Annex 1

in support of the Committee for Risk Assessment (RAC) for evaluation of limit values for asbestos at the workplace

ECHA/RAC/ A77-O-0000006981-66-01/F

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Scope of the task and literature search

As explained in the Preamble of the Opinion document, ECHA was tasked to review the current OEL set in Article 8 of Directive of 2009/148/EC and to include an evaluation of different types of asbestos fibres as defined in Article 2 of that Directive. The current OEL is 0.1 fibres per cm^3 as an eight-hour time-weighted average (TWA) for all asbestos types.

This report is based on international assessments such as, NFA (2019), IARC (2012), DECOS (2010), Afsset (2009a,b) and AGS (2008). This has been complemented by a literature search of published papers from the last ten years.

ECHA evaluation and recommendation

Asbestos is a non-threshold carcinogen. Consequently, no health-based OEL can be identified and an exposure-risk relationship (ERR) expressing the excess risk for lung cancer and mesothelioma mortality (combined) in function of air concentration is derived. The ERR was calculated for all asbestos, i.e. combining all studies regardless of the asbestos fibre type the population was exposed to. The ERR focuses on air concentrations at and below the current OEL.

The tables below present the outcome of the scientific evaluation to derive limit values for asbestos and the cancer exposure-risk relationship.

Derived Limit Values

OEL as 8-hour TWA:	No proposal
STEL:	No proposal
BLV:	No proposal
BGV:	No proposal

Notations

Notations:	None

Cancer exposure-risk relationship *

Air concentration of mixed asbestos[1]		Excess life-time cancer risk (cases per 100 000 exposed)
Fibres/cm^3	Fibres/m^3	
0.001	1000	1.2
0.002	2000	2.5
0.005	5000	6.2
0.01	10000	12
0.02	20000	25
0.05	50000	62
0.1	100000	125

* Assuming exposure 8 hours per day and 5 days per week over a 40 year working life period (starting at 20 years) and calculating risk until 89 years of age.

[1] The exposure-risk relationship is based on fibre measurements according to the Phase Contrast Microscopy method of WHO (1997) and combined information from study populations exposed to different asbestos fibre types.

1. Chemical Agent Identification and Physico-Chemical Properties

Although the definition of asbestos is not a conventional chemical agent definition, the definition is well established in the scientific and regulatory framework as further described below. That definition consequently forms the basis of existing exposure, analytical monitoring and hazard data as described in Chapters 2 and 4 to 9 and the regulatory framework described in Chapter 3.

Asbestos is a generic name given to the fibrous variety of six naturally occurring silicate minerals that have been used in commercial products (USGS, 2001). Thus, the term "asbestos" is not a mineralogical definition; it is a commercial designation for fibrous minerals that possess high tensile strength, flexibility, resistance to chemical and thermal degradation, and high electrical resistance and that can be woven. These include the serpentine group, mineral chrysotile (also known as 'white asbestos'), and the five amphibole group minerals – actinolite, amosite (also known as 'brown asbestos'), anthophyllite, crocidolite (also known as 'blue asbestos'), and tremolite (IARC, 1973; USGS, 2001). Reflecting the mineralogical origin, amosite is sometimes called cummingtonite-grunerite asbestos or grunerite asbestos and crocidolite as riebeckite asbestos (NIOSH, 2011).

The structure of silicate minerals may be fibrous or non-fibrous. The terms 'asbestos' or 'asbestiform minerals' refer only to those silicate minerals that occur in polyfilamentous bundles, and are composed of flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another (USGS, 2001; HSE, 2005). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a 'non-asbestiform' habit. These minerals may have the same chemical formula as the 'asbestiform' variety (NIOSH, 2008).

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified. Serpentine silicates, like chrysotile, are classified as 'sheet silicates' because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as 'chain silicates' because the tetrahedral are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In natural samples, the composition varies with respect to major and trace elements (USGS (2001), HSE (2005), IOM (2006)). The substance identity and physico-chemical properties of asbestos fibres are summarised in Appendix 2.

In chrysotile asbestos, the silicate sheet is 'rolled' around a virtual axis to form a tube known as a fibril (DECOS, 2010). A fibre normally contains several fibrils and is often inclined to curl. The fibrils give the fibre its strength and flexibility. Chrysotile asbestos has a silky structure and its micro-fibrils can have a diameter of less than 0.03 µm. In practice, asbestos fibres are usually a few tens of micro-meters in length. For past commercial applications, the most appropriate fibre dimensions, especially length, varied according to the intended technical use (see Chapter 5).

For the purposes of Directive 2009/148/EC[2] on the protection of workers from the risks related to exposure to asbestos at work, Article 2 of the Directive defines that *'asbestos' means the following fibrous silicates:*

[2] https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32009L0148

(a) asbestos actinolite, CAS No 77536-66-4;

(b) asbestos grunerite (amosite), CAS No 12172-73-5;

(c) asbestos anthophyllite, CAS No 77536-67-5;

(d) chrysotile, CAS No 12001-29-5;

(e) crocidolite, CAS No 12001-28-4;

(f) asbestos tremolite, CAS No 77536-68-6

Article 7 of the Directive further specifies that *for the purpose of measuring asbestos in the air, only fibres with a length of more than 5 micrometres, a breadth of less than 3 micrometres and a length/breadth ratio greater than 3:1 shall be taken into consideration.* This follows the fibre specifications of the WHO 1997 method (WHO, 1997), for the length/breadth ratio also the term aspect ratio is often used.

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

The six asbestos fibres are covered by a group entry of Annex VI of the EC Regulation 1272/2008 on classification, labelling and packaging of substances and mixtures. All asbestos fibres are classified as known human carcinogens (Carc. 1A). They are also all classified as causing damage to organs through prolonged or repeated exposure (STOT RE 1). The hazard statement for the latter classification (H372**, see table below) does not specify the route as the classification was translated from Directive 67/548/EC and the necessary information was not available from the documentation. As explained in section 7.3, inhalation of asbestos fibres is an established cause for lung fibrosis (asbestosis) and various non-malignant conditions of visceral and parietal pleura.

Table 1. EU classification: Summary of asbestos fibres as defined by Article 2 of Directive 2009/148/EC

Group entry Index No	Group entry ID	EC/List No	CAS No*	Annex VI of CLP hazard class and category	Hazard statement code
650-013-00-6	Asbestos, chrysotile	601-650-3	12001-29-5	Carc. 1A STOT RE 1	H350 H372 **
650-013-00-6	Asbestos, actinolite	616-471-6	77536-66-4	Carc. 1A STOT RE 1	H350 H372 **
650-013-00-6	Asbestos, amosite	601-801-3	12172-73-5	Carc. 1A STOT RE 1	H350 H372 **
650-013-00-6	Asbestos, anthophyllite	616-472-1	77536-67-5	Carc. 1A STOT RE 1	H350 H372 **
650-013-00-6	Asbestos, crocidolite	601-649-8	12001-28-4	Carc. 1A STOT RE 1	H350 H372 **
	Asbestos, tremolite	616-473-7	77536-68-6	Carc. 1A STOT RE 1	H350 H372 **

*The Annex VI entry only refers to "asbestos", but the CAS Nrs listed are consistent with the six asbestos fibre types. To be noted that chrysotile has two CAS Nrs in Annex VI, 12001-29-5 (used above) and 132207-32-0.

** the ** in the hazard statement code H372 ** refers to the fact that the route of exposure is not defined due to translating the information from the documentation available under the old legislation (see text before table)

3. Chemical Agent and Scope of Legislation - Regulated uses of asbestos in the EU

3.1 Regulatory history of prevention of asbestos hazards at Community level

As explained in Chapter 1, asbestos is the generic commercial designation for six naturally occurring silicate mineral fibres. As further described in Chapter 7, the knowledge concerning the hazardous properties of these different asbestos fibres as well as their past different industrial applications (Chapter 5) is extensive today. Due to the long latency time between exposure and adverse health effects, the knowledge on hazardous properties has accrued over decades following early case reports before World War II, more systematic observations in heavily exposed working populations since 1950s and 1960s and more recently has focused on evaluation of health risks linked to lower and lower exposure levels. Consequently, several regulatory actions to prevent these hazards have been introduced at Community level, gradually moving to more and more stringent measures concerning the following:

- Restricting placing on the market and use of asbestos fibres or products containing them
- Occupational Exposure Limits
- Handling of asbestos containing products already in place in buildings, ships, vehicles etc.

This regulatory history is summarised below. The placing on the market and use of asbestos has now reached in practice a complete ban with only one specific use of chrysotile at two industrial sites still allowed until 2025 with the other site no longer having worker exposure. It is, however, noteworthy that due to the large amount of previously used asbestos products still in place in Europe, the preventive actions related the two last bullets above will remain a priority for many years to come.

In addition to exposure resulting from past use of asbestos in commercial products, occupational exposure to asbestos may also occur from handling of natural soil and rock material containing asbestos (see section 5.3.4), for instance in mining or construction industries. Consequently, prevention of asbestos hazards is an issue also in sector specific legislation. It is, however, beyond the scope if this section to describe all those legal obligations.

Placing on the market and use

Apart from the most recent ones, the restrictions concerning new use of asbestos-containing products were introduced under the umbrella of Council Directive 76/769/EEC[3] of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. In the below text describing the further amendments, the reference to Nth amendment of that umbrella Directive in the official title of each Directive is no longer repeated.

Council Directive 83/478/EEC[4] specified that the crocidolite asbestos fibre and products containing it may, with three possible exceptions (granted by the Member State), no

[3] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31976L0769

[4] https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:31983L0478

longer be placed on the market and used; whereas this same Directive established obligatory labelling provisions for all products containing asbestos fibres.

Council Directive 85/610/EEC[5] specified that (any type of) asbestos fibres can no longer be placed on the market and used in toys, materials and preparations applied by spraying, retail products in powder form, smoking accessories, catalytic heaters, paints and varnishes.

Commission Directive 91/659/EEC[6] specified that all of the amphibole type of asbestos fibres and products containing them may no longer be placed on the market and used; whereas this same directive specified that the chrysotile type of asbestos fibre and products containing it may no longer be placed on the market and used for fourteen categories of products (including those already specified by Directive 85/610/EEC).

Commission Directive 1999/77/EC[7] specified that the placing on the market and use of chrysotile asbestos and of products containing this fibre added intentionally shall be prohibited, except for one specific use (use of diaphragms containing chrysotile fibres for existing electrolysis installations) for which Member States could exempt the placing on the market until they reach the end of their service life, or until suitable asbestos-free substitutes become available, whichever is the sooner.

The above restrictions were then incorporated in the Annex XVII (Restrictions) of the REACH Regulation (EC) 1907/2006[8], which prohibited manufacture, placing on the market and use of asbestos fibres and of articles and mixtures containing these fibres added intentionally, except for the one derogation concerning chrysotile asbestos mentioned in the previous paragraph.

Commission Regulation 2016/1005[9] amended Annex XVII of the REACH regulation by specifying that the derogation concerning chrysotile asbestos use in existing electrolysis installations would apply only until 1 July 2025. The Regulation noted that out of five electrolysis installations in relation to which Member States reported in 2011 that they had granted exemptions, only two remained in operation and in one of them there was no longer worker exposure.

Occupational Exposure Limit development

Council Directive 80/1107/EEC[10] of 27 November 1980 on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work laid down certain provisions which have to be taken into account for this protection. It also provided for the laying down in individual Directives of limit values and specific requirements for those agents listed in Annex I, which included asbestos, but did not yet set such limit values. As above, the reference to the original Directive or its amendment is not repeated in the official titles of the below later Directives.

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[5] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.1985.375.01.0001.01.ENG&toc=OJ:L:1985:375:TOC

[6] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31991L0659

[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31999L0077

[8] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32006R1907

[9] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32016R1005

[10] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex:31980L1107

Council Directive 83/477/EEC[11] on the protection of workers from the risks related to exposure to asbestos at work set the following limit values (8-hour reference period):

a) non-crocidolite asbestos: 1.0 fibres/cm^3,

b) crocidolite asbestos: 0.5 fibres/cm^3,

c) mixtures containing both crocidolite and non-crocidolite asbestos: level calculated on the basis of the limit values laid down in (a) and (b), taking into account the proportions of crocidolite and other asbestos types in the mixture

Council Directive 91/382/EEC[12] modified the limit values (8-hour reference period) as follows:

a) chrysotile asbestos: 0.6 fibres/cm^3,

b) other forms of asbestos fibres, either alone or in mixtures, including mixtures containing chrysotile: 0.3 fibres/cm^3

Directive 2003/18/EC[13] of the EP and Council modified the limit value as follows:

a) Employers shall ensure that no worker is exposed to an airborne concentration of asbestos in excess of 0.1 fibres/cm^3 as an eight-hour time-weighted average (TWA)

Directive 2009/148/EC[2] of the EP and Council of 30 November 2009, while introducing a number of preventive measures for asbestos work, kept the limit value unchanged, i.e. 0.1 fibres/cm^3 as an eight-hour time-weighted average (TWA) for all asbestos types.

As regards the analytical monitoring methods, Directive 83/477 referred to optical microscopy and fibres longer than 5 µm and with a length/breadth ratio of greater than 3:1 and further described the principles of the methodology in its Annex I and called for establishment of a single method to be used for measurement of asbestos-in-air concentration at Community level. Directive 91/382 did not amend the sections of Directive 83/477 concerning the analytical methodology but stipulated that the Council will review the technical progress by 31 December 1995. Directives 2003/18 and 2009/148 refer to phase-contrast microscopy method of WHO (1997) or equivalent and a fibre definition of longer than 5 µm, breadth not greater than 3 µm and with a length/breadth ratio of greater than 3:1.

Handling of asbestos already in place

The above Community legislation concerning measures related to handling of asbestos products has gradually evolved from the measures relevant at the time when asbestos products were still manufactured and used to the more recent situation of safe handling and dismantling of asbestos products already in place. Directive 2009/148/EC[2] of EP and Council stipulates that the exposure of workers to dust arising from asbestos or materials containing asbestos at the place of work must be reduced to a minimum and in any case below the limit value laid down in Article 8 of that Directive. The Directive sets a number of measures to ensure the safe handling of asbestos at the place of work. These include, among others,

- a notification system to authorities of the Member State before starting any asbestos work,

[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31983L0477

[12] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:31991L0382

[13] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32003L0018

- before beginning demolition or maintenance work, to take all necessary steps to identify presumed asbestos-containing materials and apply the provisions of the Directive if there is any doubt about the presence of asbestos in a material or construction
- numerous measures to prevent the exposure of the workers performing the work
- use of warning signs
- measures to prevent asbestos dust or asbestos products from spreading outside the premises or site of action
- limiting the access to the work site
- a number of measures concerning planning of work before starting demolition work or work on removing asbestos and/or asbestos-containing products
- regular training for all workers who are, or are likely to be, exposed to dust from asbestos or materials containing asbestos
- before carrying out demolition or asbestos removal work, firms must provide evidence of their ability in this field
- rights of the workers
- aspects related to their health surveillance of the workers involved in asbestos work

Further details on the practical implementation of these measures at EU and national level are described in section 5.3.

3.2 REACH Registrations

As explained in section 3.1, the use of asbestos is already banned in the EU and there are no REACH registrations for any of the six asbestos fibre types.

3.3 Authorised uses under Annex XIV of REACH

Not applicable

3.4 Restricted uses under Annex XVII of REACH

As described in section 3.1. the restrictions adopted before REACH, were then incorporated in the Annex XVII (Restrictions) of the REACH Regulation (EC) 1907/2006, which prohibited manufacture, placing on the market and use of asbestos fibres and of articles and mixtures containing these fibres added intentionally. The Annex XVII of REACH was amended by Commission Regulation 2016/1005 to put an end date to the only existing derogation for chrysotile asbestos use.

3.5 Other related chemical legislation

Asbestos is already banned in the EU. Therefore, there are no allowed uses under Plant Protection Products Regulation (EC) 1107/2009, Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC (respectively), or Biocidal Products Regulation (EU) 528/2012. Under Regulation (EC) 1223/2009 of EP and Council on cosmetic products, asbestos is listed in Annex II as a substance prohibited in cosmetic products.

4. Existing Occupational Exposure Limits

Directive 2009/148/EC[2], the most recent applicable to exposure to asbestos at work, established EU binding level for fibres with a length of more than 5 micrometres, a

breadth of less than 3 micrometres and a length/breadth ratio (aspect ratio) greater than 3:1.

In various EU Member states lower OEL values and additional short-term exposure limits (STEL) are available. Those are presented in **Error! Reference source not found.** but the list should not be considered as exhaustive.

Table 2. Existing Occupational Exposure Limits (OELs) for Asbestos fibres

Country/ Organisation	Asbestos TWA -8 hrs Fibres/cm³	Asbestos Short term Fibres/cm³	Comments
Austria	0.1		
Belgium	0.1		
Denmark	0.1	0.2	
European Union	0.1		
Finland	0.01 (1) (3) 0.1 (1) (3)		(1) asbestos demolition work, (2) other types of work (e.g. mining) (3) BOEL
France	0.01		
Germany (AGS)	0.1 (1)(2) 0.01 (3)	0.8 (2)(4)	(1) BOEL (2)Workplace exposure concentration corresponding to the proposed tolerable cancer risk. (see background document: Germany AGS) (3) Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk. (see background document: Germany AGS (4) 15 minutes average value
Hungary	0.1		
Ireland	0.1		
Italy	0.1		
Latvia	0.1		
Norway	0.1		
Spain	0.1		
Sweden	0.1		
Switzerland	0.01		
The Netherlands	0.002		

Country/ Organisation	Asbestos TWA -8 hrs Fibres/cm³	Asbestos Short term Fibres/cm³	Comments
United Kingdom	0.1	0.6 (10 mins)	All fibrous forms. LV of 0.1 fibres per cm³ is for a 4 hour reference period (1997 WHO phase contrast optical fibre counting method). An 'Approved Code of Practice' (L143, ISBN 0 7176 6206 3) requires action to be taken when short-term exposure exceeds 0.6 fibres per cm³ (10 minutes reference period). UK regulations and codes of practice are summarised at http://www.hse.gov.uk/asbestos/regulations.htm
USA - NIOSH	0.1 (1)		(1) in a 400 litre air sample, 100 min-TWA
US-NIOSH	0.1		

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

As reviewed by IARC (2012) asbestos minerals are widespread in the environment and are found in many areas where the original rock mass has undergone metamorphism (ATSDR, 2001; USGS, 2001). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada (Virta, 2006). They may occur in large natural deposits or as contaminants in other minerals; e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc. The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth's crust and their chemical composition reflects the environment in which they form (Virta, 2006). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such as the Coalinga chrysotile deposits in California, USA, are reported to contain 50% or more (USGS, 2001; Virta, 2006).

Despite the natural occurrence of asbestos minerals in many parts of the world, including Europe, by far the most important source of human exposure has so far been from activities linked to the industrial use of asbestos, mined or quarried from these natural deposits. In the EU such exposure first occurred in production and use of asbestos products but following the banning of asbestos, it is now more common in unsafe handling of asbestos products in place, especially during building maintenance, renovation and demolition activities and consequent waste disposal. There may also be exposure when using asbestos-containing articles put on the market before the ban, as well as in relation to working or residing in buildings containing deteriorated asbestos materials.

However, it is also noteworthy that despite the ban concerning manufacture and import, due to the natural occurrence of asbestos minerals, occupational (and environmental) exposure continues to be possible through activities related to processing of the bedrock and soil. In the occupational setting exposure may occur in activities such as mining and quarrying and their relevant downstream activities when the activities or downstream processing relate to materials in/from areas where asbestos minerals naturally occur (See section 5.3).

5.2 Production and Use Information

As explained in section 3.1, the use of asbestos is already prohibited in the EU. However, much of the previously used asbestos products are still in place. This applies especially in settings which have a long lifespan, such as buildings. The asbestos in place poses a challenge for maintenance, renovation and demolition activities for many years to come and consequently the below sections describe the past use of asbestos focusing on those relevant for the current workplaces.

Historically, there is anecdotal evidence that before the industrial use, asbestos use had begun already 4500 years ago, e.g. to strengthen clay pottery in Finland and later in crematory shrouds, lamp wicks and incombustible napkins and tablecloths in a number of cultures (see Virta (2006) for summary).

