario factory	18	3.2738
14	Hughes <i>et al.</i> <sup>76</sup>	Mixed	cement and textile factories	New Orleans plants	0.3	0.1735
18	Selikoff and Seidman <sup>80</sup>	Mixed	Insulation application	U.S. insulation workers	1.3	0.0595
19a	McDonald <i>et al.</i> <sup>39,39,b</sup>	Chrysotile	Textiles	South Carolina plant	0.088	0.0925
19b	McDonald <i>et al.</i> <sup>41</sup>	Mixed	Textiles	Pennsylvania plant	1.4	0.2381
20	Peto <sup>40</sup>	Mixed	Textiles	Rochdale plant	1.3	0.4048

a Excluded because value is based on just one mesothelioma case

b Excluded because the more recent publication regarding this cohort by Hein *et al.* 2007 was used.<sup>66</sup> The numbering of the cohorts is aligned with the numbering of the lung cancer cohorts (see Table 9).

The  $K_M$  values for this meta-analysis were taken from the most recent analysis by Berman and Crump<sup>33</sup>. Two publications concerned the same South Carolina textiles factory; the most recent study by Hein *et al.*<sup>66</sup> was used, while the study by McDonald *et al.*<sup>39</sup> was excluded. The study by Hughes<sup>76</sup> was not included in

\* The objections to the use of Berman en Crump's<sup>33</sup>  $K_L$  values do not apply to the  $K_M$  values used in the same publication for mesothelioma, since the authors calculated the  $K_M$  value by forcing the regression line through the origin (the background mortality for mesothelioma is virtually zero).

the analysis because it included only a single case of mesothelioma, which is insufficient for a  $K_M$  value to be modelled.

### 7.1.2 Results of the meta-analysis

As indicated at the beginning of this section, it is likely that chrysotile and amphibole asbestos differ in their mesothelioma-inducing potential; the higher the  $K_M$  value, the higher the carcinogenic potential. In the table below, the Committee gives the pooled  $K_M$ -value (weighted based on the study precision, or standard errors) for all the studies collectively and for various subgroups: exposure to chrysotile only, exposure to amphiboles only, and mixed exposure (exposure to both chrysotile and amphiboles). Because of the heterogeneity of these studies, the weighting is as for lung cancer based on a so-called ‘random effects’ model.

From the analysis (Table 14), it will be apparent that there are major differences between the pooled- $K_M$  values for chrysotile and those for amphibole asbestos. There are also clear differences across the pooled- $K_M$  values of the three fibre-type subgroups. The results presented in Table 13 are broadly in line with the results of Berman and Crump’s analysis;<sup>23</sup> this is not surprising when one considers that the Committee’s meta-analysis was largely based on the same cohort data. However, the Committee’s meta-analysis also makes use of data on four cohorts that were not available until after 2003. The article version of Berman and Crump’s report (2008)<sup>33</sup> also includes updates to the original 2003 report.

In view of the differences referred to above, the studies are subdivided on the basis of asbestos fibre type for the purpose of quality assessment.

In line with the assessment protocol described in section 6, the studies were scored on variables indicative of study quality. In this way, studies with a valid exposure assessment component were selected for inclusion in the analysis. The relevant characteristics of the various studies are listed in Annex G. The selection criteria are described in detail in subsection 6.1.

*Table 14* Summary of all the studies considered, with a subgroup analysis by asbestos type, showing the pooled  $K_M$  value ( $\times 10^{-8}$  in  $(\text{fibres/ml} \times \text{years}^4)^{-1}$ ) and, between brackets, the confidence interval.

Inclusion	Number of studies	Pooled $K_M$ value ( $\times 10^8$ ) and 95% confidence interval
All studies	12	0.34 (0.245-0.433)
Only chrysotile	4	0.017 (0.007-0.027)
Only amphiboles (crocidolite, amosite)	2	7.95 (0.015-15.891)
Mixed (amphiboles and chrysotile)	8	2.46 (1.638-3.284)

Table 15 shows that, if the same quality criteria are applied as in the selection of studies for the lung cancer meta-analysis, only two studies meet the pre-defined quality assessment criteria: the study by Hein *et al.*,<sup>66</sup> concerning exposure to chrysotile, and the study by Peto *et al.*,<sup>40</sup> concerning a cohort that was exposed to chrysotile and, for a few years, to amosite. There are no studies involving cohorts exclusively exposed to amphibole asbestos (only) that satisfy the quality criteria.

*Table 15* Summary of all the cohort studies considered, and the studies that passed each successive step of the selection procedure for the various types of asbestos, showing the pooled  $K_M$  values and confidence intervals for each type of asbestos.

Inclusion	Asbestos type and study numbers (see Table 11), with the pooled $K_M$ value (( $\times 10^{-8}$ in (fibres/ml $\times$ years <sup>4</sup> ) <sup>-1</sup> ) and the confidence interval between brackets		
	Chrysotile	Mixed exposure	Amphiboles
All 12 studies (except 4 and 19a)	1a, 1b, 3, 5 0.017 (0.007-0.027)	1c, 13, 14, 18, 19b, 20 1.076 (0.330-1.821)	7.8 7.953 (0.015-15.891)
Step 1. Only studies with acceptable documentation	1a, 1b, 5 0.017 (0.006-0.029)	1c, 14, 19b, 20, 0.709 (0.101-1.316)	
Step 2. Only studies that used internal conversion factors	1a, 1b, 5 0.017 (0.006-0.029)	1c, 14, 20 0.389 (-0.047-0.825)	
Step 3. Only studies with accurate job histories	5 0.150 (-0.015-0.315)	20 1.300 (0.507-2.093)	
Step 4. Only studies with data covering >50% of the follow-up period			

### 7.1.3 Discussion and choice of $K_M$ values

All recent analyses – including the present meta-analysis, the analyses carried out by Hodgson and Darnton,<sup>27,27</sup> Berman and Crump,<sup>23,33</sup> Stayner<sup>85</sup> – strongly indicate a difference between the various types of asbestos in terms of mesothelioma-inducing potential. Hodgson and Darnton's<sup>27</sup> analysis found that at lower exposure concentrations (levels which are more relevant for modern health and safety standards purposes), the carcinogenic potential of crocidolite (an amphibole) was a factor of 100 greater than that of chrysotile.