Asbestos fibres have properties such as high tensile strength, flexibility and physical and chemical durability. The insulating, resilient and reinforcing properties made them widely exploited. The industrial uses started to grow in the late 1800s and grew rapidly during the first half of 1900s (Virta, 2006). In most European countries the per capita use of asbestos peaked either in the 1960s or 1970s. The first national ban of the main asbestos use, i.e. asbestos cement product use in construction, was introduced in Sweden in 1976 (Burdorf et al., 2005). The first total bans at national level were introduced in the 1980s (IARC, 2012). Globally the peak use for asbestos was achieved around 1977, when about 25 countries were producing a total of almost 4.8 million tonnes of asbestos per year and about 85 countries were manufacturing asbestos products (Virta, 2006).

Before the ban, the use of asbestos was widely spread in Western societies. For example in Finland a survey that was limited to building materials identified 250 product names of asbestos-containing materials during the 1900s (Riala et al., 1989). The main uses were thermal laggings, sprayed asbestos and asbestos cement products like flat or corrugated panels. Asbestos sheets, blankets, ropes, yarns were also used. Even flooring materials (vinyl asbestos flooring tiles, magnesia floors, vinyl cushion floorings), bitumen felts and adhesives, putties, insulating boards, plasters for ceramic tiles and some paints contained asbestos. There were numerous uses also outside the construction sector, e.g. in shipbuilding, car industry (e.g. brake linings and clutch plates), and manufacture of electrical appliances for consumers (e.g. toasters, hair dryers, irons) and other industries. According to Virta (2006), by 1958, the asbestos producers' inventory reported about 3000 applications. NTP (2016) estimated the same number of industrial applications and product names during the peak use in 1960s and 1970s. BAuA (2014) estimated more than 3500 asbestos containing products having been used in Germany.

Certain fibre characteristics, such as length and strength, were used to determine the most appropriate application. For example, longer fibres tended to be used in the production of textiles, electrical insulation, and filters; medium-length fibres were used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and, short fibres were used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts (NTP, 2005).

Most of the asbestos used after the late 1800s was chrysotile and the most commonly used amphibole asbestos types were amosite and crocidolite (Virta, 2006; DECOS, 2010). More than 90% of all asbestos mined historically was chrysotile (NIOSH 2011). The share of chrysotile of all asbestos use in Europe is not known. In US it is reported that 98% of the imported asbestos in 1900-2003 was chrysotile and that most of the domestic (relatively small) mines produced chrysotile. Asbestos cement products are estimated to have accounted for 66% of world consumption during the peak use years and chrysotile was the main asbestos type used in that production (Virta, 2006). In Germany asbestos cement products were estimated to have accounted for 75% of all asbestos used (BAuA, 2014) and in Spain for 77% of all asbestos used in 1947-85 (CNSST, 2020).

5.2.1 General population

Even though the use of asbestos has been banned in Europe, people are still being exposed to asbestos because it is still present in many settings. Incidental exposure may take place in the context of e.g. building renovations and maintenance or through naturally occurring asbestos present in the environment.

The ambient asbestos concentrations in the 1980' were 0.0001-0.001 fibres/ cm^3 (100 to 1,000 fibres/m^3) in rural areas in Netherlands. In urban areas, the outdoor atmospheric background concentrations were between 0.001-0.016 fibres/cm^3 (1,000 and 16,000 fibres/m^3), but up to 0.08 fibres/ cm^3 (80,000 fibres/m^3) near of busy roads and tunnels according DECOS report for asbestos (DECOS, 2010). Asbestos was previously used in brakes of the cars and trucks and asbestos cement waste was used for paving roads and yards.

Similar ambient asbestos concentrations were measured in 1987 in Germany; being below 0.002 fibres/cm^3 in urban area and below 0.007 fibres/cm^3 near the places where asbestos containing activities were performed. In rural area the ambient asbestos concentration was below 0.0004 fibres/cm^3 (DGUV, 2013).

5.3 Occupational exposure

Unless indicated otherwise, the workplace air monitoring results referred to in this Section have been conducted with WHO phase contrast microscopy method or equivalent (see Section 6).

5.3.1 Principles for safe handling of asbestos

Directive 2009/148/EC sets a number of measures to ensure the safe handling of asbestos at the place of work. The preventive principles and main practical provisions defined by the Directive are described in the section 3.1. The more detailed implementation of these measures is described below. In the Directive 2009/148/EC, the most important measures are the **notification to the authorities**, **the risk assessment** and **the work plan as well as training and protection of the workers involved**. In addition, employees must be given the opportunity to have a **medical examination**. Moreover, before starting with demolition and refurbishment work the companies should give proof of their expertise and, if the national legislation requires, be in possession of an official licence for working with asbestos. It is noted that a cancer follow-up study of UK asbestos removal workers indicated that more than half of the workers were short term workers spending less than 2 years in the trade (Frost et al., 2008). This is a particular challenge for training and ensuring compliance with best practices.

More detailed practical guidelines for the information and training of workers involved with asbestos removal or maintenance work were prepared by EU in 2012 (EU, 2012). The Guidance includes examples of what kind of measures should be applied when there is a possibility to be exposed to asbestos. National regulations and practices may go beyond these and there are many activity specific guidance and technical specifications for asbestos work, for example in the UK (HSE, 2013), Germany (Baua, 2020a, DGUV, 2020), Baua 2020b), Spain (INSHT), Finland (Linnainmaa et al 2019 and Kahkonen et al 2019) and France (various guides INRS (2012), INRS (2016), INRS (2019a) and standards NF X 46-010, NF X 46-020, NF X 46-102, NF F01-020, NF X 46-101, NF L 80-001 and NF X 46-100).

According to the EU Practical Guidelines (EU, 2012), the safe asbestos removal work and safe handling of asbestos containing material should be done in enclosures with efficient dust removal installations and equipment (air filter systems). The enclosure work area can be entered only via personnel locks. Normally a two-chamber lock is sufficient for work on asbestos-cement products, one for cleaning the protective clothing when leaving

the working area, and a second one for changing the clothing. For preventing dust and fibres to spread, the negative pressure between enclosure and surrounding area should be sufficient and at least 20 Pascal if the fibre concentration is high. Workers should have regular training to the work and also to appropriate use of personal protection equipment (PPE), which should be available for free. For respiratory protection, the "face-fit" of the respiratory protection equipment (RPE) needs to be checked. Critical issues for achieving the safe use conditions are an effective ventilation, efficient high efficiency particulate air (HEPA) filters in air handling units and efficient use of PPE for workers. The performance of the asbestos enclosures, air handling units and respiratory equipment needs to be controlled and confirmed regularly before and during the work (Linnainmaa et al., 2019).

5.3.2 General occupational exposure levels divided by industrial sectors and jobs

The economic activity sectors in European Union where exposure to asbestos is most common are construction, mining and personal and household services (household is an employer) according to the CAREX (CARcinogen EXposure) database where exposure data are from early 1990s (FIOH, 2020b). The total number of occupationally exposed workers in Europe has been over 1 200 000 during the period 1990-1993. Despite the total ban of asbestos approximately 61000 employees were still exposed to asbestos during demolition and reconstruction work in Germany in 2004 (Hagemeyer et al., 2006). In Finland, there were around 1300 workers who were exposed to asbestos in 2014 according to the ASA registry (FIOH, 2020a). Epidemiological studies also demonstrate that over the decades there has been a shift in the exposed population from heavily exposed e.g. asbestos product manufacturing and shipyard workers to e.g. construction-related settings (see section 7.7.1 and Appendix 3).

Occupational exposure can occur when residential and other buildings are renovated or demolished or undergoing maintenance activities, when soil purification activities are undertaken, and when items such as ships, drilling platforms and machines that have asbestos insulation are repaired. The trend in occupational inhalation exposure for asbestos as seen in Table 3 has started to decline already from 1950 in Germany because of improvements in occupational hygiene regulations and restriction of using asbestos e.g. spraying of asbestos was forbidden in 1979 (Hagemeyer et al., 2006).

Table 3. Examples of asbestos fibre concentrations in the air (90th percentiles, fibres/cm^3) of different workplaces in Germany (Hagemeyer et al., 2006)

Work area		1950-54[a]	1970-74	1980	1990
Textile industries	FRG	100	10	3.8	0.9
	GDR	100	12	6.2	2.2
Production of gaskets	FRG	60	6.6	4.7	0.7
	GDR	60	8.0	7.8	1.6
Production of cement	FRG	200	11	1.1	0.3
	GDR	200	13	1.9	0.7
Production of brake pads	FRG	150	9.1	1.4	0.7
	GDR	150	11	2.4	1.6
Insulation work	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated.

FDR Federal Republic of Germany, GDR German Democratic Republic

There are several databases and reviews for asbestos exposure globally. However, only a few of them describes recent occupational exposures. During asbestos work, occupational exposure measurements are often performed since the Directive 2009/148/EC obliges employers to assess risks and prevent exposure to asbestos. However, this information generally remains with the company and it is not publicly accessible, even though it would be relevant information in the context of exposure and risk assessment for asbestos. To be noted that earlier the measurements were mainly performed with phase-contrast optical microscopy (PCM) but nowadays electron microscopy (TEM or SEM) is considered more accurate to characterize occupational exposure to asbestos (see Chapter 6). There is no generic simple correlation between concentrations measured by the two methods as factors like fibre type, type of asbestos-containing material and type of asbestos removal method influence (Eypert-Blaison et al., 2018b).

A job-exposure-matrix (JEM) was developed on historical asbestos exposure across all relevant occupations in the Dutch industry during the period 1945–1994 (Swuste et al., 2008). There is a decreasing trend in asbestos exposure in all exposure groups and handling of raw asbestos, asbestos containing products and waste have created highest exposures in asbestos-cement industry in the Netherlands during 1970-1990 (Table 4). A similar AsbJEM was created in Australia (van Oyen et al., 2015) and it provides quantified estimates of asbestos exposure for Australian jobs since 1945 to >2004. The highest asbestos exposures in Australia have been in asbestos manufacturing, shipyard and insulation industry. It is, however, noted that such JEMs may combine exposures over several decades (AsbJEM) thus including also exposure settings that are no longer allowed in the EU.

Table 4. Arithmetic and geometric mean exposures to airborne asbestos (fibres/cm^3) in different exposure groups in the asbestos-cement industry in The Netherlands during the period 1975-1989 (the time period has been modified by leaving out period 1970-1974)(Swuste et al., 2008)

	1975-1979				1980-1984				1985-1989			
	n	AM	GM	GSD	n	AM	GM	GSD	n	AM	GM	GSD
Handling raw asbestos	10	1.19	0.97	1.95	10	0.26	0.22	1.77	10	0.22	0.19	1.65
Manufacturing	10	0.89	0.67	2.09	10	0.12	0.10	1.68	10	0.09	0.06	2.87
Handling products	28	0.73	0.51	2.25	26	0.26	0.20	2.12	17	0.21	0.15	2.30
Transportation	3	0.23	0.21	1.89	7	0.09	0.08	1.57	5	0.04	0.03	2.85
Waste management	3	1.55	0.98	3.11	5	0.34	0.30	1.69	5	0.20	0.18	1.74
Supervision and inspection	3	0.23	0.22	1.43	n/a				n/a			

n number of directly available asbestos measurements, AM arithmetic mean, GM geometric mean, GSD geometric standard deviation, n/a not available

A quantitative job-exposure matrix (SYN-JEM) for five lung carcinogens (asbestos being one of the carcinogens) was developed based on statistical modelling of large quantities of personal measurements from 1970s until 2009 from Europe and Canada (Peters et al.,

2016). Time-, job-, and region-specific exposure levels for asbestos were estimated based on 27 958 measurements which had job code available and the sampling duration was between 60 and 600 min. Majority of the measurements are from national exposure databases from Germany (MEGA), the UK (NEDB), France (COLCHIC) and Norway (EXPO). Also industry-specific databases and measurements from different institutes were collected. For asbestos measurements, PCM was used in >95% of samples, except for the German asbestos measurements where >99% were analysed with EM. Geometric mean (GM) of airborne asbestos for low exposed jobs has decreased from 0.061 fibres/cm^3 to 0.004 fibres/cm^3 and for high exposed jobs from 0.074 fibres/ cm^3 to 0.005 fibres/cm^3 between 1980 and 2000. The highest exposed jobs in 2000 were in heating, in ventilation, and in refrigeration engineering (technicians; GM 0.029 fibres/cm^3), in building sector (insulators; GM 0.016 fibres/cm^3), in ship construction (joiners; GM 0.016 fibres/cm^3 and metal shipwrights; GMs 0.012 fibres/cm^3), and among chemistry technicians (GM 0.012 fibres/cm^3).

In Finland, the average exposure level for asbestos has also decreased over the years being 0.67 fibres/cm^3 in 1950, 0.49 fibres/cm^3 in 1970, and after the prohibition of using asbestos major decrease in the average exposure level occurred being 0.06 fibres/cm^3 in 1990 and 0.04 fibres/cm^3 in 2008. It was predicted that 2020 the average exposure level for asbestos will be 0.03 fibres/cm^3 in Finland (Kauppinen et al., 2013).

According to the Finnish FINJEM database during the period of 2004 to 2015, the most asbestos exposed sectors and jobs were building construction sector (assistant workers, pipe insulations), and repairs of engines and machines, and mining work (FIOH, 2020a). Other occupations that have caused exposure to asbestos are electricians and tele operators, painters (paints and varnishes), and brick-, tile- and floor layers. However, the exposure levels were low compared to the 0.1 fibres/cm^3 limit value, mainly less than 10% of the limit value.

During the period 2004 to 2015 the occupational limit value for asbestos, 0.1 fibres/cm^3 was exceeded very rarely in situations other than inside the enclosed environment where asbestos removal work took place. In these situations, airborne concentrations could reach levels over 10 fibres/cm^3. Also, from the outlet air of these enclosed spaces and sometimes even inside respiratory protective equipment high exposures were measured. However, when all the available asbestos measurements are considered, most of the asbestos concentrations were below the detection limit (0.01 fibres/cm^3) (FIOH, 2020a).

The Finnish Institute for Occupational Health carried out asbestos measurements in Finnish workplaces between 2016–2019 (personal sampling; N=187), the average level was 0.13 fibres/cm^3, median 0.005 fibres/cm^3, 95th percentile 0.57 fibres/cm^3, and range below 0.01 to 7.6 fibres/cm^3 (data extracted from the FIOH Register of Occupational Hygiene Measurements). A majority of the measurements, and all those exceeding the current limit value, were carried out in mining and processing of rock materials. The current limit value of 0.1 fibres/cm^3 was exceeded in 13% (24/187) of the measurements. However, sampling was carried out outside personal protective equipment (respirators), which were used in 15 of the 24 cases where the current limit value was exceeded. The measurements were performed with SEM and counting fibres thicker than 0.05 µm.

In Spain in 2017, the concentration of 0.1 fibres/cm^3 was exceeded in 0.1% of samples from asbestos worksites (MTMSS). It is to be noted that the exposure period in such work is limited to maximum of 4 hours per day in Spain, and it is not clear if the reported concentrations are converted to 8 hour TWA values taking into account the period of day when there was no exposure. The measurements were performed with PCM.

5.3.3 Exposures during handling of asbestos containing products

As explained, around 3500 construction products that contained asbestos had been used in Germany in renovations and new buildings before the restriction on asbestos came into force in 1993. The number of currently registered enterprises involved in working tasks with asbestos-containing materials in Germany in 2017 were about 20 455. Yet despite the registration and licensing provisions, it is not always known in many actual worksites that various construction materials such as plasters, glues, fillers, paints etc can contain asbestos. For this reason, it is estimated that in Germany around 750 000 workers, representing numerous construction related occupations, may be exposed to various levels of asbestos during renovation works in buildings with asbestos containing materials (BAuA, 2020c). Further guidance to ensure avoiding such exposures has recently been published (BAUA, 2020b). The situation is likely to be similar in many other EU countries.

In France, 265 measurements (both with PCM and TEM) from 29 construction sites where workers were handling asbestos containing materials (ACM) were exploited during 2009 (Eypert-Blaison et al., 2018b). Data were sorted by the ACM type and removal technique. Asbestos containing plasters, sprayed-applied asbestos and interior and exterior paints and coatings generated very high exposure levels (≥0.1 fibres/cm^3) and some removal techniques (e.g. scrabing with spatula, grinding /sanding, chiseling/chipping, hydroblasting) generated considerable levels of dust with all ACM. It was noticed in the study that RPE selected based on PCM analysis are not always efficient enough when the airborne concentrations analysed with EM were considered; i.e. the exposure levels corrected for the assigned protection factor of the used RPE were still above the OEL. The finishing sector workers in building work (such as plumbers, electricians etc.) were found to be at risk of developing asbestos related disease. No generic simple correlation between the measurements with the two analytical monitoring methods was found but overall PCM underestimated asbestos exposure compared to the TEM.

INRS (2019b) reported results from 76 681 regulatory measurements between 2012-2018 coming mostly from worksites with either removal of asbestos containing material or disposal and handling of asbestos waste. The fibre concentrations in air represent those outside the personal protective equipment and were analysed with TEM. The mean and median levels were 0.4 fibres/cm^3 and 0.025 fibres/cm^3, respectively, with levels ranging from < 0.00001 to 200 fibres/cm^3. In the above-mentioned study of Eypert-Blaison et al. (2018b), the arithmetic mean was 0.09 fibres/cm^3 and maximum 23 fibres/cm3 when considering WHO fibres not adjusted for the RPE protection factor. Those results are further described in the context of section 9.1.2 and in Appendix 4.

Further to the current task of reviewing the OEL, other considerations to ensure the worker safety in handling of asbestos already in place, stemming from the above observations, are presented in section 9.4.

5.3.4 Other asbestos exposures

Asbestos fibres are naturally occurring minerals. As explained in section 5.1, they are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism. Therefore, even if intentional commercial uses are banned and handling of past commercially used products is regulated, exposure is possible when handling other minerals (e.g. talc, dolomite and olivine) where asbestos occurs as an impurity. Some of these minerals are in granular or powder form and they relatively easily aerosolise during handling. Therefore, attention is needed in such industries. In experimental studies mixtures of asbestos in dry soils with asbestos content as low as 0.001% were able to produce airborne respirable asbestos concentrations greater than 0.1 fibres/cm^3 in dust clouds where the overall respirable dust concentrations were less than 5 mg/m^3 (Addison et al., 1988).

However, occurrence of asbestos as an impurity is not limited to the above granular or powder type minerals. In a Finnish geological survey fibrous minerals, including asbestos (e.g. tremolite and actinolite), were detected in many limestone mines and rock aggregate quarries (Junttila et al., 1994). More recently, airborne asbestos concentrations of 10-50% of the current national OEL (0.1 fibres/cm^3) have been measured in some mines in Finland (FIOH, 2020a). Compared to asbestos removal work, the awareness of potential asbestos-related risks is lower in the mining industry and related activities; consequently risk management guidelines have been published e.g. in Finland (Kahkonen et al., 2019) and in Germany (AGS, 2013). Depending on the mineralogical characteristics of the bedrock and soil, situations similar to the Finnish example may occur also in other countries.

5.4 Routes of exposure and uptake

Inhalation is the route for exposure relevant in occupational setting and pertinent for deriving an OEL. Those exposures are described above. As described in section 7.1. there is no evidence of human exposure via the dermal route but oral exposure via drinking water may occur in the general population. However, routes of exposure other than inhalation are not further described for the occupational setting.

6. Monitoring Exposure

6.1 External exposure

At present, the number and size distribution of fibres in a sample can only be determined by direct microscopic examination. This may be performed using either light or electron microscopy. However, using light microscope only fibres thicker than 0.2 um can be determined. EM can detect also thinner fibres. As described in sections 7.7.1 and 9.1.2 there are indications that the carcinogenicity increases by increasing fibre length and decreasing fibre width, which emphasises the importance of counting also the thinner fibres. For all methods the presence of non-fibrous dust particles (in particular in high concentrations) complicates the counting and identification of fibres. These may necessitate lowering sampling volumes to avoid the loading of particles in the filter and the consequent increase of the methods limit of detection.

The ANSES Expert appraisal for establishing Occupational Exposure Limit for asbestos fibres (Afsset, 2009b) includes an overview of techniques and analytical methods that can be to determine the concentration of asbestos fibres in air. The table from ANSES report is reproduced (with slight modifications) in **Error! Reference source not found.** below.

Below the table, one actual method for each of the techniques appearing on the table has been described in further detail. These selected actual methods have been included giving preference to analytical methods used or recommended by OSH bodies to be used to comply with a national OEL for asbestos

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Table 5. Overview of techniques and methods for monitoring of asbestos fibres in air with phase contrast microscopy (PCM), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) (adapted from Afsset (2009b))

Type of microscope	Sampling and analysis protocol	Preparation of sample	Magnification for counting	Fibre counting criterion			Minimum measurable diameter (µm)	Fibre identification method	Type of information
				L/d	L (µm)	d (µm)			
PCM	XP X 43-269: 2002 (obsoleted) (AFNOR, 2002)	Direct [4]	400-500	≥3	>5	<3	0.2	-	Numerical concentration
	WHO: 1997 (WHO, 1997)								
	ISO 8672: 2014 (ISO, 2014)								
	NIOSH 7400 method A: 2019 (NIOSH 2019) (1)								

Type of microscope	Sampling and analysis protocol	Preparation of sample	Magnification for counting	Fibre counting criterion			Minimum measurable diameter (µm)	Fibre identification method	Type of information
				L/d	L (µm)	d (µm)			
	HSG 248 (Annex 1)(HSE, 2005)								
	IRSST 243: 1995 (IRSST, 1991)								
	MTA/MA-051/A04 (INSHT, 2004)								
SEM	ISO 14966: 2019 (ISO, 2019b)	Direct [4]	2000	≥3	>5	<3	0.2	Morphology elementary composition via EDXA (2)	Numerical concentration Size Type
	VDI 3492:2013-06		2000-2500						
	BGI-213-546(BGI, 2013)								

Type of microscope	Sampling and analysis protocol	Preparation of sample	Magnification for counting	Fibre counting criterion			Minimum measurable diameter (µm)	Fibre identification method	Type of information
				L/d	L (µm)	d (µm)			
TEM	NIOSH 7402 (NIOSH, 1994)	Direct(4)	10000	≥3	>5		0.25		
TEM	ISO 10312: 2019 (ISO, 2019a)		20000	≥5	>0.5		0.01	Morphology elementary composition via EDXA (2) crystallography via SAED (3)	
			5000	≥3	>5		0.03		
	ISO 13794: 2019 (ISO, 2019a)	Indirect(4)	20000	≥5	>0.5	<3	0.01		
			5000	≥3	>5		0.03		
	NFX 43-050: 1996 (AFNOR, 1996)		10000	≥3	>5		0.01		
			20000-30000		>0.5				

(1) The NIOSH 7400 method does not impose any counting criteria on the diameter
(2) EDXA: Energy Dispersive X-ray Analysis
(3) SAED: Selected Area Electron Diffraction
(4) Direct and indirect sample preparation methods are further explained in section 6.1.2.1 and 6.1.2.2 below
(5) Depending on the magnification, SEM methods can detect fibres as thin as about 0.05 µm. However, in some SEM standards fibres thinner than 0.2 µm are not included in the fibres to be counted.

The French standard NF X43-269 gives an overview of the microscopy techniques available to measure the number of asbestos fibres in air and provides advice on which technique is more adequate to the case depending on the objective of the measurement and the type of fibres suspected to be present.

6.1.1 WHO 1997 phase contrast microscopy method

The asbestos directive 2009/148/EC states *that "fibre counting shall be carried out wherever possible by phase-contrast microscope (PCM) in accordance with the method recommended in 1997 by the World Health Organization (WHO) or any other method giving equivalent results"*

In the WHO method, a sample is collected by drawing a known volume of air through a membrane filter by means of a sampling pump. The filter is then rendered transparent ("cleared") and mounted on a microscope slide. Fibres on a measured area of the filter are counted visually using phase-contrast optical microscopy (PCM), and the concentration of fibres in the volume of air is calculated using the number of fibres detected on the counted area of the filter, the fraction of the area counted of the total filter area and the air volume filtered.

The limit of quantification slightly varies depending on the laboratory specific parameters, like the fraction of area of the filter counted. The limit of detection is approximately of 13 fibres/mm^{-2} (of filter area) which corresponds to different values on air depending on the laboratory specific parameters as illustrated in the table below

Table 6. Technical characteristics defining the limit of quantification (LOQ) of the WHO 1997 phase contrast microscopy method

Volume of air (L)	Flow rate	Sampling time	LOQ
240	2 l/ min (recommended flow rate)	2 hours	0.02 fibre/cm^3
960	2 l/ min (recommended flow rate)	8 hours	0.005 fibre/cm^3
1920	16 l/ min (maximum acceptable flow rate)	2 hours	0.0025 fibre/cm^3
7680	16 l/ min (maximum acceptable flow rate)	8 hours	0.0006 fibre/cm^3

Limitations: any fibre (regardless of whether it is asbestos or not) is counted because all particles meeting the dimensional counting criteria are taken into account. Chain-like particles may appear fibrous. High levels of non-fibrous dust particles may obscure fibres in the field of view and increase the detection limit. Fibres smaller than 0.2 µm in diameter cannot to be counted, which is a significant limitation of this method.

6.1.2 Electron microscopy

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) methods can detect thinner and shorter fibres than PCM and also fibre type can be identified with additional analysers based on elemental composition and crystal structure. However, the fibre counting accuracy is poorer than for PCM. The latter is a result of the smaller area that can be realistically scanned at a higher magnification. Accuracy is more limited with long (>5 µm) fibres. NIOSH Method 7402, Asbestos by TEM, is used to determine asbestos fibres in the optically visible range and is intended to complement NIOSH Method 7400 (PCM). Examination of a fibre sample by either TEM or SEM allows the detection of much smaller fibres than light microscopy, and so more thorough data can be collected on fibre length and diameter distribution. Of these two methods, TEM has greater sensitivity for small fibres, and is the most common method for measuring asbestos in non-occupational setting like in ambient air or inside schools or residential buildings. SEM is widely used method to quantify the asbestos fibres in Europe, for counting purposes it is mainly used with a magnification of 2000x allowing the quantification of fibres only thicker than 0.2 µm (for measuring dimensions of the identified fibres, higher magnifications are used). Using SEM with a magnification of 6000x fibres of ≥0.05 µm in diameter can be detected. In addition, most modern electron microscopes are equipped with instrumentation that allows determination of the crystalline and elemental composition of the fibre (see below).

Two different procedures are used for preparation of samples for TEM analysis (HEI, 1991). Direct transfer methods retain particles in the same relative position during analysis as they were on the original filter with a minimum of change to the airborne particles. Indirect methods involve dispersing the particulate matter from the original filter into a liquid and capturing the suspended particulates onto intermediate filters that are used to prepare the TEM specimens. By varying the proportion of liquid, one is able to concentrate or dilute the sample analysed. In addition, one is able to remove organic and other unwanted particulate matter by ashing or dissolution, thereby selectively concentrating the asbestos. In dispersing the particles in water, the sample may be gently sonicated. In the process, fibre bundles may be separated into individual fibrils or fibres broken. (ATSDR, 2001)

The electron microscopic methods can be coupled with different analytical techniques that allow the discrimination of different types of asbestos fibres from each other and from other fibres. This can be done via Energy Dispersive X-ray Analysis (EDXA)and/ or Selected Area Electron Diffraction (SAED). The EXDA is based on the elementary analysis of the fibres, the presence of different elements (e.g. Si, Fe, Mg) and the peak height determine the type of asbestos present. The SAED technique consists of observation of the pattern of diffraction spots obtained on the TEM viewing screen from a randomly oriented fibre or particle. Such a pattern indicates that the material is crystalline. The pattern is then recorded and its consistency with known mineral structures is checked.

6.1.2.1 Transmission electron microscopy- Direct sampling preparation

Example NIOSH method 7402 (NIOSH, 1994)

NIOSH 7402 uses transmission electron microscopy (TEM) to qualify and quantify asbestos fibres found in the air. This technique provides complimentary results to fibre counts determined by NIOSH 7400 (PCM) and provides more accurate asbestos fibre counts as non-asbestos particles are identified and excluded. Samples are collected using a 25 mm air monitoring cassette equipped with a 50 mm electrically-conductive cowl and a mixed cellulose ester (MCE) membrane filter. After collection, samples are processed to collapse the filter, creating a non-grainy background for easier fibre counting and identification by transmission electron microscopy. Fibres with a diameter <0.25 µm will not be counted by this method.

The method is designed to be used as a complement of NIOSH method 7400 (asbestos and other fibres by PCM). The quantitative working range is 0.04 to 0.5 fibres/cm^3 for a 1000-L air sample. The LOD depends on sample volume and quantity of interfering dust, and is <0.01 fibres/cm^3 for atmospheres free of interferences.

Interferences: Other amphibole particles that have aspect ratios greater than 3:1 and elemental compositions similar to the asbestos minerals may interfere in the TEM analysis. Some non-amphibole minerals may give electron diffraction patterns similar to amphiboles. High concentrations of background dust interfere with fibre identification.

6.1.2.2 Transmission electron microscopy- Indirect sample preparation

Example NFX 43-050: 1996 method (AFNOR, 1996)

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

The method foresees static sampling, and it explicitly mentions three scenarios (sampling outdoors, sampling on buildings containing asbestos materials and sampling in buildings after asbestos removal).

The limit of detection is dependent on sampling volume and also on the levels of particle dust. A limit of detection of 0.001 fibres/cm^3 can be achieved when levels of airborne dust are around 10 µg/m^3 (e.g. clean rural environment).

Interferences: the method does not distinguish individual asbestiform amphibole fibres from those particles with a longitudinal shape originating from the non-asbestiform amphibole counterpart of the same mineral (cleavage fragments).

6.1.2.3 Scanning electron microscopy

Example ISO 14966 ((ISO, 2019b))

The sample is collected on a gold coated capillary-pore membrane filter. The fibres collected are counted and analysed by means of scanning electron microscopy and energy dispersive X-ray microanalysis. Before analysis, the gold coated filter can be treated in a plasma asher to remove organic particles, to the extent that this is possible

This method permits the detection and identification of asbestos, calcium sulfate and other inorganic fibres having a width of (D) ≥0.2 µm. Fibrous particles with D < 0.2 µm are not taken into account for the calculation of the measuring result because the method here described were intended to be used instead of the phase-contrast optical microscopy method although it would be possible to measure also thinner fibres (>0.05 um) if the full possibilities of SEM would be used, particularly when using field-emission SEM. When fibres below 0.2 µm are counted it is recommended to list them separately from the rest.

A limit of detection of approximately 300 fibres/m^3 (0.0003 fibres/m^3) is obtained if an air volume of 1 m^3 per square centimetre of filter surface area passes through the filter, and an area of 1 mm^2 of the filter area is examined in the SEM. This corresponds to an evaluated sample air volume of 0,01 m^3.

Interferences: high concentrations of dust interfere with the fibre identification. Misinterpretations, particularly for the identification of asbestos fibres are possible,

- if silicate fibres of an elemental composition similar to asbestos are used in work areas;
- if the fibres are contaminated (e. g. for mortar, colours and paints, asbestos cement, magnesium plaster floor and thus result in additional peaks);
- if non-fibrous particles are lying within the direct neighbourhood of fibres (high loading of the sample collection filter, coarse dust particles, chainlike smoke particles, especially welding fumes, tobacco smoke);
- due to non-uniform loading of particles on the filter (as a result of e.g. high air humidity during sampling, presence of mists or aerosol droplets, respectively, in the air sample).

There have also been attempts to develop automated electron microscopy methods for asbestos identification (Cossio et al., 2018). However, such techniques are not yet in use in routine analysis of air samples. In addition, like in the case of TEM (see above) it would be possible to develop indirect methods to concentrate and dilute the sample analysed and to remove organic and other unwanted particulate matter by ashing or dissolution, thereby selectively concentrating the asbestos. This could improve the sensitivity of the SEM method.

6.1.2.4 Challenges of measurement of asbestos

The main limitation of phase contrast microscopy is that it cannot detect fibres thinner <0.2 um, although there are indications that also these thinner fibres are relevant for carcinogenicity of asbestos (see chapter 9.1.2). In contrast to phase contrast microscopy, the use of electron microscopy techniques allows to discriminate between asbestos and non-asbestos fibres and to detect and count thin asbestos fibres (D<0.2 µm).

Since the establishment of the current EU OEL, a number of EU countries have reduced their national OELs for asbestos such that it requires the use of EM techniques as a main technique or as complementary to PCM analysis. This has necessitated the development of national standardised methods based on international EM methods and some updates of the previous international standards.

However, while the analytical techniques for EM are similar, the methods available differ in certain aspects such as magnification recommended, number of fields counted and the counting rules (in particular whether thin and/or short fibres should be counted). A further harmonisation of the analytical methods or the recommendation of a specific counting method(s) for asbestos is desirable.

Moreover, achieving lower limits of detection (a prerequisite for setting lower OELs), necessitates either sampling higher volumes, development of sample treatment practises or increasing on the number of fields counted (i.e. the area of the filter that is analysed). Higher sampling volumes are only possible in relatively clean atmospheres as dust particles interfere with fibre identification by obscuring them. The limits of detection described for methods in this Chapter consider relatively clean environments and would be higher for dusty atmospheres. Improving the detection limits in dusty atmospheres would require a significant development of the sample collection and/or sample treatment practices.

Increasing the number of fields counted would result in lower limits of detection but would also make the analysis more time-consuming and cumbersome.

All the above aspects seem to call for more European level harmonisation and are also linked to the conversion of the PCM based epidemiological risk data to the EM based limit values as further discussed towards the end of section 9.1.2.

Comparison of results between historical epidemiological data and current methods

The measurement techniques used to monitor asbestos exposure at workplaces have changed during the time when exposure took place in the long-term cohorts that form much of the basis of the current knowledge on asbestos-related cancer risks. These need to be considered when interpreting those studies. The related issues are further described in section 9.1.2. and in Appendix 5.

6.2 Biomonitoring of exposure (internal exposure)

Induced sputum and bronchoalveolar lavage (BAL) are considered relatively non-invasive biological sampling techniques. Asbestos bodies observed in sputum and concentration of asbestos bodies or asbestos fibres in BAL correlate with asbestos body and asbestos fibre concentration in lung parenchyma and especially BAL asbestos body counting with optical microscopy is frequently used to support other exposure assessment methods in occupational disease diagnosis (De Vuyst et al., 1998). However, such methods are not recommended to monitor asbestos exposure in non-symptomatic and healthy subjects or worker population studies.

7. Health Effects

Unless indicated otherwise, the workplace air monitoring results referred to in this Section have been conducted with WHO phase contrast microscopy method or equivalent (see Section 6).

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

Absorption and deposition

Inhalation route

As discussed by IARC (2012) and IOM (2006) inhalation is the most important route of exposure to asbestos and other mineral fibres, and is associated with the development of non-malignant diseases of the lungs and pleura, and malignant diseases arising especially in the lung, larynx, and pleural and peritoneal linings. The deposition of particles and fibres in the lungs is dependent on their aerodynamic diameter, which is a function of geometry, aspect ratio, and density (IARC (2002); IOM, 2006). Fibres can deposit by sedimentation, by impaction at bronchial bifurcations or by interception of the fibre tip with the bronchial wall. Smaller diameter fibres are more likely to deposit in the alveoli.

Particles and fibres can be cleared from the nasal and tracheobronchial regions by mucociliary transport. Following deposition in the distal airways and alveoli, short fibres are removed slowly following phagocytosis by alveolar macrophages. Fibre length is a limiting factor in macrophage-mediated clearance; fibres longer than the diameter of human alveolar macrophages (approximately 14–25 µm) are less likely to be cleared. Following impaired clearance, fibres may also interact with lung epithelial cells, penetrate into the interstitium, and translocate to the pleura and peritoneum or more distant sites by crossing the visceral pleura via paracellular migration or by direct penetration. In addition, translocation to the pleural space may take place when fibres are transported via lymphatics or the bloodstream (Kane et al., 2020). The rigidity (‘needle-like’ shape)

of a fibre is considered crucial for its ability to translocate (Kane et al., 2018). The slow rate of these long-term biological processes may explain at least part of the differences observed for latency times for lung cancer (site of contact hazard) and distant (pleural) or even more distant (peritoneal) target organs of mesothelioma observed in human data.

There is no human data concerning the deposition or absorption of inhaled asbestos fibres. Mossman et al. (2011) reviewed the patterns of deposition and retention of various types of fibres after inhalation, mechanisms of translocation within the lung, and dissolution of various fibre types both in lung compartments and in assays *in vitro*. There are five mechanisms that are important with respect to the deposition of fibres in respiratory tract airways. These are interception, impaction, sedimentation, diffusion, and electrostatic precipitation. The relative contribution of each of these mechanisms varies in different regions of the respiratory tract. The deposition in human lungs has been studied with mathematical models, using replicate (human lung) hollow airway casts and by comparing distributions found in air and lung samples collected at an asbestos mine. For crocidolite fibres interception elevated total deposition, with the effect increasing with fibre length, especially for fibres >10 µm in length. The effect was more pronounced at 60 L/min than at 15 L/min. This is consistent with greater axial alignment of the fibres during laminar flow within the airway. It was also observed that lung fibrosis was associated with increased fibre retention, and fibre retention was clearly associated with increasing fibre length and diameter. The critical fibre length for mechanical clearance from the lungs was greater than 17 µm.

Some human data are also available that are relevant for clearance and distribution of asbestos fibres and are described below under the heading of distribution.

Dermal route

There is no human data indicating dermal absorption of asbestos fibres.

The only adverse health effect that has been reported after dermal contact with asbestos is the formation of small "warts" or corns that have been reported in highly exposed historical cohorts (see ATSDR (2001). These occurred after direct skin contact with solid or airborne asbestos. No quantitative dose-response data are available. However, this phenomenon seems to be a local one, not related to dermal absorption. The workers with lesions reported an original pricking sensation and the feeling of a small splinter-like foreign body. This indicates that the lesions are associated with penetration of the skin by a macroscopic spicule, although histological examination of the corns did not reveal the presence of a fibre. The corns developed within about 10 days and were painful at first. They later became highly cornified and do not appear to be of pathological concern.

Oral route

Cook and Olson (1979), using transmission electron microscopy, observed asbestos in human urine, which abated when drinking water was filtered. This seems to indicate that ingested fibres enter into systemic circulation. There is no further human data indicating absorption of asbestos fibres from the gastrointestinal tract.

As reported by IARC (2012) and ATSDR (2001) the general population can be exposed to asbestos in drinking-water. Asbestos can enter potable water supplies through the erosion of natural deposits or the leaching from waste asbestos in landfills, from the deterioration of asbestos-containing cement pipes used to carry drinking-water or from the filtering of water supplies through asbestos-containing filters. However, the role of oral asbestos exposure e.g. in risk of gastro-intestinal cancers is not clear (IARC 2012). It is considered that while workers exposed via the inhalation route would also have oral exposure through ingestion of asbestos fibres cleared from the airways via mucociliary transport, such exposure is already covered by the human epidemiological and further consideration of oral route is not important for the quantitative setting an OEL.

Distribution

Clearance

Churg and Wright (1994) reviewed the human data on clearance of asbestos and other natural mineral fibres in human lungs. They concluded that very little information was available on actual fibre clearance rates from human lungs. However, those data indicate clearance half-times of years for crocidolite, years or even up to 20 years for amosite, whereas for chrysotile the available, rather indirect data suggest that the vast majority of fibres are cleared within months, although some fibres may be sequestered and very slowly cleared. Based on 90 lung samples and information on timing of exposure de Klerk et al. (1996) estimated an annual clearance of 9% corresponding to a clearance half-time of 92 months (7.7 years) for crocidolite in Australian asbestos miners. Similarly, based on 70 lung samples of crocidolite exposed gas mask factory workers Berry et al. (2009) estimated an annual clearance of 7.5 % corresponding to a clearance half-time of 9.2 years for crocidolite. Berry and colleagues also reported that the proportion of fibres longer than 6 µm increased over time implying that the shorter fibres were eliminated more rapidly than the longer ones.