The analysis carried out for the Committee also shows a clear difference between chrysotile on the one hand and amphiboles (or a combination including amphiboles) on the other. When quality-based selection criteria are applied, only two cohort studies qualify for inclusion in the Committee's pooled analysis: one concerning chrysotile-only exposure (Hein<sup>66</sup>) and one concerning a mixed exposure to amosite and (mostly) chrysotile (Peto<sup>40</sup>). The  $K_M$  value from Hein's study was  $0.15 \times 10^{-8}$ , while that from Peto's study was  $1.3 \times 10^{-8}$ . Peto's study concerned

mixed exposure to amosite and chrysotile, where the percentage of amosite averaged 5% (range 2.5-15%).<sup>40</sup>

The data available regarding exposure to amphibole asbestos only are less reliable; the weighted average  $K_M$  for the two available studies of exposure to amphiboles only is  $7.95 \times 10^{-8}$ . Unfortunately, neither study satisfied the first criterion for inclusion in the meta-analysis (see subsection 6.1.3). However, since exposure to amphibole asbestos on its own is a realistic possibility, the Committee has calculated a  $K_M$  value for this form of exposure, albeit a less reliable value.

The Committee has used the three  $K_M$  values referred to above to calculate concentrations that (it suggests) correspond to the environmental and occupational risk levels.

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## **7.2 Calculation of the concentrations that correspond to the reference environmental and workplace risk levels for mesothelioma**

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### *7.2.1 Principles and assumptions*

The Committee's calculations were based on the general principles and assumptions set out in subsection 6.2.1.

In order to define the relationship between exposure to asbestos and mesothelioma, it is important to know not only the  $K_M$  value, but also the exponent of the time factor (see subsection 3.2 for the details of the formula). Various studies have convincingly shown that the risk of mesothelioma is exponentially associated with time since first exposure, the value of the exponent being about 3. For its mesothelioma calculations, the Committee has chosen to use the US EPA model,<sup>24</sup> in which the exponent of the time factor has a value of 3 and the latency period is ten years. Berman and Crump (2008) recently tested this model (and the associated values) against the most recent data from cohort studies that yield information on the individual level, and again observed a good fit.

In a model, the  $K_M$  values, the exponent of the time factor, and the latency period are interrelated. Having decided to adopt the  $K_M$  values calculated by Berman and Crump<sup>33</sup> using the EPA model,<sup>24</sup> the Committee considered it best to use the EPA model for its own calculations. The Committee in any case considers the EPA model<sup>24</sup> to be preferable to Peto's older model\*,<sup>32</sup> because the

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\* In the past, Peto's model has sometimes been used for some risk analysis; the model uses an exponent of 3.2 for the time factor and disregards the latency period.<sup>32</sup>

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choices and calculations underpinning the EPA model are fully documented and made transparent.

Research into the mesothelioma-related mortality to be expected in the Netherlands revealed that, on the basis of the mortality figures for the period 1969-1998, the age-specific incidence densities of pleural mesothelioma increase exponentially with time since first exposure, to the power of 3.3.<sup>1</sup> In this context, time since first exposure was defined as age at death minus twenty-five years (the latter being the average age of first occupational exposure to asbestos). The exponent calculated in the context of this one-off study is not substantially different from the value used in the EPA model.

**7.2.2 Exposure concentrations corresponding to the reference environmental and workplace risk levels for mesothelioma**

The calculated exposure concentrations corresponding to the reference environmental risk level for mesothelioma (on the basis of lifetime exposure and expressed in fibres/m<sup>3</sup>) are presented in the table below. It should be noted that, due to the use of life tables in the calculations, the relationship between the  $K_M$  values in the table and the calculated exposure concentrations for the various risk levels is not linear.

*Table 16* Environment. Exposure concentrations corresponding to the reference environmental risk levels for mesothelioma. The values relate to lifetime exposure, expressed in fibres/m<sup>3</sup>, as measured by TEM.

Risk level	Type of asbestos	Applied value of $K_M \times 10^8$	Exposure-concentrations in fibres/m <sup>3</sup>
Risk 10 <sup>-4</sup>	Chrysotile	0.15	20,000
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	2,300
Risk 10 <sup>-6</sup>	Amphibole	7.95	500
	Chrysotile	0.15	200
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	22
	Amphibole	7.95	5

The following occupational exposure levels have been calculated for mesothelioma (assuming exposure over a period of forty years of working life). The values

are expressed in fibres/m<sup>3</sup> and in fibres/ml, as measured by TEM. Due to the use of life tables in the calculations, the relationship between the K<sub>M</sub> values in the table and the calculated exposure concentrations for the various risk levels is not linear.

*Table 17* Workplace. Exposure concentrations corresponding to the reference workplace risk levels for mesothelioma. The values relate to occupational exposure (eight hours per day, five days per week, for forty years), expressed in fibres/m<sup>3</sup> (with fibres/ml in brackets), as measured by TEM.

Risk level	Type of asbestos	Applied value of K <sub>M</sub> × 10 <sup>8</sup>	Exposure concentration in fibres/m <sup>3</sup> (fibres/ml)
Risk 4.10 <sup>-3</sup>	Chrysotile	0.15	2,800,000 (2.8)
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	320,000 (0.32)
	Amphibole	7.95	68,000 (0.068)
Risk 4.10 <sup>-5</sup>	Chrysotile	0.15	28,000 (0.028)
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	3,200 (0.0032)
	Amphibole	7.95	680 (0.00068)

Like the environmental values, the workplace values are TEM-based values. They can be converted to PCM-based values by applying the conversion factor of 2 referred to above (values obtained by TEM are twice as high as values obtained by PCM).