Albin et al. (1994) analysed pulmonary fibre burden in 69 deceased asbestos cement factory workers and 96 referents. The asbestos cement factory workers had had a mixed exposure with chrysotile as the main fibre type, tremolite as a contaminant of chrysotile and crocidolite as intermittently used fibre type. They found a pulmonary fibre concentration pattern compatible with relatively rapid pulmonary turnover of chrysotile and slower turnover for tremolite and crocidolite. The information permitted, however, only analyses with crude methods to evaluate accumulation and elimination, without quantitative estimates of clearance rates.

As further discussed by IARC (2012) the lungs of some chrysotile workers at autopsy contain low levels of chrysotile but substantial numbers of tremolite fibres, which is present in some chrysotile-bearing ores. For this reason, tremolite has been suggested to contribute to the carcinogenic effects seen in chrysotile miners (McDonald et al. (1997), McDonald and McDonald (1997), McDonald (1998)). However, this theory is debated and the relevance of this difference in clearance for cancer risk is further discussed in section 7.7.1 separately for mesothelioma and lung cancer.

It has been postulated that the difference in clearance half times between chrysotile and amphiboles on one hand and the different life-expectance between rats and humans on the other hand may be one factor explaining why the mesothelioma potency between these fibres seems similar in rat carcinogenicity assays while the human data indicate a difference in potency (see Berry (1999) and Hodgson and Darnton (2000) for discussion).

Migration

During their residence in the human lung, asbestos fibres may acquire iron via a complex mechanism that may originate from the adsorption and disruption of ferritin, eventually yielding so-called asbestos bodies. These are preferentially formed onto long amphibole fibres but have also been found onto chrysotile fibres (Roggli (2004)). The asbestos body consists of a core of optically transparent asbestos fibre surrounded by a golden yellow, iron-protein coat. The coat may be variably segmented into spherical or rectangular units spaced along the fibre; the ends of the body are frequently knobbed. Although the presence of asbestos bodies in asbestos-related diseases is well documented, their biological role is still controversial. As similar bodies can form on fibres other than asbestos, e.g. erionite, the term ferruginous body is also used.

In addition to lung and pleura, asbestos fibres and/or asbestos bodies have been observed in human samples from abdominal organs, including the spleen, abdominal lymph nodes, liver, kidney, omentum, mesentery, ovaries, esophagus, stomach, and small and large intestines (see IOM 2006 and IARC 2012). More recently, chrysotile

fibres were observed in the tissue surrounding laryngeal squamous cell carcinoma of 3 out of 4 asbestos-exposed patients while no chrysotile fibres were detected in one single control patient that was unexposed to asbestos (Wronkiewicz et al., 2020). Asbestos fibres have also been observed in placentas and various foetal tissues of stillborn infants and to a lesser quantity in placentas of liveborn healthy infants (Haque et al. (1996), Haque et al. (1998)).

The route of translocation of asbestos fibres from the lungs to pleura, peritoneum and other organs is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals (IOM, 2006). It has been suggested that most of the fibres reach the peritoneum through the lymphatics (Kurimoto et al., 2009, Uibu et al., 2009). In particular, diaphragm is extremely rich in lymphatics both on the pleural and peritoneal side that connect into a common sub-mesothelial lacunar system, thus allowing the passage of fibres from the thoracic cavity to the abdomen (Li et al., 1996, Miserocchi et al., 2008). As asbestos fibres are eliminated by the lung and the pleura through the lymphatics it is possible that this clearance occurring at the thoracic level and its contribution to the translocation of the asbestos fibres to the peritoneum could explain the difference in the latency times observed between pleural and peritoneal mesothelioma (see section 7.7.1) The difference in the latency times observed between pleural and peritoneal mesothelioma could also be compatible with a passage from the respiratory tract to peritoneum via the digestive tract after mucociliary clearance. Dodson et al. (2003) reviewed the data on asbestos fibre length. There were observations based on human samples that the fraction of short fibres of all fibres is higher in pleural tissue than in lung parenchyma.

Metabolism

Asbestos fibres are considered very biopersistent, with the exception of chrysotile that undergoes selective leaching under strong acidic or chelating conditions, resulting in removal of Mg2+ ions (see IARC 2012). Chrysotile may also lose magnesium *in vivo*, following phagocytosis by alveolar macrophages.

However, asbestos fibres are not metabolised in the usual sense of the term and there is no human data indicating metabolism of asbestos fibres.

Excretion

There is no human data concerning excretion of asbestos fibres.

7.1.2 Animal data

Absorption and deposition

Inhalation route

Inhaled asbestos fibres are deposited in various parts of the airways of experimental animals.

Accumulation of asbestos fibres has been reported in alveolar epithelial cells and macrophages, pulmonary interstitium, lymphatics and lymph nodes, and the vascular compartment (reviewed in NFA 2019). Chrysotile has mainly been located in bronchial, bronchiolar and alveolar bifurcations, with the majority of fibres located in the bifurcations of the alveolar ducts (Brody et al. (1981), NFA, (2019)).

Amosite fibres have been detected in macrophages and multi-nucleate foreign body giant cells but also in the interstitial space and parietal pleurae of rats (Bernstein et al., 2011, Davis et al., 1991). Amosite fibres have been shown to penetrate the airway wall immediately after exposure of rats. They have been located under the airway wall or in macrophages on the surface of the ciliated epithelium. Small amounts of fibres can also move to the interstitial space of the lung parenchyma (Bernstein et al., 2010). The study

by Bernstein et al. (2011), which used both amosite and chrysotile, did not detect any chrysotile fibres in the pleural cavity, whereas numerous amosite fibres were detected.

In rat inhalation studies, crocidolite fibres have been observed in alveolar macrophages, mediastinal lymph nodes, pulmonary interstitium and the diaphragm (Bernstein et al., 2015, Oghiso et al., 1984, Roggli et al., 1987). Deep lung deposition (fraction of 13-19%) was observed in a dog inhalation study with crocidolite. The total deposition in the respiratory tract was 54-72%. (Griffis et al., 1983).

Distribution and clearance

Inhalation route

As also discussed in section 7.1.1, it is difficult for macrophages to eliminate longer fibres by phagocytosis. This has been extensively studied in animal models and shown to lead to a phenomenon called "frustrated phagocytosis" which later may result in chronic inflammation(Mossman and Gualtieri, 2020). This is particularly relevant for rigid, biopersistent, poorly soluble fibres. For further details, see section 8.1.

There is a general difference in the persistence of chrysotile versus other types of asbestos fibres in the lungs of exposed animals. Chrysotile fibres break into shorter parts, and they seem to be bio-soluble to some extent. Thus, chrysotile fibres are less persistent than other asbestos fibre types. Amosite, crocidolite and tremolite fibres, on the other hand, are highly persistent and the clearance is low (NFA 2019).

Marked differences in clearance of different types of fibres was observed in the study of Bernstein et al. (2020b). Rats were exposed by inhalation for 13 weeks (6 h/day, 5 days/week) to chrysotile brake dust (0.20, 0.34 or 0.67 mg/m^3, corresponding to 2.4, 4.9 or 6.6 fibres/cm^3), chrysotile (0.17 or 0.64 mg/m^3, corresponding to 119 or 233 fibres/cm^3), crocidolite (1.28 mg/m^3, corresponding to 181 fibres/cm^3), or amosite (2.32 mg/m^3, corresponding to 281 fibres/cm^3). The deposition was followed 90 days post exposure. At that time point (day 180), the brake dust fibres >20 µm were completely cleared, but 23-84% of the lung concentrations of shorter fibres remained in the lungs. Only minor amounts of >20 µm chrysotile fibres were detected (7% of dose), and 11-22% of shorter fibres remained in the lungs. In contrast, very low clearance of crocidolite was observed: 89% of >20 µm fibres and 87% of 5-20 µm were still present in the lungs. No clearance of <5 µm crocidolite fibres occurred during the 90-day recovery period. Similarly, no clearance of amosite fibres >20 µm or 5-20 µm was observed. 69% of <5 µm amosite fibres were detected.

A considerable decrease in the lung content of long (>20 µm) chrysotile fibres was observed during recovery periods of 50 or 92 days in rats, which had been exposed to chrysotile nose-only 5 days/week, 6 h/day for 13 weeks. The exposure concentrations were 1.3 mg/m^3 (corresponding to 76 fibres/cm^3 with a length>20 µm, and a total fibre concentration/cm^3 of 3413) or 3.6 mg/m^3 (207 fibres/cm^3 >20 µm, total fibre concentration 8941/cm^3). Long fibres were broken to shorter fibres or particles. (Bernstein et al., 2006)

After sub-acute inhalation exposure of rats to chrysotile at a concentration of 4.3 mg/m^3 (435 fibres/cm^3 with a length >20 µm; 6 h/day, 5 days), the clearance of fibres was followed during recovery periods of 1, 2, 7, 14 days and 1, 3, 6, and 12 months. Three months after exposure, no fibres longer that 20 µm were found in the lungs and the clearance half-time was calculated as 1.3 days. For 5-20 µm long fibres the half-time was 2.4 days. (Bernstein et al., 2004)

In the study by Bernstein et al. (2005), rats were exposed to chrysotile (1.7 mg/m^3; 200 fibres >20 µm) or tremolite (11.5 mg/m^3; 100 fibres >20 µm) 6 h/day, 5 days. After 12 months of recovery, 99.2% of the chrysotile remaining in the lungs was <5 µm. Significant amounts of tremolite, on the other hand, remained deposited in the lungs over the rat's life-time.

Bernstein et al. (2015) compared the lung deposition of three types of asbestos: brake-dust of chrysotile brake-drums (189 fibres/cm^3 ≥20 µm; total fibre concentration 6953/cm^3), a mixture of chrysotile and brake-dust (3.6 fibres/cm^3 ≥20 µm; total fibre concentration 389/cm^3), and crocidolite (93 fibres/cm^3 ≥20 µm; total fibre concentration 2013/cm^3). The rat exposure duration was five days, 6 h/day. The occurrence of short (<8 µm) chrysotile fibres decreased rapidly during the first 30 days, and slower up to 180 days after exposure. A 50% decrease in longer chrysotile fibres was observed within 30 days, but later there was almost no clearance. In the third group of rats exposed to crocidolite, clearance was not observed, and the fibres persisted in the lungs throughout the life-time.

Rapid clearance of short chrysotile fibres from rat lungs was observed in animals after exposure to a concentration of 10 mg/m^3, 3-5 h/day, 3 days. Longer fibres (>8 µm), on the other hand, were retained in the lungs up to 6 months. (Coin et al., 1996)

The lung burden of fibres was followed up during 18 months in rats after 13 weeks of inhalation exposure (6 h/day, 5 days/week) to Libby amphibole fibres (1.0, 3.3, or 10 mg/m^3; mean length 3.7 µm, 1% >20 µm). A decline in the lung burden was seen over time, with the reduction being fairly similar among the exposure groups and no impaired clearance at the higher concentrations. (Gavett et al., 2016)

A 50% decrease in lung burden of amosite fibres (>20 µm) during an 1-year recovery period was observed in rats after exposure to 6.4 mg/m^3 amosite for five days, 6 h /day (Bernstein et al., 2011).

In the study by Cullen et al. (2000) rats inhaled to 1000 amosite fibres/cm^3, 7 h/day, 5 days/week for 12 months. At the end of a 12-month recovery period, 44% of the fibre dose was still detected in the lungs.

Inhalation of 8 mg/m^3 of crocidolite fibres during a period of 5 or 20 days resulted in a higher rat lung retention of fibres 20 days after the end of the exposure period than in the rats inhaling chrysotile, following the same protocol. There was no substantial decrease in the number of crocidolite fibres during the recovery period (BeruBe et al., 1996).

The mean crocidolite fibre length was progressively increased in rat lungs examined 2 days, 8 days, 4 weeks, 2 months, or 3 months after one-hour inhalation exposure at 3.5 mg/m^3 or 4.5 mg/m^3. No changes in the diameter of the fibres in the lungs were observed. (Roggli et al., 1987). Similar results were obtained in the study by Hesterberg et al. (1996), in which rats inhaled crocidolite (10 mg/m^3) 6 h/day, 5 days. The increase in mean fibre length is expected to be due to elimination of shorter fibres.

Oral route

A review of studies investigating the migration of asbestos fibres after oral intake was compiled by Cook (1983). The studies show varying results but does indicate a potential for asbestos fibres to penetrate the gastrointestinal mucosa and migrate to other organs.

Migration of fibres from the gastrointestinal tract was observed in one baboon after administration of cumulative doses of 800 mg each of chrysotile and crocidolite asbestos by oral gavage. Fibres were detected in the stomach, heart, spleen, pancreas and blood. (Kaczenski and Hallenbeck, 1984). In an earlier oral gavage study in a baboon, chrysotile fibres were detected in the urine (Hallenbeck and Patel-Mandlik, 1979).

The study by Hasanoglu et al. (2008) described the migration of asbestos fibres from the gastrointestinal tract to the lungs of rats after administration of 1.5 g/L or 3 g/L of asbestos in drinking water. Asbestos bodies were also detected in spleen. No data on distribution to other organs or excretion were provided.

7.1.3 Summary

Amphibole asbestos fibres are very biopersistent while there is a difference in the persistence of chrysotile versus amphibole fibres. In the animal data there is indication that chrysotile fibres break into shorter parts, and they seem to be bio-soluble to some extent. Human data indicate that for amphibole fibres half times in the lungs can be as long as years or even decades, while for chrysotile fibres the range is measured more likely in months.

Asbestos fibres deposited in the lungs can translocate to pleura, local lymph nodes, diaphragm and more distant organs. The mechanisms of translocation are not fully understood but there is indication of lymphatic translocation. The translocation may be affected by fibre length with longer fibres tending to translocate from lungs less readily than shorter ones.

According to IOM (2006), in contrast with studies of fibre deposition in the lower respiratory tract, little is known about fibre deposition and clearance from the upper respiratory tract, particularly the larynx.

7.2 Acute toxicity

7.2.1 Human data

Acute oral toxicity

There is no human data on acute oral toxicity.

Acute dermal toxicity

There is no human data on acute dermal toxicity.

Acute inhalation toxicity

There is no human data on acute oral toxicity.

7.2.2 Animal data

Acute oral toxicity

No data on LD50-values or other acute effects was found.

Acute dermal toxicity

No data on LD50-values or other acute effects was found.

Acute inhalation toxicity

No data on LC50-values or other acute effects were found. Some inhalation studies are available, mainly investigating the effects on cell proliferation (Chang et al., 1988, Barry et al., 1983). In addition, several studies with intratracheal instillation of asbestos fibres have been published. The reported effects were related to local pulmonary injury and inflammation (NFA 2019).

7.2.3 Summary

No relevant acute toxicity data were identified.

7.3 Specific target organ toxicity/Repeated dose toxicity

7.3.1 Human data

Asbestos is an established causative agent for diffuse interstitial pulmonary fibrosis (asbestosis), pleural effusion, diffuse fibrotic thickening of the visceral pleura and hyaline plaques of the parietal pleura (ATSDR (2001), ATS (2004), IOM (2006), Algranti and Markowitz (2016), Musk et al. (2016)). These non-malignant asbestos-related respiratory diseases are established occupational disease entities (EC, 2009). However, for reasons outlined below, setting the OEL based on cancer exposure-response seems the most appropriate quantitative risk assessment approach. Consequently, the human data on non-malignant respiratory diseases is only summarised below, based on the above-mentioned reviews and complemented with more recent references when appropriate.

Persons with fully developed clinical asbestosis have shortness of breath (dyspnea), often accompanied by rales or cough, and display deficits in pulmonary function variables, especially those characteristic of restrictive pattern and reduced gas diffusion due to the impairment affecting more pronouncedly the lung parenchyma and deeper lung in comparison to upper airways. In severe cases, impairment of respiratory function may ultimately result in death, and asbestosis has been associated with excess mortality in a number of asbestos worker cohorts. Available evidence indicates that all asbestos fibre types are fibrogenic, although there may be some differences in potency between them. As reviewed by ATSDR (2001), cumulative exposure levels that have been associated with radiographic, histologic, spirometric, or clinical signs of lung fibrosis in groups of chronically exposed workers have been in excess of 10 fibre-years/cm^3 (f-y/cm^3), which would correspond to average exposure of 0.25 fibres/cm^3 during a 40 year working career. This is higher than the current OEL set by Directive 2009/148/EC. Although there is some uncertainty in extrapolating from the high past exposure levels to the current workplace conditions as well as concerning a threshold mechanism for asbestosis (see ATSDR 2001), it seems justifiable that for the purposes of setting regulatory standards, asbestos-related cancer is a more sensitive endpoint.

The most common asbestos-related pleural lesions are pleural plaques. These are generally oval areas of acellular collagen deposits, usually located on the inferior and posterior surfaces of the parietal pleura. The incidence of pleural abnormalities (usually detected by x-ray examination) is often quite high (10–60%) in people employed in asbestos-related occupations. Pleural plaques have also been common in household contacts and family members of asbestos workers, as well as in people with environmental asbestos exposure. The health significance of asbestos-induced pleural plaques is not precisely defined; some researchers consider pleural plaques to be essentially benign, whereas others have noted isolated pleural plaques to be associated with decreased respiratory function (ATSDR (2001), Clin et al. (2011b), Kerper et al. (2015)). It is also controversial whether pleural plaques, when adjusting for the risk related to cumulative asbestos exposure, are an exposure-independent individual predictor of increased risk for lung cancer or mesothelioma (ATSDR (2001), Ameille et al. (2011), Pairon et al. (2014), Brims et al. (2020)). These studies have analysed the cancer predictive value both in heavily exposed workers, like asbestos miners, and in downstream users with lower average exposure. Diffuse pleural thickening can lead to decreased respiratory function, probably because of the restrictive effect of pleural fibrosis (ATS, 2004). However, for pleural effusion and diffuse fibrotic thickening of the visceral pleura, which have also various other causative agents than asbestos, there are no quantitative exposure-response relationships by level of asbestos exposure.

It is noted that in the diagnosis of both parenchymal and pleural non-malignant asbestos-related diseases, computed tomography, especially high resolution computed tomography is commonly used today due to its higher sensitivity as compared to standard chest X-ray (ATS (2004), Kusaka et al. (2005)).

More recently case reports and one case-control study have also suggested an association between asbestos exposure and retroperitoneal fibrosis (Uibu et al. (2004), Goldoni et al. (2014)). Retroperitoneal fibrosis is a rare and poorly understood condition and also the nature of the association between asbestos exposure remains poorly understood (Swartz (2015)).

In addition there is indication that asbestos exposure increases the risk of cardio- and cerebrovascular diseases (Sjogren et al., 2020). Of the cardiovascular diseases, indications of risk were reported specifically for classical pulmonary heart disease (*cor pulmonale*), where pulmonary resistance e.g. from fibrosis affects the right ventricular function of the heart resulting in cardiac insufficiency, but also for cardiovascular diseases in general (Sjogren et al., 2020). A recent meta-analysis of 16 studies estimated an overall SMR for cardiovascular related diseases of 1.1 (95% CI, 1.0–1.2) while there was little evidence for increased risk of ischaemic heart disease (Rong et al., 2015). However, most studies analysed mortality in comparison to the general population and adjustment for known non-occupational risk factors, like smoking and diet, was not possible. Very few of the studies provided risk estimates by cumulative exposure (Sjogren et al., 2020).

7.3.2 Animal data

An overview of subchronic or chronic inhalation studies with NOAEC and LOAEC values for non-cancer endpoints is presented in NFA (2019). The main findings are related to fibrosis and hyperplasia, as well as local inflammatory effects, with NOAEC/LOAEC values normally between 1 and 10 mg/m^3. The most relevant inhalation studies are described below, but oral or intratracheal studies are not described, as those routes of administration are considered less relevant for OEL considerations.

In a study comparing different asbestos fibre types, rats were exposed by inhalation for 13 weeks (6 h/day, 5 days/week) to chrysotile brake dust (0.20, 0.34 or 0.67 mg/m^3, corresponding to 2.4, 4.9 or 6.6 fibres/cm^3), chrysotile (0.17 or 0.64 mg/m^3, corresponding to 119 or 233 fibres/cm^3), crocidolite (1.28 mg/m^3, corresponding to 181 fibres/cm^3), or amosite (2.32 mg/m^3, corresponding to 281 fibres/cm^3). There was a clear difference in the effects observed using chrysotile or chrysotile brake dust in comparison with effects caused by amosite or crocidolite. Persistent inflammation, microgranulomas, and fibrosis was observed in animals exposed to amosite or crocidolite. Extensive collagen development and inflammation occurred in the lungs and on the visceral and parietal surfaces. Exposure to chrysotile or chrysotile brake dust, on the other hand, resulted in only slight interstitial inflammation, no peribronchial inflammation and occasional very slight fibrosis. The investigations were performed at exposure day 45, end of exposure (day 89) or day 180. The results reflect some level of biosolubility and breakage of chrysotile to shorter fibres. However, it is important to note the differences in doses (fibres/cm^3) (Bernstein et al., 2020b, Bernstein et al., 2020a)

Inhalation exposure of rats to a concentration of 9 mg/m^3 of chrysotile for 3 months (420 h in total) resulted in increases in numbers and volume inflammatory type II cells in the epithelium, as well as an increase in the interstitial cell population (Barry et al., 1983).

In another subchronic study rats inhaled 10.7 mg/m^3 chrysotile 91 days (6 h/day, 5 days/week). After a recovery of 2 to 16 months, aggregation of macrophages, thickened alveolar duct bifurcations, microcalcifications and slight pulmonary fibrosis were observed. (Oghiso et al., 1984)

13-week exposure (5 days/week, 6 h/day) to chrysotile (a) 1.3 mg/m^3 corresponding to 76 fibres/cm^3, >20 µm; total concentration of 3413 fibres/cm^3, or b) 3.6 mg/m^3 corresponding to 207 fibres/cm^3, >20 µm; total concentration of 8941 fibres/cm^3) resulted in increased numbers of neutrophils, lactate dehydrogenase (LDH) and total protein in bronchoalveolar lavage fluid (BALF) at the end of exposure. LDH and total

protein levels also remained elevated after 92 days of recovery. In addition, slight fibrosis was observed at the highest dose, but not at the lower dose. (Bernstein et al., 2006)

No fibrosis or other lesions were observed in the lungs of monkeys or rats after inhalation exposure to 1 mg/m^3 of short chrysotile fibres, 7 h/day, 5 days/week for 18 months, followed by a 10 month recovery period for monkeys and up to 6 months for rats (Platek et al., 1985).

In the study by Crapo et al. (1980) rats were inhaling short or intermediate chrysotile fibres for 1 h, 7 h, 5 days, 3 months or 12 months (7 h/day, 5 days/week; dose 3.1 mg/m^3 for short and 9.4 mg/m^3 for intermediate length fibres). Pathological findings in the alveolar epithelium and interstitium of the lungs were observed at 12 months with intermediate fibres. Both types of fibres induced the numbers of macrophages and increased the volume of the alveolar epithelium and the interstitium after 3 months of exposure. After 12 months of exposure, decreases in total lung capacity and vital capacity were observed in both exposure groups, however, being more pronounced in animals exposed to intermediate chrysotile fibres.

In a 13-week study, rats were exposed by inhalation to 3.3 mg/m^3 amosite or 1.0, 3.3 or 10 mg/m^3 of Libby amphibole fibres 6 h/day, 5 days/week. Exposure to each fibre type up to 3 months caused inflammation and induced the presence of inflammatory markers and cytokines in BALF. No interstitial fibrosis was observed in the subchronic study, but in a 10-day study with exposure to 25 mg/m^3 of Libby amphibole presented in the same report. (Gavett et al., 2016)

The main findings in the lungs of rats included thickened alveolar duct bifurcation, aggregation of macrophages, and slight pulmonary fibrosis examined 2-16 months after 91 days of exposure (6 h/day, 5 days/week) to 11.2 mg/m^3 crocidolite or 10.7 mg/m^3 chrysotile. In addition, subpleural collections of alveolar macrophages and lymphocytes were observed in animals exposed to crocidolite. Exposure to chrysotile caused microcalcifications. (Oghiso et al., 1984)

Exposure to 10 mg/m^3 crocidolite up to 12 months (6 h/day, 5 days/week) caused cell damage and collagen deposition in the interstitium of airway bifurcations. Weak fibrosis was also detected. (Johnson, 1987)

Studies investigating the connection between asbestos exposure and cardiovascular disease were recently reviewed by Sjögren et al. (2020). An inhalation study with atherosclerosis-prone ApeE-/- mice indicated no correlation between degree of chrysotile asbestos-induced lung inflammation or fibrosis and cardiovascular effects (Fukagawa et al., 2008). The results of a study with intratracheal instillation of Libby amphibole fibres in rats suggested an increased risk of cardiovascular effects in healthy individuals (Shannahan et al., 2012).

7.3.3 Summary

Asbestos causes non-malignant respiratory diseases, e.g. diffuse pulmonary fibrosis (asbestosis) and fibrotic changes and hyaline plaques of pleura. Effects have been observed in humans and in experimental animals. There is also some indication of asbestos exposure being associated with retroperitoneal fibrosis, but the nature of this association remains poorly understood.

For clinically or radiologically manifest asbestosis, there is conclusive evidence that it occurs only in association with exposure to concentrations higher than the current EU OEL. For non-malignant pleural diseases there are no robust data on quantitative exposure-risk relationship. This lack of information applies also to pleural plaques, by far the most common pleural abnormality, which has also been observed following non-occupational exposure. Nevertheless, the clinical significance of pleural plaques as well

as their cancer predictive value, if adjusted for level of exposure, remains controversial after studies conducted in populations with varying exposure levels.

It is concluded that while the non-malignant asbestos-related diseases are established occupational disease entities (EC, 2009), setting the OEL based on cancer exposure-response information seems the most appropriate approach because asbestos related cancer risks occur, and can be quantified, at lower levels than the non-malignant health effects.

7.4 Irritancy and corrosivity

7.4.1 Human data

There is no human data on irritancy and corrosivity.

7.4.2 Animal data

There is no animal data on irritancy and corrosivity.

7.4.3 Summary

There are no indications of asbestos fibres being irritant or corrosive.

7.5 Sensitisation

7.5.1 Human data

Respiratory sensitisation

There is no human data on respiratory sensitisation.

Skin sensitisation

There is no human data on skin sensitisation.

7.5.2 Animal data

Respiratory sensitisation

There is no animal data on respiratory sensitisation.

Skin sensitisation

There is no animal data on skin sensitisation.

7.5.3 Summary

There is no indication of asbestos fibres being respiratory or skin sensitising.

7.6 Genotoxicity

7.6.1 Human data

There is little human data on genotoxicity. However, a mechanism considered crucial for the induction of genotoxic effects is the formation of reactive oxygen or nitrogen species, as a consequence of chronic inflammation, or via Fenton-type reactions catalysed by iron

occurring on the surface of the fibre. Reactive oxygen species are known to cause DNA damage. For further details, see section 8.1.

Studies on asbestos-exposed human workers have identified increased frequencies of chromosome aberrations and sister chromatid exchanges. Increased concentrations of 8-oxodeoxyguanosine, indicating DNA damage, and increased frequencies of DNA double strand breaks have been detected in the white blood cells or urine of exposed workers. However, there seems to be no correlation between exposure to asbestos and induction of micronuclei.(Dusinska et al., 2004, Marczynski et al., 1994, Marczynski et al., 2000a, Marczynski et al., 2001, Marczynski et al., 2000b)

7.6.2 Animal data

Oral doses of 100 or 500 mg/kg bw chrysotile to rhesus monkeys did not result in increased levels of chromosome aberrations in the bone marrow. In the same study, chrysotile was administered as a single oral or intraperitoneal dose (0.4-400 mg/kg bw) to mice. No induction of micronuclei was observed in the bone marrow. (Lavappa et al., 1975)

An increased frequency of chromosome aberrations was observed in peritoneal cells of mice after intraperitoneal injection of 50 mg/kg bw chrysotile (Durnev et al., 1993).

Transient increases in DNA synthesis in stomach, small intestines and colon tissue was observed four weeks after oral gavage exposure of rats with 100 mg/kg bw chrysotile. No effects were seen in liver or pancreas. (Amacher et al., 1974, Amacher et al., 1975)

In a study with wild type F334 rats and Big blue rats (with a *lacZ* reporter gene), amosite was administered by intratracheal instillation as a single dose of 1 or 2 mg, or as four 2 mg doses during a week. Increased mutation frequencies in lung DNA were observed after 16 weeks of recovery in the 1x2 mg or 4x2 mg groups of Blue rats, but not at 4 weeks of recovery. In the wild type rats, DNA strand breaks were detected in macrophages and type II cells by the Comet assay. In addition, micronuclei were detected in lung epithelial cells at 16 weeks, but not at the earlier time point. (Topinka et al., 2004)

Transgenic mice (*lacI* reporter gene) were exposed to 5.75 mg/m^3 crocidolite for 5 days by inhalation (6 h/day), and euthanized 1, 4 or 12 weeks after the beginning of the exposure. An increased mutation frequency in lung samples was observed at 4 weeks, but not at the earlier or later time points (Rihn et al., 2000). The mutation frequency was however only 15% and can be regarded as similar to the control group (NFA 2019).

The incidence of K-ras oncogene mutations was not increased in the lungs of mice exposed to 120 µg crocidolite by pharyngeal aspiration. The examination was performed one year after the exposure. (Shvedova et al., 2014)

DNA fingerprint analysis of tumours induced by an intraperitoneal injection of 2 mg crocidolite indicated a mutation frequency of 14.8% (in comparison, the mutation frequency induced by benzo[a]pyrene was 18.2% and that of nickel powder 40.9%) (Kociok et al., 1999)

Intraperitoneal injection of 2 mg or 5 mg crocidolite caused an increased mutation frequency in the DNA of omenta in *LacI* transgenic rats at 12 and 24 weeks of recovery. The crocidolite-related mutations differed from spontaneous mutation, indicating a difference in mechanisms. The authors concluded that the results "give strong evidence for the involvement of reactive oxygen or nitrogen species in crocidolite-induced mutagenesis in vivo". (Unfried et al., 2002)

Administration of 50 mg/kg bw crocidolite by oral gavage did not induce formation of micronuclei or sister chromatid exchanges in the bone marrow of rats. If crocidolite was administered together with benzo[a]pyrene, cytogenic effects were seen. A similar

pattern was seen with anthophyllite, showing cytogenic effects only in combination with benzo[a]pyrene. (Varga et al., 1996a, Varga et al., 1996b)

7.6.3 *In vitro* data

A number of *in vitro* studies have been published, showing genotoxicity for example in cultured rat mesothelial cells (IOM, 2006, Kane et al., 2020). However, the value of such studies is considered uncertain as it is difficult to mimic the complex *in vivo* conditions (with fibres penetrating cells and tissues) in *in vitro* settings (NFA 2019). On the other hand, *in vitro* investigations do provide relevant mechanistical information, which is important for the understanding of the effects.

Several in vitro studies with rat mesothelial cells exposed to asbestos showed chromosome alterations and abnormal mitoses (Achard et al., 1987, Jaurand et al., 1986, Kane et al., 2020, Levresse et al., 1997, Yegles et al., 1995, Yegles et al., 1993). DNA breakage, which is linked to production of reactive oxygen species, has been reported both in rat and rabbit mesothelial cells (Dong et al., 1994, Fung et al., 1997, Levresse et al., 2000, Liu et al., 2000, Pietruska and Kane, 2007, Renier et al., 1990). An induction of p53 and p21 was reported in proliferating and serum-deprived mesothelial cells and the occurrence of apoptosis was reported in several studies (Acencio et al., 2015, Kopnin et al., 2004, Levresse et al., 1997, Liu et al., 2000). Surprisingly, the study by Liu et al. (2000) indicated that reduced phagocytosis by mesothelial cells resulted in a reduced level of DNA breakage.

7.6.4 Summary

In a number of *in vivo* studies, increased gene mutation frequencies were observed in animals exposed to asbestos. The results of a few studies investigating cytogenicity (e.g., increased frequencies of chromosome aberrations) show effects at site of contact, but not systemic genotoxicity (e.g., induction of micronuclei in bone marrow).

As discussed in section 8.1., the observed genotoxicity is expected to be indirect, occurring as a result of for example production of reactive oxygen/nitrogen species and oxidative stress.

7.7 Carcinogenicity

Asbestos has been considered by IARC working groups in 1972, 1976 and 1987 (IARC, 1973, IARC, 1977, IARC, 1987) and more recently in the monograph evaluation in 2009 (IARC, 2012).

The latest evaluation concluded that there is sufficient evidence in humans for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) and that asbestos causes mesothelioma and cancer of the lung, larynx, and ovary. Also, positive associations have been observed between exposure to all forms of asbestos and cancer of the pharynx, stomach, and colorectum. It further concluded that there is sufficient evidence in experimental animals for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite). All forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) were classified as carcinogenic to humans (Group 1). As regards quantitative risk assessment it is noted that robust quantitative exposure-responses were noted for lung cancer and mesothelioma. For other cancer sites the studies used categorical analyses, grouping job titles into exposure categories or SMR type of analyses without a precise exposure-response analysis by cumulative or other quantitative exposure metric.

In addition to the occupational setting, it is noted that there are numerous scientific papers concerning the health effects of environmental and para-occupational asbestos

exposure and also on the health effects of non-occupational exposure to asbestos-like fibres, erionite and fluoro-edenite.

Erionite is a fibrous zeolite found as an environmental contaminant in certain volcanic tuffs (IARC 2012). A large excess of mesothelioma (up to 80% mesothelioma deaths of all deaths) has been reported among residents of and emigrants from Turkish villages in Cappadocia having been exposed since birth because erionite from regional sediments was used in houses and construction; e.g. during white washing their homes and during other activities involving erionite containing soil. There is no robust epidemiological evidence of erionite related risk for cancers other than mesothelioma. IARC (2012) concluded that there is sufficient human and sufficient animal evidence for carcinogenicity of erionite (mesothelioma) and it was evaluated *carcinogenic to humans (Group 1)*. There were only limited commercial applications of erionite in specific industries (IARC 2012) while there were no wide-spread uses similar to asbestos (e.g. in commercial building materials) and no epidemiological studies in the occupational setting have been conducted. However, exposure is possible in areas where erionite occurs naturally and as impurity of other zeolites.

Fluoro-edenite is a fibrous calcic amphibole, identified e.g. in the volcanic products of Mount Etna near Biancavilla in Sicily, Italy (Bruno et al., 2015). Fluoro-edenite as such was not used commercially but occurred in the sandy volcanic material extracted from the local quarry that have been used in the local building industry (walls, plaster, mortar, and concrete) and in soil used to pave roads, plazas, and other areas (IARC, 2017). Flouro-edenite has also been identified in the cavities of the Ishigamiyama lava dome of the Kimpo volcano, Kumamoto, southwestern Japan. A number of surveillance studies among residents of Biancavilla have observed an excess of mortality and incidence of mesothelioma, while the epidemiological evidence for other cancers is less robust (IARC 2017). For "fluoro-edenite fibrous amphibole" IARC (2017) concluded that there is sufficient human and sufficient animal evidence for its carcinogenicity (mesothelioma) and it was evaluated *carcinogenic to humans (Group 1)*.

It is also noted that among the Libby MT vermiculate miners in the US and those exposed environmentally around the mine, the increased cancer risk previously attributed to tremolite, actually is related to exposure to a more complex fibrous amphibole mineral ("Libby amphibole") typically consisting of winchite (84%), richterite (11%) and tremolite (6%) and classified as carcinogenic by EPA (EPA, 2014). Increased mesothelioma risks have also been reported in a Minnesota community living near to an insulation manufacturing plant having used Libby vermiculite as raw material (Konen et al., 2019).

It is not possible to differentiate the individual hazardous effect of winchite, richterite and tremolite in the cohorts exposed to Libby amphibole. There are also no studies with robust quantitative exposure-risk relationship estimates for erionite or fluoro-edenite for mesothelioma.

As described in the Preamble of this document, the mandate of this review was limited to asbestos fibre types defined in Art 2 of Directive 2009/148/EC. As described in Chapter 5, the most important current occupational safety and health problem related to asbestos in EU is the safe handling of the asbestos products used in the past and still in place. That problem is related to the six silicate fibres currently defined as asbestos according to Art 2 of Dir 2009/148/EC that may result in exposure due to their past commercial use. However, at local level, preventive actions are necessary to avoid ill-health in areas where the above similar fibres occur naturally. As there are no quantitative exposure-risk data that would allow specific recommendations as regards those fibres, the local actions would either need to assume that the quantitative exposure-risk established in section 9.1.2 for asbestos holds as a surrogate for those fibres, or to generate additional scientific data to establish specific exposure-risk relationships that support those local actions. Carcinogenicity of erionite, fluoro-edenite, winchite and richterite are not further described in this report.

7.7.1 Human data

In the following sections, the most relevant data available for asbestos fibres at the time of the latest IARC evaluation are described together with data that has been published since then. The focus is on data that are relevant for quantitative exposure-response estimation for asbestos exposure and cancer.

Mesothelioma

Pleural and peritoneal mesothelioma are malignancies that occur in the mesothelial cells lining the pleural or peritoneal cavity. Mesothelioma is rare in the general population, but often occurs in asbestos exposed populations. ATSDR (2001) estimated an annual mesothelioma mortality rate of 2.8 and 0.7 per million in the US general population for men and women, respectively. Mesothelioma usually results in death within one or two years from diagnosis. Although there has been modest improvements from 1960 to 2005 in the survival since diagnosis (partly due to simply earlier diagnosis), the median survival is still less than a year from the diagnosis (Musk et al., 2011). Misclassification of disease is a particularly important problem for mesothelioma which did not have a specific diagnostic category in WHO's ICD system until the 10th revision that was published in 1994. The histological diagnosis is also demanding, and many countries have set up specialist pathologist panels to verify the diagnosis.

First case reports suggesting an association with asbestos exposure were published in the 1950s by Weiss (1953) and Van der Schoot (1958). The first more comprehensive report of a possible association between asbestos exposure and mesothelioma concerned an outbreak of mesothelioma in a crocidolite mining region of South Africa (Wagner et al., 1960). The majority of the cases reported had worked in the mines, but cases were also reported among resident individuals with no history of occupational exposure.

Since then an asbestos-related excess of mesothelioma has been observed in a large number of case-control studies as well as in cohort studies in a variety of industries using and producing asbestos and asbestos-containing products. IARC (2012) reviewed 19 case-control studies and 17 cohorts reporting mesothelioma risk by asbestos exposure. IARC concluded that there is sufficient evidence in humans that all forms of asbestos are carcinogenic in humans and that asbestos causes mesothelioma.

Unlike for lung cancer, smoking is not a risk factor for mesothelioma. While the role of exposures other than asbestos, e.g. simian virus 40, in the causation of mesothelioma has been raised, asbestos, and non-commercial similar fibres erionite and more recently fluoro-edenite, are still the only established causal factors identified for mesothelioma (IARC 2012 and IARC 2017). Lacourt et al. (2014) conducted a large population-based case-control study in France. Based on 437 cases and 874 controls they calculated population attributable fractions (PAF) of 87% in men and 65% in women for asbestos exposure (occupational and non-occupational) in pleural mesothelioma. Rake et al. (2009) compared 622 mesothelioma cases and 1420 population controls in the UK and calculated PAFs of 86% and 38% for asbestos exposure in men and women, respectively. They also observed a shift towards downstream users in the occupational groups contributing to these excess case estimates; approximately half of the male cases were construction workers, and only four had worked for more than 5 years in asbestos product manufacture. Causes other than asbestos cannot be excluded for mesothelioma. However, given how widespread the use of asbestos has been in Europe, how long the latency time is and that even short exposure episodes are relevant, it seems extremely difficult to identify all relevant past asbestos exposures even with a comprehensive questionnaire or thorough interview. Therefore, it remains likely that undetected past exposures make asbestos account for more cases than the above PAF estimates.

While the causal association between asbestos exposure and mesothelioma is well-established, several issues are of potential relevance for quantitative exposure-response

assessment as well as for choice of measurement methods to control exposure. These concern the role of fibre type, fibre dimensions, mesothelioma localisation and time since exposure. Most relevant studies on these issues are summarised in the following paragraphs.