### 7.2.3 Comparison with previous risk analyses and MPR and NR values

#### Amphibole asbestos

About the time that the WHO published its guidelines (1987), information had started to appear in the literature indicating that amphibole asbestos might have a greater mesothelioma-inducing potential than chrysotile asbestos. As a precaution, the WHO accordingly formulated its guidelines concerning mesothelioma on the basis of amphibole exposure.<sup>25,25</sup>

The values in Table 18 that are taken from the Guidance Document<sup>6</sup> and the policy document *Asbestos in the environment*<sup>58</sup> are similarly based on amphibole exposure.

Table 18 Results of the analyses for mesothelioma and amphibole exposure cited in the WHO report<sup>25</sup>, WHO guideline value, value proposed in the RIVM Guidance Document<sup>6</sup>, the current MPR value<sup>58</sup> and the values recommended in this report for amphiboles. All the values are given in the form of a TEM-based concentration corresponding to a one in 10<sup>-4</sup> risk from lifetime exposure, expressed in fibres/m<sup>3</sup>.

Results of the analyses cited in the WHO report	WHO guideline value (1987)	Values proposed in the Guidance Document (1987)	Current MPR value given in the policy document 'Asbestos in the environment' (TK91)	The Committee's proposed values (2010)	
				Mixed (chrysotile and up to 20% amphiboles)	Amphiboles
2,000 <sup>86</sup>	1,000-10,000	1,000-10,000	10,000	2,300	500
1,000 <sup>87</sup>					
500 <sup>35,54</sup>					
833 <sup>24</sup>					

<sup>86</sup>:Aurand 1981

<sup>87</sup>:Schneiderman 1981

<sup>35,54</sup>:NRC 1984 and correctie Bresly 1986

<sup>24</sup>: US EPA 1986

From the table, it will be apparent that there is not a great deal of difference between the values given in the risk analyses cited in the WHO report and the Committee's newly calculated values. Moreover, the results of the previous risk analyses are fairly similar to one another. This is not surprising, since all the analyses were based on (broadly) the same cohort studies and the decisions made regarding the selection and processing of the study data have a modest impact on the ultimate  $K_M$  values. The more recent analyses such as that by Berman and Crump<sup>23,33</sup>(2003 and 2008) are also based largely on the same cohort studies; more particularly, the (pooled)  $K_M$  values used also derive from these studies. None of the reported analyses, except for that by the Committee, involved transparent or quality-based selection of studies for inclusion; the values in Table 18 are based on the average (in most cases the geometric average) of the cohort study results. Although the Committee did apply selective inclusion criteria, this did not lead to an outcome that was substantially different from the previous analyses.

The environmental amphibole asbestos values calculated by the Committee for mesothelioma are a factor of 20 lower than the corresponding current MPR values. This is partly because the RIVM Guidance Document on Asbestos<sup>6</sup> and the Health Council report<sup>34</sup> simply adopted the WHO guideline values, which were significantly higher than the figures suggested by the risk analyses that the WHO referred to in its report (see Table 18).<sup>25</sup> The policy document *Asbestos in the*

*environment* equates the highest value in the WHO's guideline range to the MPR value; a policy decision was made that, for outdoor settings, the atmospheric asbestos concentration should be limited to that corresponding to the NR level (although, where most substances are concerned, the MPR value is used).<sup>58</sup> The limit is a specification of the quality level that must be attained; higher concentrations are not permitted. So, although the MPR for outdoor settings is twenty times higher than the figure calculated by the Committee, a policy decision was previously made to set an atmospheric asbestos limit a hundred times lower than what one would normally expect (the NR concentration is 1 000 fibres/m<sup>3</sup> for chrysotile and 100 fibres/ m<sup>3</sup> for amphiboles).

### Chrysotile

In relation to mesothelioma, the RIVM Guidance Document on Asbestos<sup>6</sup> assumes an exposure limit for chrysotile asbestos that is ten times higher than that for amphiboles\*. Otherwise, the MPR is calculated in the same way as that for amphiboles (but, because of the latter assumption, the values are ten times higher: 10,000 to 100,000 fibres/m<sup>3</sup>). For chrysotile asbestos, the policy document *Asbestos in the environment* adopts an MPR value of 100,000 fibres/m<sup>3</sup>.<sup>58</sup> The chrysotile concentration calculated by the Committee to correspond to a mesothelioma risk level equal to the MPR is a factor of 5 lower. However, as described in section 6, the corresponding figure calculated by the Committee on the basis of lung cancer risk is considerably lower: a chrysotile concentration of 3,200 fibres/m<sup>3</sup>. This value is about thirty times lower than the current MPR value for chrysotile, which was calculated on the basis of the mesothelioma risk. Since the WHO's guideline value for lung cancer<sup>25</sup> (which was adopted by the RIVM in its Guidance Document on Asbestos<sup>6</sup>) is ten times higher than the WHO's guideline value for mesothelioma (for a discussion of the WHO guideline value for lung cancer, see subsections 3.3. and 6.2), the figures put forward in the RIVM Guidance Document (from which the MPR value is derived) are based on mesothelioma risk, rather than lung cancer risk.

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#### 7.2.4 *Uncertainties in the values put forward by the Committee*

The uncertainties referred to in subsection 6.2.4, concerning the fibre length and diameter distributions in the various studies, and concerning linear extrapolation, apply equally in relation to the Committee's mesothelioma calculations.

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\* The Committee calculates the potential of amphiboles to be fifty times greater than that of chrysotile.

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The  $K_M$  values used by the Committee for chrysotile and mixed exposure (to chrysotile and amphiboles) are both based on a single cohort study (the only study judged to be of sufficient quality). For amphibole asbestos, a less reliable (weighted average)  $K_M$  value has been used: a value derived from the only two available cohort studies concerned with exposure to amphibole asbestos only, both of which satisfied only one of the four exposure assessment quality criteria for inclusion in the meta-analysis.