Fibre type

As reviewed by IARC (2012), although all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos. An excess of mesothelioma has been reported in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell et al., 1997), and in South Carolina asbestos textile workers who were predominantly exposed to chrysotile asbestos imported from Quebec (Hein et al., 2007). However, the fact that the chrysotile asbestos mined in Quebec was contaminated with a small percentage (< 1.0%) of amphibole asbestos (tremolite) has complicated the interpretation of these findings. McDonald et al. (1997) found in a nested case–control study for mesothelioma in the Thetford mines of Quebec that an association with asbestos exposure was evident in mines from a region with higher concentrations of tremolite, and not in another region with lower concentrations of tremolite. Begin et al. (1992) noted that although tremolite levels may be 7.5 times higher in Thetford mines than in Asbestos mines, the incidence of mesothelioma in these two Quebec mining towns was proportional to the size of their workforce. This suggests that the tremolitic content of the ores may not be a determinant of mesothelioma risk in Quebec.

In a mesothelioma case–control study in South Africa, an association was reported with exposures to crocidolite and amosite asbestos, but no cases were found to have been exclusively exposed to chrysotile asbestos (Rees et al., 1999). One possible explanation for these negative findings for chrysotile is that South African chrysotile asbestos may contain relatively little tremolite (Rees et al., 1992). Another possible explanation is that chrysotile mining began later, and production levels were lower than in the crocidolite and amosite mines of South Africa. Cases of mesothelioma have been reported among chrysotile asbestos miners in Zimbabwe, which has been reported to be uncontaminated with tremolite asbestos (Cullen and Baloyi, 1991). As the chrysotile related risk is lower for mesothelioma, a long follow-up is required to observe an excess risk. More recent studies, with very long follow-up are indicative of a risk of chrysotile. E.g. excess mesothelioma mortality (was reported in miners and millers from a chrysotile mine in Balangero, Italy (Mirabelli et al., 2008), reportedly free of amphibole contamination (Piolatto et al., 1990). Excess risks for mesothelioma from chrysotile have also been reported in more recent follow-ups of this cohort as well as in US asbestos textile cohorts as further described later in this section.

The mesothelioma causing potency of chrysotile and amphiboles have been described and analysed in four meta-analyses by Hodgson and Darnton (2000) and (Berman and Crump, 2003, Berman and Crump, 2008a, Berman and Crump, 2008b). Hodgson and Darnton's study was commissioned by the British Health and Safety Executive, while Berman and Crump's evaluation (2003) was commissioned by the US Environmental Protection Agency (EPA). Berman and Crump's 2008 analysis was a follow-up to their 2003 analysis. The two teams made use of different analytical techniques. The Dutch Expert Committee on Occupational Safety (DECOS 2010) and Garabrant and Pastula (2018) have performed some updated analyses of these two original meta-analyses (see below)

Hodgson and Darnton calculated the average asbestos exposure for each cohort and the additional mortality attributable to mesothelioma per cohort. The exposure-response relationship across cohorts collectively was based on the point estimates of mesothelioma risk and average fibre exposure 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. On the other hand, the approach ignored within cohort differences in exposure and mesothelioma risk and assumed that the mean cohort exposure is an unbiased estimate of the true mean exposure, which is not necessarily the case and depends on the sampling strategy. Hodgson and Darnton also investigated which model best fitted the observed relationship between exposure and response. Hodgson and Darnton used the percentage of mesothelioma deaths of all deaths expected (at an age of first exposure of 30) per unit of cumulative exposure as the measure for their analysis. Based on their analyses, they estimated that the ratio of the potency for mesothelioma (pleural and peritoneal combined) was 1:100:500 for chrysotile, amosite and crocidolite, respectively.

Berman and Crump analysed the exposure-response relationship for each cohort separately, considering within cohort differences in exposure and risk. The exposure response relation was characterized by a so called potency factor, in case of mesothelioma abbreviated as K_M. Using all cohort specific K_M values, they then performed a meta-analysis to derive various mesothelioma meta risk slope factors (meta-K_Ms). Berman and Crump assumed that the mortality rate from mesothelioma increases linearly with the intensity of exposure, and for a given intensity, increases indefinitely after exposure ceases, approximately as the square of time since first exposure (lagged 10 years) as assumed by the EPA 1986 model (See section 9.1.2 for a detailed description of the model). This model was tested with the crude data from several studies and found still to provide a good fit to the data.

Berman and Crump (2008b) concluded that the K_Ms showed evidence of a trend, with lowest K_Ms obtained from cohorts exposed predominantly to chrysotile and highest K_Ms from cohorts exposed only to amphibole asbestos, with K_Ms from cohorts exposed to mixed fibre types being intermediate between the K_Ms obtained from chrysotile and amphibole environments. Despite the considerable uncertainty in the K_M estimates, the K_M from the Quebec mines and mills was clearly smaller than those from several cohorts exposed to amphibole asbestos or a mixture of amphibole asbestos and chrysotile.

In Berman and Crump (2008a) regression models were fitted to the study K_M values that included information from surrogate studies to estimate fibre type (chrysotile versus amphiboles) and fibre length (short versus long) specific potency slopes. Alternative models were also fitted with exposure metrics based on different fibre widths. For mesothelioma, the hypothesis that chrysotile and amphibole asbestos are equally potent was strongly rejected by every metric (p values ranging from < 0.0001 to 0.001). The hypothesis that (pure) chrysotile is non-potent for mesothelioma was not rejected by any metric (p values ranging from 0.29 to 1). Best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of amphibole asbestos (depending on fibre dimension metric).

The IARC (2012) working group noted that there is uncertainty concerning the accuracy of the relative potency estimates derived from the Hodgson and Darnton and Berman and Crump analyses because of the severe potential for exposure misclassification in the studies.

The Dutch Expert Committee on Occupational Safety (DECOS 2010) performed a meta-analysis including the studies used by Berman and Crump (2008b) with the exception that only the latest study of one of the cohorts was included and excluding one study that was based on only one mesothelioma case. DECOS further applied a quality scoring covering documentation and assessment of the exposure used in the studies and calculated separately K_M values for the studies that were ranked highest according to those scores. When using all studies the ratio of K_Ms was 1:140:470 for chrysotile:mixed:amphibole exposure. When using only the highest ranking studies the ratio was 1:9 for chrysotile:mixed exposure, while none of the amphibole studies was scored with a high quality score and could not be used in this part of the analysis. These results also imply that K_M values, but in particular those for amphiboles, are estimated with considerable uncertainty.

Some more recent studies, not included in the above meta-analyses, have further analysed the mesothelioma risk in workers exposed to chrysotile.

Garabrant and Pastula (2018) compared mesothelioma risks in populations occupationally exposed to non-asbestos "elongate mineral particles" to the risk observed in asbestos exposed cohorts. In that context they also updated the mesothelioma potency estimates of Hodgson and Darnton (2000) for chrysotile, amosite and crocidolite by adding 6 studies not included in the 2000 analysis (either more recent follow-ups of studies included or completely new cohorts). However, not all new studies provided the necessary quantitative information. The relative mesothelioma potencies were 1:83:376 for chrysotile:amosite:crocidolite.

Loomis et al. (2009) followed 5770 asbestos textile production workers from 4 plants in North Carolina. Based on 4 deaths of pleural cancer and 4 deaths of mesothelioma among 2853 total deaths SMRs were increased both for pleural cancer (SMR 12; 95% CI 3.4 – 32) and mesothelioma (SMR 11; 95% CI 3.0 – 28). There were too few deaths from pleural cancer and mesothelioma for exposure–response analysis of those outcomes. Three workers with deaths coded to pleural cancer had been employed at a plant, where some processing of amosite is known to have occurred, but none of them had worked in insulation areas with such potential exposure. The remainder, including all four workers whose deaths were coded to mesothelioma, had worked at a plant, where there was no record of amphibole asbestos having been used. The pleural and mesothelioma deaths combined comprised 0.3% of all deaths. This percentage was nearly identical to the estimate developed for the chrysotile cohorts in a review article by Stayner et al. (1996). Based on the approach that Hodgson and Darnton (2000) used in their meta-analysis, Loomis et al (2009) estimated that the percentage of deaths per unit of cumulative fibre exposure was 0.0058% per fibre-year/cm^3 (f–y/cm^3) (0.0098% per f–y/cm^3 for workers followed ≥ 20 years). This estimate was considerably higher than the estimate developed by Hodgson and Darnton of 0.0010% per f–y/cm^3 for cohorts exposed to chrysotile. In a commentary Hodgson and Darnton (2010) pointed out that the estimate of mesothelioma mortality by unit exposure was still at least an order of magnitude lower than for amphiboles (0.5 and 0.1% per f–y/cm^3 for crocidolite and amosite, respectively), while acknowledging the uncertainty arising from low numbers of mesothelioma in each cohort. Hodgson and Darnton further concluded that the Loomis et al (2009) study further strengthened the proposition that the chrysotile related mesothelioma risk has been higher in asbestos textile plants than in mining.

In a further analysis of three of the plants of the above North Carolina asbestos textile cohort Loomis et al. (2019) reported a statistically significant associations of pleural cancer and mesothelioma mortality with cumulative exposure to chrysotile asbestos fibres, as well as with the duration of exposure and time since exposure. The associations were stronger but statistically less precise for the follow-up period when mesothelioma was a specific diagnostic entity in the ICD system. See further description of this study and the K_M in section 9.1.2 and Appendix 3.

In the recent cohort update from the Italian Balangero chrysotile mine Pira et al. (2017) reported seven deaths from pleural cancer among 1056 men, with an SMR of 5.5 (95% CI, 2.2 - 11.4). Ferrante et al. (2020) followed a slightly smaller number (972) of Balangero workers who had been employed at least 6 months. The mortality follow-up for 1965-2013 found 6 cases of pleural mesothelioma (SMR = 4.3; 95% CI 1.6 - 9.4) and two cases of peritoneal mesothelioma (SMR = 3.3; 95% CI 0.4 - 12). When analysed by tertiles the risk of mesothelioma increased by duration of exposure (p = 0.03) and cumulative exposure (p = 0.06) adjusted for latency, calendar period and age. Incident cases were also followed for 1990-2013 through a mesothelioma register. Based on 6 cases of pleural mesothelioma the incidence increased by duration of exposure and was statistically significantly increased in cumulative exposure categories of 27-345 and ≥ 346 f–y/cm^3. According to Pira et al. (2017) there is anecdotal evidence that crocidolite was occasionally present at the Balangero mine for material testing and mixture

preparation. Piolatto et al. (1990) reported that the examination of several samples of chrysotile from the mine ruled out the presence of contamination with amphiboles at detectable concentrations and that a new fibrous silicate, named balangeroite, was characterised (0.2%–0.5% of the total mass samples of asbestos commercialised from the Balangero mine). Although similar in shape to amphiboles, balangeroite is characterized by low biopersistence (Turci et al., 2009).

Wang et al. (2013a) reported two male and one female mesothelioma deaths among 865 asbestos textile workers in Chongqing, China corresponding the SMR of 33 (95% CI 9.1-120) and 170 (95% CI 30 – 940) in males and females, respectively. No risk estimates per cumulative exposure were calculated. Wang et al. (2013b) did not identify any mesothelioma cases in the 26-year follow-up of 1539 male Chinese chrysotile mine workers.

Jiang et al. (2018) conducted a study of predominantly female (83%) 46 mesothelioma cases and 230 controls in South Eastern China and found a statistically significantly increased odd ratio for possible (OR=10; 95% CI 1.4 - 65) and definite (OR = 64; 95% CI 12 – 330) definite exposure to hand-spinning chrysotile. There was also indication of dose-response by duration of exposure and semi-quantitatively estimated cumulative exposure. It is noted, however, that the study covered both domestic and occupational exposure. Moreover only 5 mesothelioma cases were identified at diagnosis during 2009-2011 while 41 were included retrospectively from hospital records based on a diagnosis in 1998-2008. Consequently only 22% of the cases and 100% of controls were alive at investigation meaning that the questionnaire-based assessment of exposure of the mesothelioma cases was relied heavily on information from next of kin compared to controls and information may not be comparable.

Some evidence of a difference in mesothelioma causing potency between crocidolite and amosite has been reported by Gilham et al. (2016) in a study comparing lung tissue burden of 133 mesothelioma patients to those of 262 lung cancer patients. A logistic model in which one crocidolite fibre is equivalent to 1.3 (95% CI 0.4 to 3.3) amosite fibres gave the best fit. It is noted that the comparison group (lung cancer) was comprised of a disease for which both crocidolite and amosite are established causes and also that any clearance of fibres between exposure and lung sampling was not accounted for.

Fibre size

Lippmann (1988) and Lippmann (1990) reviewed the animal and human data concerning fibre characteristics on lung deposition, retention, and disease for asbestos and other durable mineral fibres and suggested that mesothelioma risk is linked to fibres longer than 5 μm and narrower than 0.1 μm.

Berman and Crump (2008a) meta-analysis provides some indication that the potency for mesothelioma increases with fibre length. It should be realized that, a priori, the power of such analyses is limited given the number of studies involved in the comparison. When considering all fibre widths, the hypothesis that shorter fibres (5-10 μm) and longer fibres (> 10 μm) are equipotent was nearly rejected ($p = 0.09$). As regards fibre width there was little evidence that thin fibres (< 0.2 μm or < 0.4 μm) were stronger predictors of mesothelioma than all fibre widths combined. It is noteworthy that these comparisons assessed relative potencies and not absence of mesothelioma potential for a given fibre dimension. Secondly, the fibre size information for some studies was based on surrogate data from similar industries to estimate the fibre-size distribution for the studies included.

Dodson et al. (2003) reviewed the data on asbestos fibre length and pathogenicity and called for caution regarding exclusion of the role of short fibres in the causation of mesothelioma. They pointed out that the fibre size distribution observed by optical microscopy (that was used in the historical settings) and electron microscopy differs a lot with the latter technique being able to detect more short and thin fibres. Secondly, there

are observations that the fraction of short fibres is higher in pleural tissue than in lung parenchyma.

More recently Barlow et al. (2017) reviewed *in vitro*, animal and human data concluding, without separating mesothelioma, lung cancer and asbestosis, that "fibres longer than 10 µm and perhaps 20 µm are required to significantly increase the risk of developing asbestos-related disease in humans and that there is very little, if any, risk associated with exposure to fibres shorter than 5 µm".

Tumour location

As reviewed by IARC (2012) the ratio of pleural to peritoneal mesotheliomas has varied considerably in different epidemiological studies of asbestos-exposed cohorts. In the cohort studies included in the meta-analysis conducted by Hodgson and Darnton (2000), the percentage of mesotheliomas that were peritoneal varied from 0 to over 50%. Hodgson and Darnton reported that peritoneal mesotheliomas increased with the square of cumulative exposure to asbestos (i.e. a supra-linear relationship); whereas pleural mesotheliomas increased less than linearly with cumulative exposure to asbestos. This implies that the number of peritoneal mesotheliomas would dramatically increase relative to the number of pleural mesotheliomas at high asbestos exposure levels. In the latest follow-up of the Australian crocidolite miner cohort the mesothelioma rate increased with amount of exposure and the peritoneal mesotheliomas occurred preferentially in the highest exposure group, 37% compared with 15% overall (Berry et al., 2012). However Welch et al. (2005) found an association (OR = 5.0; 95%CI 1.2–22) between asbestos exposure and peritoneal cancer in a population-based case–control study. This study included a large percentage of men with what were judged to be low exposures to asbestos.

Time since exposure (first and last)

There is a long latency time from first exposure to occurrence of mesothelioma, at least 10 years but typically 30 to 40 years or more. For example in the latest follow-up of one of the high risk cohorts, Australian crocidolite miners, the shortest latency time observed was about 13 years, the average 35.4 years since first exposure and longest lag 58 years (Berry et al., 2012). Only 5% of the 282 pleural mesotheliomas and none of the 49 peritoneal mesotheliomas occurred earlier than 20 years since first exposure. Similar observations have been made in other cohorts, i.e. very few cases before 20 years from first exposure (e.g. Loomis et al. (2019), Luberto et al. (2019)) and indications of peritoneal mesothelioma lag times being somewhat longer than for pleural mesothelioma (Luberto et al., 2019). In the latest follow-up of Italian chrysotile miners 5 of the 6 incident pleural mesotheliomas occurred more than 40 years after first exposure (Ferrante et al., 2020).

Boffetta et al. (2019) performed a meta-analysis on the effect of time since end of exposure for the risk of mesothelioma and found no indication that the risk would decrease after cessation of asbestos exposure.

Barone-Adesi et al. (2019) studied 750 pleural and 175 peritoneal mesotheliomas from 43 pooled Italian cohorts and found rates of pleural cancer increasing until 40 years of time since first exposure but remaining stable thereafter. A monotonic increase of peritoneal cancer with time since first exposure was observed. When introducing an additional asbestos clearance term in the traditional model that takes into account cumulative exposure and time since exposure, the data fitted better than the traditional one for pleural ($p=0.004$) but not for peritoneal ($p=0.09$) mesothelioma.

The difference between pleural and peritoneal mesothelioma could be due to the route followed by the asbestos fibres to translocate to the peritoneum. It has been suggested that most of the fibres reach the peritoneum through the lymphatics (Kurimoto et al., 2009, Uibu et al., 2009). In particular, the diaphragm is extremely rich in lymphatics both on the pleural and peritoneal side that connect into a common sub-mesothelial

lacunar system, thus allowing the passage of fibres from the thoracic cavity to the abdomen (Li et al., 1996, Miserocchi et al., 2008). As most of the asbestos fibres are eliminated by the lung and the pleura through the lymphatics it is possible that this clearance occurring at the thoracic level and its contribution to the translocation of the asbestos fibres to the peritoneum could explain the difference in the temporary pattern between pleural and peritoneal mesothelioma.

The analyses of time effects are complicated by the fact that not only start and end of exposure and overall cumulative exposure, but also the time distribution of the overall cumulative exposure between start and end has an influence. Lacourt et al. (2017) studied 1196 male pleural mesothelioma cases and 2369 controls matched on birth year. Occupational exposure to asbestos was assessed using a job exposure matrix and the risk was represented in logistic regression models using a flexible weighted cumulative index of exposure. Subjects who accumulated 20 f–y/cm^3 over their entire job history with high doses during the first years and low doses thereafter were at higher risk of pleural mesothelioma than those who accumulated most of the doses later (OR=2.37; 95% CI 2.01 - 2.87).

The time since start of exposure and duration of exposure are parameters that in addition to exposure level are included in the EPA (1986) absolute mesothelioma risk model (see section 9.1.2).

Lung cancer

The first reports indicating that lung cancer could be induced by exposure to asbestos were published by Gloyne (1935) and Lynch and Smith (1935). These described lung cancer cases observed in heavily exposed workers with asbestosis. The first cohort study that demonstrated epidemiologically an excess of lung cancer among asbestos exposed workers was a study of UK asbestos textile workers that reported a statistically significantly increase mortality (11 observed and 0.8 expected deaths, $p < 0.00001$) (Doll, 1955). Since 1955, an association between lung cancer and occupational exposure to asbestos has been demonstrated in numerous cohort and case– control studies. IARC (2012) reviewed 23 case-control studies as well as 44 cohort studies from asbestos mining and milling, asbestos product manufacture and various downstream users like insulators, shipyard and construction workers. IARC concluded that there is sufficient evidence in humans that all forms of asbestos are carcinogenic in humans and that asbestos causes lung cancer.

While the causal association between asbestos exposure and lung cancer is well-established, several issues are relevant for quantitative exposure-response assessment. These concern the role of fibre type, fibre dimensions, lung cancer type, and interaction with smoking. Most relevant studies on these issues are summarised in the following paragraphs.

Fibre type

It is controversial whether chrysotile asbestos is less potent for the induction of lung cancer than the amphibole forms of asbestos. This controversy has been referred as the "amphibole hypothesis" (Cullen (1996), Stayner et al. (1996), McDonald (1998)). The argument is based on the observation that chrysotile asbestos fibres are less biopersistent in the lung than amphibole fibres (see section 7.1) and the observation on tremolite/chrysotile exposure and respective lung fibre content in Canadian chrysotile miners already described in the previous section on human studies on mesothelioma.

Several meta-analyses with slightly different approaches have been conducted in which the relative potency of different fibre types have been considered in relation to lung cancer. Lash et al. (1997) included 15 cohort studies with quantitative information on the relationship between exposure and risk. The exposure-response slopes from these studies were analysed using fixed and random effect models. Substantial heterogeneity in the slopes was found. The heterogeneity in the slopes was largely explained by

industry category, dose measurements, smoking and standardization procedures. Addition to the industry-specific dose-response coefficient of a variable for cohorts exposed predominantly to chrysotile added no significant information (p = 0.58), suggesting that after accounting for industry type, fibre type added no significant heterogeneity.

Hodgson and Darnton (2000) included 17 cohort studies and calculated the average asbestos exposure for each cohort and the additional mortality attributable to lung cancer per cohort. 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. An exposure response relation was described across the different studies. Substantial heterogeneity in the findings for lung cancer was also found in this analysis particularly for the chrysotile cohorts. The heterogeneity in the findings for the chrysotile cohorts was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (Liddell et al. (1997)), and asbestos textile workers in South Carolina (Dement and Brown (1994); Hein et al. (2007)), which differed by nearly 100-fold. No explanation has been found for these extreme differences although several possible explanations have been investigated. Co-exposure to mineral oils in the South Carolina textile plant was proposed as a possible explanation. A nested case–control conducted with the South Carolina cohort failed to provide evidence to support the hypothesis that mineral exposure was associated with an increased risk of lung cancer in this study population (Dement and Brown, 1994). Differences in fibre size distributions have also been considered to be a potential explanation. Based on their analysis, Hodgson & Darnton (2000) concluded that the ratio between lung cancer risk for chrysotile and the amphiboles was somewhere between 1:10 and 1:50. In addition, the Quebec study is among the first asbestos health effect studies with considerable study quality issues (job title information lacking for a substantial part of the cohort, migration between mines not accounted for, exposure assessment with limitation) while the South Carolina has considerably fewer limitations and is considered one of the more informative cohort studies (Lenters et al., 2011)

Berman and Crump (2008a, 2008b) analysed the exposure-response relationship for each cohort separately, and then performed a meta-analysis to derive various (linear) lung cancer risk slope factors (K_L = [RR-1]/cumulative exposure). Based on 15 cohorts Berman and Crump (2008b) concluded that for lung cancer, although there is some evidence of larger K_L from amphibole asbestos exposure, there is a good deal of dispersion in the data, and one of the largest K_L is from the South Carolina textile mill where exposures were almost exclusively to chrysotile. This K_L is clearly inconsistent with the K_L obtained from the cohort of Quebec chrysotile miners and millers, as discussed before.

Berman and Crump (2008a) performed analyses that were specific for both fibre type (chrysotile versus amphiboles) and fibre size (length and width). Fibre size information was only available for one of the cohort studies, and for the other studies it was obtained from studies that were conducted in similar industrial settings. Substantial variation was found in the findings from these studies with results for lung cancer varying by two orders of magnitude. The hypothesis that chrysotile is equipotent as the amphiboles for lung cancer was not rejected for fibres of all widths (p = 0.07) or for thick (width > 0.2 µm) fibres (p = 0.16). For thin fibres (width < 0.2 µm), there was significant (p = 0.002) evidence that chrysotile fibres were less potent than amphiboles. The analysis showed a nine times higher increased risk for long (> 10 µm) amphiboles compared to long chrysotile fibres of all widths, and had even higher estimates for specific diameters (a ratio of 16:1 for long amphibole versus long chrysotile for fibres with widths < 0.4 µm). Sensitivity analyses were also conducted in which the South Carolina or Quebec miners and millers cohorts were dropped from the analysis using fibres of all widths. Dropping the South Carolina cohort resulted in a highly significant (p = 0.005) result

that potency was greater for amphiboles than for chrysotile. Dropping the Quebec cohort resulted in there being no significant (p = 0.55) evidence of a difference in potency between the fibre types.

Lenters et al. (2011) performed a meta-analysis in which it was explored whether the quality of exposure assessment component of the study could explain the heterogeneity in exposure-response slope estimates. The studies were assessed for quality concerning five exposure assessment characteristics. It was found that studies with well-documented exposure assessment, larger contrast in exposure, greater coverage of the exposure history by exposure measurement data, and more complete job histories had higher meta- K_L values than did studies without these characteristics. Including all 19 studies yielded a meta- K_L 4.2 times lower than when using only studies that fulfilled all five criteria. The difference between K_L for chrysotile, mixed exposure and amphiboles was of borderline significance (p = 0.06) with K_L being in the ratios of about 1:3:8. However, this analysis could only be performed including all studies as there were too few studies that passed all quality criteria. Bivariate analyses including only one quality criterion at a time together with the fibre type, revealed that fibre type effects remained similar after adjustment for each study quality characteristics except one, which reduced the risk estimates of amphiboles and mixed exposures vs chrysotile.

The approach by Lenters et al subsequently spurred criticism on overreliance on one single study and appropriate assessment of study quality by Berman and Case (2012) – a criticism that was rebutted by Lenters et al. (2012), who argued for the use of the truncated data set, in which poorer-quality studies were excluded. In a subsequent commentary Berman and Case (2013) further argued that the analysis on fibre types was heavily influenced by the South Carolina chrysotile textile cohort whatever way study quality is considered, observed effects are better attributed to fibre type than study quality. It was later pointed out that while there would be wide agreement that study quality—especially the quality of exposure estimates— should be taken account of in reviewing the epidemiological evidence, the difficult question is how this can best be achieved (Hodgson, 2013). Heederik et al. (2013) maintained that exposure assessment quality has received too little attention in evidence syntheses of asbestos and lung cancer compared with the traditional focus on fibre type.

van der Bij et al. (2013) performed a meta-regression focused on the dose-response at low exposure levels using linear regression and splines. The same 19 studies as in the Lenters et al meta-analysis were included providing 104 separate risk estimates over a cumulative exposure range of 0.11 -4710 f–y/cm^3. Both linear and a natural spline meta-regression models were fitted to the risk estimates (see section 9.1.2. for a more detailed description of the lung cancer relative risk models). The latter model allows the risks to vary non-linearly with exposure. A natural spline model fitted the data best and showed that the lung cancer risk levelled off at higher exposure levels. With this model the relative lung cancer risk for cumulative exposure levels of 4 and 40 f–y/cm^3 was estimated between 1.013 and 1.027, and 1.13 and 1.30, respectively, either with a model adjusted for intercept at zero exposure or a model without an intercept. These risk estimates are equal or higher than the estimates from linear models reported by Hodgson and Darnton (2000) and Lenters et al (2011). The data indicated a non-significant three- to fourfold difference in RRs between amphiboles and chrysotile for exposures below 40 f–y/cm^3 which was lower than reported in the above meta-analyses. Additional analyses indicated that this difference reduced to approximately a factor 2 at higher exposures. The fibre type- specific risk estimates were strongly influenced by a few studies. Studies including latency analysis, limiting the exposure to relevant time windows of exposure tended to have lower intercepts, indicating that including no latency between exposure and lung cancer could also lead to measurement error in the exposure assessment when it incorrectly reflects the relevant etiological time window of exposure. I.e. including also exposures that happened close to the diagnosis/death from cancer and therefore most likely could not have played a toxicological role in its

initiation. When analyses were limited to studies with fewer limitations in the exposure assessment, higher risk estimates were obtained.

Both in Berman and Crump (2008b) and van der Bij et al. (2013) the models that were not adjusted for intercept, i.e. not anchored to zero extra risk at zero exposure, indicated relatively high risks at zero exposure (RR of 1.5 to 2.0). Such magnitudes of risks are unlikely to reflect only a true difference in baseline risk between the asbestos exposed group and the general population (e.g. from a difference in smoking habits or socio-economic status) and may also indicate an effect of exposure measurement error leading to so called attenuation of exposure-response slopes.

All the above meta-analyses assume that other risk factors for lung cancer, especially smoking, will have had no confounding effect on the asbestos-related risk estimates while it is noteworthy that as far as cohort studies included in this analysis are concerned, information on smoking habits was usually not available and only one case-control study with adjustment for potential confounding by smoking was available for inclusion in Lenters et al (2011) and van der Bij et al. (2013) and none in the other meta-analyses.

Fibre size

Lippmann (1988) and Lippmann (1990) reviewed the animal and human data concerning fibre characteristics on lung deposition, retention, and disease for asbestos and other durable mineral fibres and suggested that lung cancer risk is linked to fibres longer than 10 μm and thicker than 0.1-0.15 μm.

The meta-analysis by Berman and Crump (2008a) gave weak evidence that long fibres (length > 10 μm) were more potent than short fibres (5 - 10 μm) in models using all widths ($p = 0.07$). However, as pointed out already in the section on mesothelioma there was a lack of size-specific exposure data from the original epidemiological studies. This was a major limitation of this analysis with regard to estimating size-specific risk estimates.

Dodson et al. (2003) reviewed the data on asbestos fibre length and pathogenicity and called for caution when attempting to exclude any population of inhaled fibres, based on their length, from being contributors to the potential for development of asbestos-related diseases. They pointed out that the fibre size distribution observed by optical microscopy (that was used in the historical settings) and electron microscopy differs a lot with the latter technique being able to detect more short and thin fibres.

Stayner et al. (2008) published findings from an analysis of the South Carolina asbestos textile cohort in which fibre size specific estimates of lung cancer mortality was evaluated using information from a reanalysis of archived air samples using transmission electron microscopy (Dement et al., 2008). Long fibres (> 10 μm) and thin fibres (< 0.25 μm) were found to be the strongest predictors of lung cancer mortality in this study.

Loomis et al. (2012) reported an analysis of lung cancer risk by fibre dimension characteristics among 6136 North Carolina and South Carolina chrysotile textile factory workers. Historical dust samples were analysed, after a long-term storage, with transmission electron microscopy and a matrix of fibre size-specific exposure estimates was constructed. Lung cancer mortality was associated with exposure to fibres of all sizes but associated most strongly with exposure to thin long fibres. This was evident from the generally larger effect sizes and better model fits observed for structures <0.25 μm in diameter and structures >5 μm long. Moreover, when indicators for both dimensions were modelled simultaneously, the rate of mortality from lung cancer rose as the mean length of fibres to which workers were exposed increased and the mean diameter decreased. The specific categories of fibre size that best predict risk were difficult to identify because every worker was exposed to fibres throughout the range of length and diameter leading to strong correlations among exposure indicators defined by

those characteristics. In an analysis using only the North Carolina cohort data Hamra et al. (2014) reported that when fibre groups were modelled independently with a frequentist model, there appeared to be an increase in the dose-response with increasing fibre length and decreasing fibre width. However, when subjected to a Bayesian hierarchical structure analysis, this trend was not observed, and the effects of distinct fibre length groups appeared largely similar. Hamra et al (2014) acknowledged that even the use of a hierarchical modelling structure did not appear to overcome all the statistical fluctuations arising from the high correlations across fibre groups.

Lung cancer cell type

de Klerk et al. (1996) reported that among Australian crocidolite miners all cell types of cancer were significantly associated with log cumulative exposure to asbestos, apart from small cell cancer. Large cell anaplastic cancers had the highest relative risk, increasing 2.1-fold for each log f–y/cm^3 of exposure, but none of the estimated relative risks for any of the four types of cancer, or for all lung cancers, were significantly different from each other. Lee et al. (1998) conducted a case-control study with 456 surgically treated lung cancer patients. In multivariable logistic regression analysis, longer time since smoking exposure remained a significant predictor of adenocarcinomas ($p < 0.02$), but history of asbestos exposure did not predict tumour histology. More recently some relatively large studies have analysed the asbestos-related lung cancer risk by histological subtype.

Offermans et al. (2014) followed the about 58 888 male participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17.3 years. Results by histology of lung cancer were fairly comparable to overall lung cancer apart from adenocarcinoma, for which associations with most exposure variables were weaker or absent.

El Zoghbi et al. (2018) studied 6251 French lung cancer patients and did not identify a difference in the weighted prevalence of asbestos exposure between squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma and other lung carcinoma. El Zoghbi et al. (2017) analysed a pooled case-only study including 7256 male lung cancer cases in France and Canada. Tobacco smoking was associated with squamous cell carcinoma and small cell carcinomas as well as an earlier age at diagnosis. Additional exposure to asbestos did not modify the effect of tobacco smoking for either histological type or age at diagnosis.

Olsson et al. (2017) pooled 14 case-control studies conducted in 1985-2010 in Europe and Canada, including 17 705 lung cancer cases and 21 813 controls with detailed information on smoking habits as well as cumulative asbestos exposure data based on quantitative job-exposure-matrices. The risk associated with cumulative asbestos exposure was stratified by smoking status (never smoker, former smoker, current smoker). In men, in each smoking category there was an increased risk by asbestos exposure for all cell types combined as well as for the main subtypes adenocarcinoma, small cell carcinoma and squamous cell carcinoma. The ORs seemed to be higher for squamous and small cell carcinoma than for lung adenocarcinoma ($P = 0.11$ for the likelihood ratio test of homogeneity from the multinomial logistic regression model when these three subtypes were included). In female current smokers, the authors observed associations of asbestos exposure with all lung cancer subtypes, with all ORs increased approximately two-fold. In former smokers, none of the associations was increased; and among never-smokers, there was no association for lung adenocarcinoma or squamous-cell lung cancer but a relatively strong association for small-cell lung cancer even at low levels of asbestos exposure (exposed to <1.2 f–y/cm^3: OR = 3.5; 95% C 1.3 - 9.6) and in the highest exposure category (> 1.2 f–y/cm: OR 3.7; 95% CI 1.8 – 7.9.

Interaction between asbestos exposure and smoking

Most lung cancers among asbestos-exposed occur in smokers and former smokers and a multiplicative model of risk caused by asbestos and risk caused by smoking was introduced more than 40 years ago (Hammond et al., 1979). The outcomes of the model suggested that for smokers with asbestos exposure the risks observed for smoking and asbestos had to be multiplied leading to very high lung cancer risks. Vainio and Boffetta (1994) reviewed the studies on these synergistic effects and identified a variable pattern ranging from supra-multiplicative to less than additive, which was considered possibly reflecting the fact that both tobacco and asbestos are complex carcinogens that can affect more than one stage of lung carcinogenesis.

Offermans et al. (2014) followed the about 58 888 male participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17.3 years. The joint effects between smoking and asbestos exposure were between additivity and multiplicativity.

The above-mentioned recent large pooled case-control study by Olsson et al. (2017) found that the joint effect of smoking and asbestos was more than additive for all lung cancer subtypes in men. There was no deviation from a multiplicative scale for all types combined or by lung cancer cell type. There were clearly fewer asbestos exposed female (482) than male (6958) lung cancer cases available for studying the interaction. However, the pattern was similar in women with indications of a more than additive interaction. However, there was indication of deviation from multiplicative interaction for all types combined, small cell carcinoma and borderline for adenocarcinoma.

The recent reviews and meta-analyses indicate that the overall data set is compatible either with a more than additive or a multiplicative joint effect between asbestos exposure and smoking (Wraith and Mengersen (2007), Ngamwong et al. (2015), Klebe et al. (2019)). As a practical note, the first recognition of an interaction between occupational asbestos exposure and smoking habits involved high exposed asbestos workers with a high risk for developing lung cancer. This risk assessment involves extrapolations to very low risk levels and associated low exposure levels. At these levels, the nature of the relation between asbestos exposure and smoking is less relevant.

As smoking is an important determinant of lung cancer risk both among asbestos-exposed and unexposed individuals. However, as reference mortality or incidence data in the general population are not available by smoking habits, for practical reasons it is usually assumed in quantitative risk assessment that the interaction of smoking and asbestos exposure is a multiplicative effect (See e.g. DECOS 2010), i.e. that the relative risk from a given cumulative asbestos exposure multiplies the lower (absolute) background risk of a non-smoker with the same factor as it multiplies the higher (absolute) background risk of a smoker. It is also assumed that no confounding by smoking occurs, i.e. that the smoking habits of workers exposed to asbestos in the future (when the new OEL is in place) are similar to the smoking habits in the reference population used.

Larynx cancer

IARC (2012) reviewed 35 asbestos exposed cohort populations from 29 publications and found indications of increased risks in a number of settings with occupational asbestos exposure, e.g. North American insulators, Australian crocidolite miners, Italian chrysotile miners, UK and Italian asbestos textile workers, Danish asbestos cement factory workers. IARC also considered case-control studies valuable for this cancer site as they overcome the relative rarity of this diagnosis in cohort studies and as they permit consideration of potential confounding by tobacco and alcohol, the two most important risk factors for this malignancy. Of the 15 case-control studies reviewed, 14 found evidence for a significantly positive association between asbestos exposure and cancer of the larynx and only one reported an OR below 1.0.

IARC also based its conclusion on the meta-analysis conducted by IOM (2006) examining the association between asbestos exposure and cancer of the larynx. As regards 35 cohort populations studies examining "any" versus no exposure, the summary relative risk was 1.4 (95%CI: 1.2–1.6). For studies comparing "high" exposure versus no exposure, the lower bound summary relative risk was 2.0 (95%CI: 1.6–2.5), and the upper bound summary relative risk was 2.6 (95%CI: 1.5–4.5). These refer to calculating, when more than one high exposure metrics categories were reported, the risk against no exposure using as gradient either the "smallest high" vs none or the "largest high" vs none. The IOM also conducted a meta-analysis of 18 published case–control studies. This meta-analysis calculated a summary relative risk of 1.4 (95%CI: 1.2–1.8), before adjusting for consumption of tobacco and alcohol. After adjusting for tobacco and alcohol consumption, the association of cancer of the larynx with asbestos exposure persisted, with an adjusted summary relative risk of 1.2 (95%CI: 1.0–1.4).

It is noted that in 24 of the 35 cohort studies analysed by IOM (2006) the risk estimates were presented only overall for asbestos exposure without stratifying it by duration, qualitative or semi-quantitative intensity or quantitative intensity or cumulative exposure. In seven studies the risk estimates were stratified by duration of exposure, but not for more detailed exposure metrics. In two studies a qualitative intensity score was used (high, medium, low). One study (Liddell et al., 1997) reported the results from Quebec chrysotile miners and millers by cumulative exposure, not based on PCM fibre measurements but by million particles per cubic foot-yrs. The SMRs were similar, and not increased, both for those with < 300 million particles per cubic foot-years (SMR 1.03, 95% CI 0.66-1.53) and those with at least 300 million particles per cubic foot-years (SMR 1.08, 95% CI 0.40-2.35). One study among Italian chrysotile mine workers (Piolatto et al., 1990) reported SMRs by cumulative exposure categories of <100, 100-400 and > 400 f/cm^3, but based on only 1, 2 and 5 cases, respectively. The SMR was statistically significantly increased only in the highest exposure category (SMR 3.85, 95% CI 1.25-8.98), the p for trend was of borderline significance (p=0.05, one sided). As explained below the extended follow-up (Pira et al., 2017) of the same cohort did not find a significant trend or a significantly increased SMR in any of the cumulative exposure categories. It is noted that the upper limit of the lowest exposure category of that study using cumulative exposure as exposure metrics corresponds to a fibre concentration of 2.5 f/cm^3 assuming a 40-year career. Of the 18 case-control studies analysed by IOM (2006), 11 reported risk estimates only for overall asbestos exposure, three by duration and four by qualitative or semi-quantitative intensity.

IARC (2012) concluded that asbestos causes cancer of the larynx. IARC considered that there was insufficient information in the published literature to discern whether any differences exist among asbestos fibre types in their ability to cause laryngeal cancer. The reasoning for this conclusion was not explicitly stated. However, it is noted firstly that many studies concerned mixed exposure and those that concerned exposure to specific fibre types had small numbers of cases and thus risk estimates with wide confidence intervals. Secondly the exposure data did not allow comparing risk estimates for specific fibre types adjusted for level of cumulative exposure.