In addition, certain assumptions have been made about the influence that the time since first exposure has on the incidence of mesothelioma. The Committee has assumed that, in this exponential relationship, the value of the exponent is 3. This assumption follows the risk analysis made by the EPA (1986).<sup>24</sup>

The Committee has calculated that, if the value of the exponent of the time factor is increased or decreased by 0.5, the outcome will increase or decrease by one order of magnitude. Since the exponent value was obtained by determining the best fit with data on a number of cohorts – in which the incidence had been tracked for up to fifty years after exposure – it is unlikely that the true value of the exponent is very different from that adopted, otherwise a good fit with the data would not have been observed.

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## **Conclusions: proposed new values for asbestos**

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At the request of the then State Secretary for VROM, the Health Council has re-evaluated the current environmental quality requirements for asbestos i.e. the concentrations that correspond to the maximum permissible risk (MPR) level and the negligible risk (NR) level. In addition, the Health Council has assessed the need for new occupational exposure limits for asbestos and the concentrations corresponding to the government's reference risk levels, as requested by the State Secretary for SZW.

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### **8.1 New meta-analyses for lung cancer and mesothelioma**

After studying all the recent analyses, the Committee concluded that none of them would serve as an optimal basis for the calculation of concentrations corresponding to the reference environmental and occupational risk levels. The reason being that none of the analyses involved the selection and inclusion of only good-quality epidemiological studies, in line with standard modern meta-analysis procedure. The Committee accordingly commissioned new meta-analyses for lung cancer and mesothelioma (section 6 and 7).

These meta-analyses led to the selection of one pooled  $K_L$  value and several  $K_M$  values. The  $K_L$  value is an expression of the gradient of the asbestos-lung cancer exposure-response relationship, while the  $K_M$  value is an expression of the gradient of the asbestos-mesothelioma exposure-response relationship. The  $K_L$  and  $K_M$  values are indicators of, respectively, asbestos's lung cancer-inducing

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potential and mesothelioma-inducing potential (specific forms of carcinogenic potential); both are expressed as the increase in risk per unit of exposure. The meta-analysis for lung cancer found that, if studies are selected for inclusion on the basis of quality, no difference is observable between the two main types of asbestos (chrysotile and amphiboles) in terms of carcinogenic potential. Hence, the calculated  $K_L$  value is valid for both chrysotile asbestos and amphibole asbestos. The resulting meta- $K_L$  value is higher than the  $K_L$  values used in previous risk analyses.

In contrast, the meta-analysis for mesothelioma does yield convincing evidence that chrysotile and amphiboles differ in their respective carcinogenic potential. However, the meta-analysis for mesothelioma found that reliable  $K_M$  values can be calculated only for chrysotile asbestos and for mixed exposure to chrysotile and (up to 20%) amphiboles. In the Netherlands, asbestos exposure is nowadays likely to involve chrysotile or a combination of chrysotile and an amphibole (crocidolite or amosite). Nevertheless, in certain situations, exposure to amphiboles alone may occur; the Committee accordingly decided to calculate a  $K_M$  value for amphibole asbestos, on the basis of data that do not satisfy the criteria for inclusion in the meta-analysis.

Since the risk analyses of the 1980s, additional research data have become available. The Committee believes that, by commissioning a new meta-analysis and making use of the most recent data, it has been able to arrive at the best possible point estimates of the  $K_L$  value and the  $K_M$  values (for lung cancer, for example, the uncertainty associated with the  $K_L$  value is less than a factor of 10). The Committee concludes that the values presented in this report are more reliable than the estimates that formed the basis of the current standards when they were formulated in 1987.

On the basis of the pooled  $K_L$  value and  $K_M$  values and a number of principles and assumptions, the Committee has calculated separate concentrations corresponding to the reference environmental and workplace risk levels for lung cancer and for mesothelioma; the calculations are presented in sections 6 and 7, respectively. Neither the calculation method used, nor the assumptions made by the Committee were more conservative than those in previous risk analyses; in all cases, the Committee sought to make the most realistic estimates possible. The uncertainty associated with the factors discussed in sections 6 and 7 may be high, but are largely unquantifiable; one should bear in mind that it is unlikely that all the factors would (systematically) tend to increase or decrease the outcome values.

Because the calculated lung cancer and mesothelioma risk concentrations are fairly similar, the two diseases may both be considered significant in terms of the health risk posed by asbestos. The concentrations put forward in this section as corresponding to the reference environmental and occupational risk levels have therefore been calculated so as to be valid for the outcomes mesothelioma and lung cancer collectively. The collective risk of the two diseases is not the sum of the separate risks; the phenomenon of competing causes of death means that the collective risk will always be less than the sum of the separate risks. This is because, if someone who is exposed to asbestos consequently dies from lung cancer, there ceases to be any risk of the exposure leading to death from mesothelioma.

## 8.2 Proposed new MPR and NR values for the environment

The proposed new MPR and NR values for chrysotile, for mixed exposure (to chrysotile and up to 20 % amphiboles), and for amphibole asbestos alone are set out in Table 19. As explained in section 3, for policy purposes, a risk of  $10^{-4}$  associated with lifetime exposure equates to the MPR. Similarly, a risk of  $10^{-6}$  associated with lifetime exposure equates to the NR.

Where amphibole asbestos is concerned, the values calculated by the Committee are determined mainly by the occurrence of mesothelioma, while for chrysotile lung cancer is the predominant outcome (the value for lung cancer is valid for all types of asbestos). Combination of the two outcomes results in concentrations that are up to about 60% lower than the values for mesothelioma and lung cancer separately.

*Table 19* Proposed new MPR and NR values and the current values for asbestos, according to asbestos type. The values are valid for lifelong exposure from the general environment, expressed in fibres/m<sup>3</sup>, as measured by TEM. The values are based on the outcomes mesothelioma and lung cancer collectively. The current MPR and NR values are based on mesothelioma as the sole outcome.

	Proposed new MPR and NR values			Current MPR and NR values	
	Chrysotile in fibres/m <sup>3</sup>	Mixed exposure to chrysotile and up to 20% amphibole in fibres/m <sup>3</sup>	100% amphibole in fibres/m <sup>3</sup>	Chrysotile in fibres/m <sup>3</sup>	Amphibole in fibres/m <sup>3</sup>
MTR (risk of $10^{-4}$ )	2,800	1,300	300	100,000	10,000
VR (risk of $10^{-6}$ )	28	13	3	1,000	100

The Committee's proposed MPR value for chrysotile asbestos is a factor of 40 lower than the current MPR value; that for amphibole asbestos is a factor of 30 lower (for a discussion of the differences, see sections 6 and 7). For all types of

asbestos, the exposure levels calculated by the Committee to correspond to the NR level are lower than or close to the current background levels in the outdoor atmosphere (10-20 fibres/m<sup>3</sup>). In the 1980s, concentrations of 1,000 to 6,000 fibres/m<sup>3</sup> were measured outdoors in Dutch inner city areas near to road junctions (IMG-TNO, 1981). In 1981, almost all motor vehicles had asbestos-containing brake linings.

### 8.3 Proposed new values for the workplace

The proposed new values for chrysotile, for mixed exposure (to chrysotile and up to 20% amphiboles), and for amphibole asbestos alone are set out in Table 20. Like the environmental values, the workplace values are TEM-based values. Such values are twice as high as corresponding values obtained by PCM; the current limit value is a PCM-based value.

Where amphibole asbestos is concerned, mesothelioma is the predominant effect of exposure. In the case of chrysotile asbestos, lung cancer is the key outcome (the value for lung cancer is valid in relation to all types of asbestos). The current Dutch occupational exposure limit is 0.01 fibres/ml, as measured by PCM (or 0.02 fibres/ml as measured by TEM); this limit applies both to chrysotile asbestos and to mixed exposure to amphiboles. The current Dutch occupational exposure limit is not based on the calculation of asbestos exposure levels that corresponds to a given risk level, but is merely an adaptation of the EU standard for chrysotile, which Dutch policy makers chose to reduce by a factor of 10. The proposed values corresponding to a risk level of  $4 \cdot 10^{-5}$  are considerably lower than the current Dutch limit values.

*Table 20* Exposure concentrations of various types of asbestos corresponding to the reference risk levels of  $4 \cdot 10^{-3}$  and  $4 \cdot 10^{-5}$  for mesothelioma and lung cancer collectively. The values relate to occupational exposure (eight hours per day, five days per week, for forty years) and are expressed in fibres/m<sup>3</sup> (with fibres/ml between brackets), as measured by TEM.

Risk level	Concentrations corresponding to reference risk level for occupational exposure measured by TEM		
	Chrysotile in fibres/m <sup>3</sup> (fibres/ml)	Mixed exposure to up to 20% amphibole in fibres/m <sup>3</sup> (fibres/ml)	100% amphibole in fibres/m <sup>3</sup> (fibres/ml)
$4 \cdot 10^{-3}$	200,000 (0.2)	130,000 (0.13)	42,000 (0.042)
$4 \cdot 10^{-5}$	2,000 (0.002)	1,300 (0.0013)	420 (0.00042)

Notes on Table 20: The current limit value is a PCM-based value: 10,000 fibres/m<sup>3</sup> or 0.01 fibres/ml; expressed as a TEM-based value, the current limit value is: 20,000 fibres/m<sup>3</sup> or 0.02 fibres/ml.

NB: The current Dutch occupational exposure limit is not based on the calculation of concentrations that correspond to a given risk level.

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- A VROM and SZW request for advice
  - B The Committee
  - C Comments on the public draft
  - D Mortality figures and life table analyses
  - E Environmental exposure and asbestos-related health risks
  - F Calculation of  $K_L$  values
  - G Summary of exposure variables for alle cohorts

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## Annexes



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## **VROM and SZW requests for advice**

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On 24 May 2006, the President of the Health Council received the following letter from the State Secretary for Housing, Spatial Planning and the Environment (VROM), under reference SAS/DBU/2006271785:

Dear President,

On 2 February 2006, I requested that you examine whether the research findings of the Erasmus Medical Center into the incidence of non-occupational mesothelioma victims in the region around Goor necessitated a reassessment of the Maximum Permissible Risk Level (Maximaal Toelaatbaar Risiconiveau, MPR) and the Negligible Risk (Verwaarloosbaar Risico, NR).

Your advisory report of 9 May made it clear that the Health Council was of the opinion that the research into the incidence of non-occupational mesothelioma victims was of good quality. At the same time your report indicated that it was not possible to evaluate the MPR and NR values on the basis of the Erasmus Medical Center research (and pointed out that this had never been the intention of the Erasmus Medical Center research). However, your report concludes that since 1987 new knowledge and insights have become available which might give cause for such a reassessment. You mention, in particular, a meta-analysis carried out by Hodgson & Darnton in 2000 and an EPA report from 2003.

I thank you for your informative response to my request, and I note and accept your advice. I therefore request that, as you recommend, you commission a study by the Health Council Substance Car-

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cinogenicity Assessment Committee (commissie Beoordeling van Carciogeniteit van Stoffen) into the possible amendment of the current MPR and NR values for asbestos.

Yours faithfully,

[signed by]

State Secretary for VROM

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On 8 September 2006, the President of the Health Council received the following letter from the State Secretary for Social Affairs and Employment (SZW), under reference ARBO/P&G/2006/72643:

Dear Mr Knottnerus,

On 9 May 2006, you sent me a copy of the advisory letter 'Asbestos' for my information. In response to this document, the State Secretary for Housing, Spatial Planning and the Environment (VROM) has requested that you carry out a study into the possible adjustment of the existing standards for asbestos and report back in mid-2007.

Research into VROM standards can also be significant in relation to occupational health and safety policy. I would therefore request that your research and advisory report also take into account the factors relevant to occupational exposure to asbestos. I am thinking here of:

- the risk-based approach and associated risk levels employed in the context of occupational health and safety policy on carcinogenic substances
- the factor used for the conversion of data obtained using different measurement methods,
- the exposure duration,
- relevant exposure to the various types of fibres in (the most common) occupational situations,
- relevant exposure to fibres of various lengths in (the most common) occupational situations.

Yours faithfully,

[signed by]

H.A.L van Hoof,

State Secretary for Social Affairs and Employment

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## The Committee

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- G.J. Mulder, *chairman*  
Emeritus professor of toxicology; Leiden University, Leiden
  - R.B. Beems  
Toxicologic pathologist; formerly employed at the National Institute for Public Health and the Environment, Bilthoven
  - P.J. Boogaard  
Toxicologist; Shell International BV, The Hague
  - J.J.A.M. Brokamp, *advisor*  
Social and Economic Council, The Hague
  - A. Burdorf  
Professor of Public Health; Erasmus MC: University Medical Center Rotterdam, Rotterdam
  - D.J.J. Heederik  
Professor of risk assessment in occupational epidemiology; Institute for Risk Assessment Sciences, Utrecht University, Utrecht
  - R. Houba  
Occupational hygienist; Netherlands Expertise Centre for Occupational Respiratory Disorders (NECORD), Utrecht
  - D.W.G. Jung, *advisor*  
Ministry of Housing, Spatial Planning and the Environment (VROM), The Hague
-

- L.A.L.M. Kiemeney  
Professor of cancer epidemiology, Maastricht University, Maastricht / National Institute for Public Health and the Environment, Bilthoven
  - H. van Loveren  
Professor of immunotoxicology; Maastricht University, Maastricht / National Institute for Public Health and the Environment, Bilthoven
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Occupational physician; Netherlands Centre for Occupational Diseases, University of Amsterdam, Amsterdam
  - A.H. Piersma  
Professor of reproductive toxicology; Utrecht University, Utrecht, and National Institute for Public Health and the Environment, Bilthoven
  - H.P.J. te Riele  
Professor of molecular biology; VU University Amsterdam, Amsterdam
  - I.M.C.M. Rietjens  
Professor of toxicology; Wageningen University and Research Centre, Wageningen
  - H. Roelfzema, *advisor*  
Ministry of Health, Welfare and Sport, The Hague
  - T. Smid  
Professor of occupational hygienist - epidemiologist, KLM Health Services, Schiphol / Professor of working conditions, Vrije Universiteit Amsterdam
  - G.M.H. Swaen  
Epidemiologist; Dow Benelux N.V., Terneuzen
  - R.C.H. Vermeulen  
Epidemiologist/environmental hygienist; Institute for Risk Assessment Sciences, Utrecht University, Utrecht
  - A.A. Vijlbrief, *advisor*  
Ministry for Social Affairs and Employment (SZW)
  - J.H. van Wijnen  
Epidemiologist, Amsterdam
  - R.A. Woutersen  
Toxicologic pathologist, TNO Quality of Life, Zeist, and Professor of translational toxicology, Wageningen University and Research Centre, Wageningen
  - P.B. Wulp  
Occupational physician; Labour Inspectorate, Groningen
-

- N. van Zandwijk  
Professor of Thoracic Oncology, Concord Clinical School Asbestos Diseases  
Research Institute, University of Sydney, Australia
- J.W. Dogger, *scientific secretary*  
Health Council of the Netherlands, The Hague

### The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.



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## **Comments on the public draft**

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In 2009, a draft version of the report was published. The following individuals and institutions submitted comments on the draft report:

- Environnement et du travail (AFSSET), Maisons-Alfort cedex, France
- W. Berman, Aeolus, Inc, Albany, USA
- J.H.M. van Cleemput, on behalf of Eternit Fabrieken BV, Goor
- C. Hegger, Rotterdam-Rijnmond Municipal Health Service, Rotterdam
- B. Sjögren, Karolinska Institutet, Stockholm
- J. Tempelman, TNO, Utrecht
- C. Waasdorp, NRVD, Arnhem
- R.D. Zumwalde, National Institute for Occupational Safety and Health, Cincinnati OH, USA.



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**Mortality figures and life table analyses**

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Mortality has been calculated on the basis of national data on mesothelioma and lung cancer mortality in five-year age bands obtained through Statistics Netherlands (Centraal Bureau voor de Statistiek, [www.cbs.nl](http://www.cbs.nl)) and the Comprehensive Cancer Centres (Vereniging van Integrale Kankercentra, [www.ikcnet.nl](http://www.ikcnet.nl)). Mortality data for the year 2003 was used, broken down by age and sex. Rates for women and men were averaged so that the calculations would describe the average risk for the population. To soften the transitions between age categories, the mortality data were 'smoothed'. The 'modelled' mortality data that were employed in the Committee's analysis.

The mortality rates (deaths per 100,000, person-years) were used in a so-called survival analysis,<sup>88</sup> as in other recent reports by the DECOS Committee. Such an analysis may be thought of as involving two cohorts (in this case, of 100,000 people), that are followed from birth. In the calculation of the lifetime risk associated with an environmental factor, it is assumed that first exposure takes place in the first year of life. For occupational exposure, it is assumed that exposure of the cohort starts at the age of twenty and lasts until the age of sixty. Every year the cohort reduces in size, through death as a result of the cause of death under study and other causes; the cohort is followed until it reaches the age of a hundred.

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The first cohort is not exposed; the second cohort is exposed to asbestos, and for this reason lung cancer and mesothelioma mortality is higher in this cohort. Assuming a given average annual fibre exposure, every year that a person in the cohort is exposed to asbestos fibres is another year contributing to their cumulative exposure. This approach employs cumulative exposure because studies of workers exposed to high levels of asbestos always work with cumulative exposure; the formulae employed are also based on cumulative exposure. Using this cumulative exposure, which is recalculated for each year, and the assumed exposure-response relationship – taken from the meta-analysis – between asbestos and death from lung cancer or mesothelioma, the number of extra deaths is calculated for each year that the cohort ages. Using this information, first the additional risk of death per year associated with exposure to asbestos can be calculated and then the lifelong additional risk of death associated with exposure.

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## **Environmental exposure and asbestos-related health risks**

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As early as the 1980s, it was suggested that environmental exposure to asbestos might be responsible for up to a third of all mesothelioma deaths.<sup>89</sup> These mesothelioma cases were attributed to asbestos exposure both in the domestic environment and in the general environment – in the neighbourhood of asbestos-processing and asbestos-producing plants, and of course in areas where natural sources of asbestos outcrop. Bourdes *et al.*<sup>90</sup> analysed all the studies that were available at that point and concluded that domestic exposure was accompanied by an increase in risk of between four and twenty-four fold, as opposed to a factor of five to nine for exposure in the general environment. In several cases, asbestos exposure was associated with local industrial activity.<sup>91,92</sup>

The Dutch observations described by Burdorf *et al.* are in line with this picture.<sup>3</sup> In the Netherlands, too, an elevated risk of mesothelioma has been reported in the immediate vicinity of former asbestos plants. The first part of the report indicated that the incidence of pleura mesothelioma (cancer of the pulmonary membrane) in the Goor area is twice as high for men and five times as high for women as it is in the rest of the Netherlands. This is a strong indication that environmental exposure to asbestos has played an important role in the substantially above-average incidence of pleural mesothelioma in this risk area. The effect of environmental exposure is particularly marked in women, because women are generally exposed to less asbestos in the course of their working lives. The second part of the report concluded that between 1989 and 2003, exposure to environmental asbestos, in particular exposure to roads and yards paved with

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asbestos-containing material, had been the most likely cause of pleural mesothelioma in fifteen women.

The Dutch findings have been confirmed by a very recent Italian study.<sup>93</sup> This well-designed case-control study described how residents living close to a former asbestos factory (103 cases) ran a risk of developing mesothelioma that was five to fifteen times as great as that of 272 control subjects. The risk abated only for those living ten kilometres or more from the factory. Measurements of airborne asbestos fibres were carried out in the immediate environment both before and after the factory closed down and in the years thereafter. Close to the factory (at a distance of approximately 400 m) levels of around 11,000 fibres/m<sup>3</sup> were measured; at greater distances these levels were still 4,500 fibres/m<sup>3</sup> (1,500 m) and 1,000 fibres/m<sup>3</sup> (in the most remote urban area tested). The measurements were carried out using a scanning electron microscope (SEM). This study is notable in that the analyses include optimal corrections to the relationships between environmental exposure and mesothelioma to take account of both occupational exposure and domestic exposure to asbestos. The researchers conclude that secondary asbestos exposure may play an important role. Local residents were probably exposed not only to airborne fibres coming straight from the factory; after all, it is unlikely that these fibres would lead to a raised risk of health problems many hundreds of metres and sometimes more than a kilometre away from the factory. However, exposure to asbestos being transported to the factory through the surrounding area, transport between a storage facility and the factory through the surrounding area, mixing asbestos cement wastes with earth to use for road surfacing in the surrounding area, and the use of milled asbestos cement for insulation purposes, may explain why the risk of mesothelioma did not return to the background level until more than ten kilometres from the factory.

The atmospheric concentrations in this study were relatively low. Nevertheless, as in the case of the Dutch research, an elevated risk was clearly demonstrated. The exposure levels at which an elevated risk appears is not clear; the limited series of airborne fibre measurements do not provide a complete picture of the actual exposure of residents living at different distances from the factory. This also means that it is impossible to base a risk analysis on these data. However, the research results do show that a raised risk of mesothelioma may be caused by a relatively low level of exposure – a level probably considerably lower than the lowest level observed to be associated with mesothelioma and asbestos in an occupational context.

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## Calculation of $K_L$ values

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The  $K_L$  values used for each study were recalculated on the basis of the information extracted for each study (as systematically presented in Berman and Crump (2008), Berman and Crump (2003) or, where necessary, in the original study report). The  $K_L$  values from Berman *et al.* (2008) have not been adopted, because in that study the regression lines were not forced through  $RR=1$  (or  $SMR=100$ ), as is normal in risk analyses of this type (see also subsection 5.3). In each case, the Committee made use of the usual regression technique for the particular measure of association used in the particular study (Standardized Mortality Ratio (SMR), Relative Risk (RR) or Odds Ratio (OR)). Various regression techniques were used because, in studies where the effects were expressed using SMRs, the expected mortality was calculated by reference to the general population, whereas in patient-control studies or cohorts studies that relied on internal analysis, the expected mortality was not known. For the SMR studies, a regression analysis was performed using SAS software on the basis of the observed number of lung cancer cases as a Poisson-distributed dependent variable and the exposure as an independent variable. The regression line was forced through an intercept (at a cumulative exposure of 0,  $SMR=100$ ). For the studies that used Relative Risk or an Odds Ratio, the  $K_L$  value was calculated by linear regression analysis from the RR or OR for the cumulative exposure, weighted for  $1/[\text{standard error}(\text{RR})]^2$ . If the standard error was not specified in the original publication, it was derived from the confidence interval of the RR or OR.

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Before performing its meta-analysis, the Committee recalculated the  $K_L$  values for all cohorts using the same method. The meta analysis was conducted applying fixed and random effects models in STATA version 10.1. The Q-statistic and I<sup>2</sup> values showed that the studies were significantly heterogeneous: the inter-study variation in  $K_L$  values was greater than could be expected on the basis of chance alone. This indicates that factors other than mere chance – such as differences in the quality of the studies – must have influenced the  $K_L$  values. Therefore, further analyses we conducted using random effects models.

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**Summary of exposure variables  
for all cohorts**

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	Cohort	Primary reference	Fibre type	Amphibole fraction (range)**	Conversion factor	Units in fibres	Cumulative exposure categories (f-yr/ml)	
							Mean of lowest; highest	Ratio highest: lowest
1	Quebec mines and mills	Liddell <i>et al</i> 1997	Chry	1.0 (0-4)	I	N	4.71; 4710	1000
2	Italian mine and mill (Balangero)	Piolatto <i>et al.</i> 1990	Chry	0.3 (0.1-0.5)	N/A	Y	50; 600	12
3	Connecticut friction products plant	McDonald <i>et al</i> 1984	Chry	0.5 (0-2)	E	N	15; 330	22
4*	New Orleans cement plants*	Hughes <i>et al</i> 1987	Chry	1 (0-2)	I	N	4.2; 229.6	55
5	South Carolina textile plant	Hein <i>et al.</i> 2007	Chry	0.5 (0-2)	I	Y	0.4 ; 185.1	463
6*	South Carolina textile plant*	McDonald 1983	Chry	0.5 (0-2)	I	N	30; 660	22
7	Wittensoom, Australia, mining and milling	Berry <i>et al.</i> 2004	Croc	97 (95-100)	N/A	Y	0.11; 219.2	1993
8	Patterson, NJ, insulation manufacture	Seidman <i>et al.</i> 1986	Am	97 (95-100)	N/A	Y	3; 375	125
9	Tyler, Texas, insulation manufacture	Levin <i>et al.</i> 1998	Am	97 (95-100)	E	Y	11.25; 337.5	30
10	Libby, Montana, Vermiculite mines and mills	Sullivan 2007	Tre	97 (95-100)	I	N	2.25; 150	67
11*	Libby, Montana, Vermiculite mines and mills*	McDonald <i>et al.</i> 2004	Tre	97 (95-100)	I	Y	8.6; 393.8	46
12	British friction product factory (Ferodo)	Berry and Newhouse 1983	Mix	0.5 (0-2)	N/A	Y	4.5; 228	51
13	Ontario cement factory	Finkelstein 1984	Mix	30 (10-50)	E	Y	15; 200	13
14	New Orleans cement plants	Hughes <i>et al.</i> 1987	Mix	5 (2-15)	I	N	(Plants 1/2) 5.6/4.2; 256/229	55/46
15	Swedish cement plant	Albin <i>et al.</i> 1990	Mix	3 (0-6)	I	Y	3.1; 88.2	28
16	Belgium cement plant	Laquet <i>et al.</i> 1980	Mix	10	N/A	Y	24.5; 2400	29
17	U.S. factory retirees (Johns Manville)	Enterline <i>et al.</i> 1986	Mix	(0-100)	E	N	182.3; 698.7	16
18	U.S. (& Canada) insulation workers	Selikoff and Seidman 1991	Mix	50 (25-75)	E	N	37.5; 375	10
19	Pennsylvania textile plant	McDonald <i>et al.</i> 1983	Mix	8 (3-15)	E	N	15; 330	22
20	Rochedale, England textile plant	Peto <i>et al.</i> 1985	Mix	5 (2.5-15)	I	Y	5.92; 256.57	43
21	Stockholm County population	Gustavsson <i>et al.</i> 2002	Mix	unknown	N/A	Y	0.56; 8.80	>100

Recruitment	End of follow-up	Start of expos.	Start of impinger/ other measurements (year)	Start of PCM measurements (year)	Measurement coverage (%)		
					Total	PCM	LaggedCE
born 1891-1920	1992	~1904	1948-66	-	>20%	0%	CE 'til age 55
1946-87	1946-87	1916	Simulation of earlier conditions	1969	26%	26%	CE
1913-59	1977	1913	1930 (No meas. 1940-70)	1970	50-70%	10%	CE
1942-69 (plant 2)	1982 or age 80	1920s	1952-69	1970	55%	25%	CE10
1940-65 exposed	2001	1896	1930-71	1965	100%	>4%	CE10
1938-1958 exposed	1977	~1920	1930-71	1965	100%	0%	CE10
1943-66	2000	1943	1948-58	1966 survey	88%	< 5%	CE
1941-45	1941-82	1941-45	No factory meas. ***	-	0%	0%	CE5 (mean CE35)
1954-72	1993	1954	1967, 70, 71 surveys	-	28%	0%	CE10
1935-81	2001	1923	1950-69	1967-82	67%	33%	CE15
1940-63	1998	1923	1944-69	1970-74	75%	10%	CE10
1941-77	1942-79	1910/1922	Simulation of earlier conditions	1967	>18%	18%	CE
1948-59	1977 or 1981	1948	1949	1969	70-80%	30%	CE (mean CE23)
Plant 1: 1942-69; Plant 2: 1937-69	1982 or age 80	1920s	1952-69	1969	55%	25%	CE10
1907-77	1927-86	1907-78	1956-69	1969	31%	13%	CE
1963-77	1977	1928	No meas., estimated back to 1928	1970-76	12%	12%	CE
retired 1941-67	1980	1920	~1955	-	40%	0%	CE
1907-66	1967-86	~1915	-	-	0%	0%	~CE10
1959	1977	~1920	1930-39, >1956	1967	75%-80%	18%	CE10
1933-74	1983	1933	1951-64	1965	<64%	36%	CE5
1950-1990 lived in city	1985-90 cases identified	-	-	1969-73	10%	10%	CE

Notes on the table of exposure variables for all cohorts:

The study by Hughes (1987) was previously categorised as 'mixed', because no distinction could be made between those workers who had worked only with chrysotile asbestos and those who had worked with asbestos mixtures (study 4 in the Annex).

Predominant fibre type: Chry=Chrysotile, Croc=Crocidolite, Am=Amosite, Tre=Tremolite, Mix=Mixed.

Conversion factor indicates whether measurements of particles (mppcf) were converted to fibres/ml with an I=internally, or E=externally derived conversion factor based on paired measurements or a generic factor, respectively.

Lagged CE indicates whether exposures in the CEx years previous to follow-up were discarded.

\* Duplicates excluded from meta-analysis.

\*\* From Berman and Crump (2008b), Table 3.

\*\*\* Estimated based on measurements taken 1967-71 at similar plants in Texas and Pennsylvania, which used the same products and machinery.