Since IARC assessment, Peng et al. (2016) performed a meta-analysis of 21 cohort studies analysing mortality from laryngeal cancer among asbestos exposed workers. The meta-SMR was 1.7 (95% CI 1.5 – 2.0). There was little evidence of heterogeneity among studies (I^2 = 0, p=0.80) and no indication of publication bias (Begg test p = 0.91, Egger test p = 0.34). The risk was increased in cohorts exposed to crocidolite (SMR 2.0; 95% CI 1.4 – 2.8), chrysotile (SMR 1.7; 95% CI 1.2 – 2.6), as well as in cohorts with mixed exposure (SMR 1.6; 95% CI 1.3 – 1.9). These fibre type specific meta-SMRs did not consider potential differences in cumulative exposure. The risk estimates available were not adjusted for potential confounding by other factors like smoking or alcohol.

Luberto et al. (2019) pooled 21 Italian asbestos cement manufacturing cohorts with 13 076 workers and calculated SMRs based on about 390 000 person-years of follow-up. There was a statistically non-significant excess of laryngeal cancer in men (SMR 1.2; 95% CI 0.9 – 1.6). There was no significant trend by cumulative exposure among men and the risk was not increased during 0-9, 10-19, 20-29 or 30-39 years since first exposure, but was significantly increases at 40-49 and more than 50 years. The risk was also increased in women (SMR 3.2; 95% CI 0.4 – 11) but based on only two cases and thus not allowing further analyses. It is noted that the calculation of cumulative exposure incorporated an approach weighing the measured cumulative exposure by asbestos fibre specific weights based on their mesothelioma potency observed in previous studies.

In the recent cohort update from the Italian Balangero chrysotile mine Pira et al. (2017) reported eight deaths from laryngeal cancer among 1056 men, with an SMR of 1.6 (95% CI, 0.7 - 3.1). There was no statistically significant trend by duration of exposure (p=0.32), time since first exposure (p=0.19) or cumulative exposure (p=0.16) and the SMR was not statistically significantly increased in any of the cumulative exposure categories of < 100, 100-400, $\geq$ 400 f/cm^3.

Offermans et al. (2014) followed 58 888 male participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17.3 years. Exposure estimates were generated using both the Dutch and the Finnish job exposure matrixes (JEM). There was a statistically non-significantly increased hazard ratio for ever vs never exposure both based on Dutch (HR 1.2; 95% CI 0.9-1.7) and Finnish JEM (HR 1.4; 95% CI 1.0- 2.0). There was no statistically significant trend by duration of exposure or semi-quantitative cumulative exposure by either JEM, while the trend by increasing duration of high exposure was significant by the Dutch JEM (p = 0.002).

No studies were identified having analysed the role of fibre size in the asbestos-associated risk of larynx cancer. The information is also limited as regards fibre type related differences or quantitative exposure-response relationship. As noted in section 7.1.4 there is also lack of, in contrast with studies of fibre deposition in the lower respiratory tract, little is known about fibre deposition and clearance from the upper respiratory tract, particularly the larynx.

Ovarian cancer

IARC (2012) reviewed the published literature examining the association between asbestos exposure and cancer of the ovaries. IARC pointed out that the data are relatively sparse, because the workforce occupationally exposed to asbestos has been predominantly male. IARC identified, however, 11 cohort studies that had assessed this association in 13 populations, ten with occupational exposure to asbestos and three with community based or residential exposure. Among the occupational cohorts increased SMRs (ranging from 1.5 to 5.4) were observed in all but one cohort and five cohorts were considered to provide strongly positive associations; two in gas mask production during 2nd world war, one in insulation board manufacture, one in asbestos cement production and one among women compensated for asbestosis. IARC additionally noted that increased incidence or mortality, although without statistical significance, was observed in three cohorts of women or girls with non-occupational exposure either as family members of asbestos cement factory workers or as living in the vicinity of a crocidolite mine. It is noted that this non-occupational exposure seems to have been quite high as demonstrated by the significantly increased mortality from respiratory cancer (SMR 2.6, 95% CI 1.9 – 3.8) as observed in the asbestos cement factory family member cohort and for lung cancer (SMR 2.2, 95% CI 1.5 – 3.1) in the crocidolite mine area resident cohort (Ferrante et al. (2007) Reid et al. (2008) Reid et al. (2009)). IARC also considered the possible misclassification of peritoneal mesothelioma as ovarian cancer in the past and noted that three cohorts specifically examined this possibility, but

all failed to find sufficient number of misclassified cases to explain the increased risk. IARC concluded that asbestos causes cancer of the ovary.

Reid et al. (2011) performed a meta-analysis of fourteen cohort and two case-control studies. When all studies were included in a meta-analysis, the meta-relative risk was 1.75 (95% CI, 1.45–2.10). When including only studies that used a pathological review of cases identified from death certificates or cancer reports, the effect estimate was reduced to 1.54 (95% CI, 1.22 – 1.95). When further reducing the studies to include only cancer incidence studies the effect estimate was 1.29 (95% CI, 0.97–1.73). Camargo et al. (2011) conducted a meta-analysis focused on cohorts clearly and unequivocally exposed to asbestos (such as asbestos cement manufacture, asbestos mining and milling, asbestos textile industry, insulators) and reporting mortality (one study reported incidence) from cancer of the ovaries. Population or hospital-based case – control studies were not included. Based on 18 cohorts the overall SMR was 1.8 (95%CI 1.4 – 2.3), with moderate degree of heterogeneity among the studies (I^2 = 35, p = 0.06) and no indication of publication bias (Egger p = 0.16). Compensation for asbestosis, magnitude of SMR for lung cancer, geographical region and sample size where statistically significant predictors of pooled ovarian cancer SMR and simultaneous inclusion of these predictors virtually eliminated the heterogeneity. Pooled SMRs were increased in heavily exposed populations, such as cohorts of women compensated for asbestosis and cohorts with lung cancer SMR > 2. SMRs for European cohorts and for small cohorts where higher than for US cohorts or larger cohorts, respectively. Pooled SMRs were larger for cohorts exposed predominantly to crocidolite (SMR 2.2; 95%CI 1.4 – 3.4) or mixed asbestos (SMR 2.0; 95%CI 1.4 – 2.8) than for cohorts exposed to chrysotile (SMR 1.4; 95%CI 0.9 – 2.2). Only six studies provided estimates by overall exposure duration, high exposure duration or cumulative exposure. The pooled SMR of high exposure groups in those cohorts was 2.8 (95%CI 1.4 – 5.7). Camargo et al (2011) also tried to assess any potential effect of misclassification of peritoneal mesothelioma as ovarian cancer by calculating the pooled SMR separately for studies that either included or did not include pathological confirmation of diagnosis. No difference was observed, but the power of this test was limited because only two studies included pathological confirmation. Estimates of cumulative exposure among asbestos-exposed workers were used for only two studies concerning NC and SC chrysotile plant cohorts. These two studies did not find an increased risk for ≥ 120 fibre-days/ml (Loomis et al. 2009) or > 30 years of employment and ≥ 5479 fibre-days/ml (Hein et al., 2007). It is noted that the underlying data have been provided to Camargo et al. (2011) separately and are not reported in the original publications that focus on lung cancer. Depending on the number of working days per year, they would correspond to 0.3-0.4 or 15-20 f-y/cm^3. Later analyses have reviewed the asbestos etiology of ovarian cancer together with other causative agents and have confirmed the asbestos-related risk of ovarian cancer (Reid et al. (2017), Slomovitz et al. (2021))

Ferrante et al. (2017) pooled data from 43 Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding). There were 43 deaths from ovarian cancer among the 2362 female cohort members (SMR 1.4, 95% CI 1.0 – 1.9). Luberto et al. (2019) reported a further analysis of those 2303 women who were members of the 21 Italian asbestos cement cohorts. There was a statistically non-significant increase in mortality from ovarian cancer overall (SMR 1.5; 95% CI 0.9 – 2.3). There was no statistically significant trend by tertile of cumulative exposure. However, the mortality was significantly increased in the highest tertile of > 620 f–y/cm^3 (SMR 2.4; 95%CI 1.3 – 4.1). There was a significantly increased mortality at > 50 years from first exposure (SMR 2.8: 95% CI 1.3 – 5.4), but no increase at 0-9, 10-19, 20-29, 30-39 or 40-49 years from first exposure. It is noted that the calculation of cumulative exposure incorporated an approach weighing the measured cumulative exposure by asbestos fibre specific weights based on their mesothelioma potency observed in previous studies.

Wang et al. (2013a) reported one death from cancer of the ovaries among 277 Chinese female chrysotile textile workers (SMR 7.7; 95% CI 1.4 – 44).

No studies were identified having analysed the role of fibre size in the asbestos-associated risk of ovarian cancer. The information is also limited as regards fibre type related differences or quantitative exposure-response relationship. Due to the predominantly male workforce in occupations with past exposure, there is a lack of data concerning quantitative exposure-risk relationship.

Other cancers

IARC (2012) reviewed the epidemiological data on asbestos exposure and risk of cancers of pharynx, oesophagus, stomach and colorectum. For these IARC noted that positive associations had been observed between exposure to asbestos and cancers of pharynx, stomach and colorectum, but the evidence was not considered strong enough to warrant classification as sufficient. For cancer of the colorectum the working group was divided.

For cancer of the pharynx the IARC working group examined 16 cohort and six case-control studies. IARC also noted the recent meta-analysis of IOM (2006). IOM reported that for cohort studies the estimated aggregated relative risk of cancer of the pharynx from any exposure to asbestos was 1.4 (95% CI 1.0 – 2.0) and that few studies had evaluated the dose-response trends and that there was no indication of higher risks associated with more extreme exposures. IOM also conducted a meta-analysis of the case-control studies and reported a summary risk estimate for any asbestos exposure of 1.5 (95% CI 1.1 – 1.7). The IOM observed that the case-control studies were inconsistent, and there was little evidence for a dose-response relationship.

For cancer of the oesophagus the IARC working group examined 25 cohort and five case-control studies. IARC also noted the recent meta-analysis of IOM (2006). IOM reported that for cohort studies the estimated aggregated relative risk of cancer of the oesophagus from any exposure to asbestos was 1.0 (95% CI 0.8 – 1.3). IOM also examined the relative risk of "high" versus no exposure calculated a lower bound summary relative risk of 1.4 (95% CI 0.8 – 2.3) and a higher bound summary relative risk of 1.4 (95 % CI 0.8 – 2.6). IOM determined that there were too few case-control studies to permit a meta-analysis. More recently Li et al. (2016) reported a meta SMR of 1.2 (95% CI 1.1 – 1.4) based on 21 cohort studies. Luberto et al (2019) followed 10275 male and 2303 female members of the 21 Italian asbestos cement cohorts. There was a statistically non-significant increase in mortality from cancer of the oesophagus in men (SMR 1.2; 95% CI 0.9 – 1.7). There was no statistically significant trend by tertile of cumulative exposure. There were no deaths from oesophagial cancer among the women.

For cancer of the stomach the IARC working group examined 42 cohort and five case-control studies. IARC also noted the recent meta-analysis of IOM (2006). IOM conducted a meta-analysis of 42 cohort studies. The IOM noted that the "majority of cohort relative risk estimates for cancer of the stomach exceed the null value (1.0), indicating excesses, although estimates varied considerably in strength." In cohorts that compared "any" versus no exposure, the summary relative risk was 1.2 (95%CI 1.1 - 1.3). The IOM noted that with respect to dose–response, the summary estimates were stable. I.e. in the cohorts that compared "high" versus no exposure, the lower bound summary relative risk was 1.3 (95%CI 1.0 - 1.8), and the higher bound summary relative risk, 1.3 (95%CI 1.0 - 1.8). The IOM conducted a meta-analysis of the five case–control studies resulting in a combined relative risk of 1.1 (95%CI 0.8 - 1.6). The summary odds ratio increased when only extreme exposure was considered (OR 1.4; 95%CI 0.9 - 2.2). The IARC Working Group also developed a scatter plot comparing SMRs for lung cancer with SMRs for cancer of the stomach in the same cohorts. A positive trend was observed between the two with a correlation coefficient (r2) of 0.66. More recently Fortunato and Rushton (2015) reported a meta SMR of 1.2 (95% CI 1.0 – 1.3) based on 40 cohort mortality and 15 cohort incidence studies. The SMR was higher for studies with a lung cancer SMR of at least 2 (SMR 1.5; 95% CI 1.2 – 1.8) than for studies with a lung cancer SMR < 2 (SMR 1.0; 95% CI 0.9 - 1.2). Ferrante et al. (2017) pooled data from 43 Italian asbestos

cohorts (asbestos cement, rolling stock, shipbuilding). The SMR for stomach cancer was not increased among men (SMR 0.9; 95% CI 0.8 – 1.0) or women (SMR 0.9; 95%CI 0.7 – 1.2). Luberto et al. (2019) reported a further analysis of members of the 21 Italian asbestos cement cohorts. The SMR for stomach cancer was not increased overall and there was no trend by increasing cumulative exposure.

For cancer of the colorectum the IARC working group examined 41 cohort and 13 case-control studies. IARC also noted the recent meta-analysis of IOM (2006). IOM conducted a meta-analysis of 41 cohort studies. In studies that compared "any" versus no exposure, the summary relative risk was 1.2 (95%CI 1.0 - 1.3). For studies comparing "high" versus no exposure, the lower-bound summary relative risk was 1.2 (95%CI 0.9 - 1.7), and the upper bound summary relative risk, 1.4 (95%CI 1.1 - 1.7). The IOM also conducted a meta-analysis of the published case–control studies. Overall, 13 studies comparing "any" versus no exposure yielded a summary relative risk of 1.2 (95%CI 0.9 - 1.5). The IARC Working Group also developed a scatter plot comparing standardized mortality ratios for lung cancer with standardized mortality ratios for cancer of the colorectum in the same cohorts. The trend was positive with a correlation coefficient (r2) of 0.59. More recently two meta-analyses have been published. Huang and Lan (2019) reported a meta SMR of 1.1 (95% CI 1.0 – 1.1) based on 47 cohorts. The SMR was higher for studies with a lung cancer SMR of at least 2 (SMR 1.3; 95% CI 1.2 – 1.5) than for studies with a lung cancer SMR < 2 (SMR 1.0; 95% CI 1.0 - 1.1). Kwak et al. (2019) reported a meta SMR of 1.2 (95% CI 1.1 – 1.3) based on 46 cohorts. The SMR was higher for studies with a lung cancer SMR of at least 2 (SMR 1.4; 95% CI 1.3 – 1.6) than for studies with a lung cancer SMR < 2 (SMR 1.0; 95% CI 0.8 - 1.1).). In the pooled data of 43 Italian asbestos cohorts (Ferrante et al., 2017) in men the SMR for colon cancer (SMR 1.0; 95% CI 0.9 – 1.1) or rectal cancer (SMR 1.0; 95% CI 0.8 – 1.1) was not increased. Similar risk estimates with wider confidence intervals were reported for women. Luberto et al. (2019) reported a further analysis of members of the 21 Italian asbestos cement cohorts. The SMR for colon cancer or rectal cancer was not increased overall and there was no trend by increasing cumulative exposure.

Peng et al. (2016) recently reported a meta-analysis on prostate cancer mortality based on 17 cohort studies in asbestos-exposed populations. The summary risk estimate was slightly increased (SMR 1.2; 95% CI 1.1 – 1.3). However, the three studies with highest weight (altogether 83% weight) where in male populations with non-occupational exposure (two studies) or with relatively low occupational exposure (one study) each showing a lung cancer risk that was either not increased or only marginally increased (risk estimates 0.96 ,1.14, 1.20). Among the male members of the pooled 43 Italian asbestos cohorts (SMR 1.0; 95% CI 0.9 – 1.1) or the 21 asbestos cement cohorts therein (SMR 1.0; 95% CI 0.8 – 1.2) the risk was not increased (Ferrante et al. 2017, Luberto et al 2019).

Other data

Based on both global and national European estimates asbestos-related cancers are currently the leading occupational fatalities (GBD (2020), Rushton et al. (2012)). This is also evident from occupational disease registry data.

Cancers diagnosed currently reflect exposures that started decades ago, and data sources used for burden of disease estimates make use of relatively crude historic exposure data to predict present or future burden of disease and do not contain sufficiently granular data to provide risk estimates that would link the risk to a given measured or estimated cumulative exposure in a known cohort or exposed population. Such approaches also often assume a fixed ratio between asbestos-related mesothelioma and lung cancer (and other cancer sites) which may not correctly account for the differences in latency time between the cancer sites when assessing long-term trends. For all these reasons, such data are not suitable for quantitative risk assessment of setting an OEL or deriving an exposure risk relationship which require information on

the relation between (cumulative) exposure and excess risk of cancer in the exposed population. For the same reasons it is not possible to compare data from such burden of disease and health impact type of approaches with results from quantitative risk assessments used for setting regulatory standards. The same methodological restrictions apply to data reported in the worker compensation systems, where, in addition to the above-mentioned limitations, also the level of under-recognition of occupational diseases is an unknown parameter that limits quality of the information. As further described in Appendix 4 and summarised in section 9.1.2 most evidence on exposure-response relations for asbestos related cancers comes from epidemiological studies (cohort studies or case-control studies) which have been conducted since 1950s. In most of these studies, exposure data is available over periods of several decades measured with different techniques but converted to and expressed in PCM measurements.

It is further noted that during the preparation of this report work was ongoing in US EPA on evaluating asbestos. The draft reports were labelled as documents not to be cited. The final report was published in December 2020, but addresses only the current uses of chrysotile still allowed for certain applications in the US (EPA, 2020). According to EPA, a separate assessment of the legacy uses and associated disposals of asbestos will be performed in a later stage.

Recent exposure-response assessments for lung cancer and mesothelioma

As described in the previous sections, lung cancer and mesothelioma are the cancer sites for which robust quantitative exposure-response relationships have been identified using human epidemiological data. In the preceding sections the most recent meta-analyses were described calculating quantitative exposure-response slope factors for lung cancer (van der Bij et al. 2013 and Lenters et al 2011) and mesothelioma (DECOS 2010) . The DECOS (2010) meta-analysis for lung cancer (as well as for mesothelioma) is further described in section 9.2.1.

During the literature review of the more recently published individual studies were identified concerning: (1) new updates of existing cohort studies for which earlier reports had been used in the above-mentioned meta-analyses, (2) completely new cohorts not yet included in these meta-analyses and, (3) new case-control studies. Those were scrutinised as to whether or not they were suitable for inclusion in an updated meta-(regression) analysis to estimate the exposure-risk relationship. That assessment is summarised in section 9.1.2 and further described in Appendix 3.

7.7.2 Animal data

Carcinogenicity studies performed with experimental animals are extensively described in IARC (2012) and in NFA (2019). In this document the focus is on presenting the key studies.

Inhalation studies

The chronic effects of five different types of asbestos fibres was assessed in the study by Wagner et al. (1974). Wistar rats inhaled 10-15 mg/m^3 of chrysotile (two different types), amosite, crocidolite or anthophyllite 7 h/day (mostly 5 days/week) for periods ranging between 1 day and 24 months. The incidence of thoracic tumours was high already after 3 months of exposure: with chrysotile A it was 44%, with chrysotile B 53%, with amosite 27%, with crocidolite 42%, and with anthophyllite 16%. However, also in the control group, lung tumours were reported at a rate higher than the normal spontaneous tumour rate, and therefore IARC (2012) considered that the tumour findings reported in exposed animals may be a “misinterpretation of histopathological lesions because of a lack of experience at that time”.

In a study comparing the effects of chrysotile (2 or 10 mg/m^3), amosite (10 mg/m^3) and crocidolite (5 or 10 mg/m^3) in Wistar rats exposed up to 12 month, the highest tumour

incidences (21-38%; mainly lung tumours and peritoneal connective tissue tumours) were observed in animals exposed to chrysotile (Davis et al., 1978). It was discussed that this may have been due to the relatively high fraction of >20 µm chrysotile fibres.

Exposure of Fischer rats to 10 mg/m^3 chrysotile during 12 months (7 h/day, 5 days/week) resulted in 12 thoracic tumours (11 adenocarcinomas and 1 adenoma) among the 48 animals (Wagner et al. 1984, reviewed in IARC, 2012).

Hesterberg et al. (1998) exposed rats to chrysotile (10 mg/m^3, 6 h/day, 5 days/week, 2 years). Rats were euthanised after 13-104 weeks of exposure and after a 23-week recovery period. The reported findings included thoracic neoplasms, pulmonary fibrosis, chronic inflammation, bronchoalveolar hyperplasia and collagen deposition.

One mesothelioma and 2 carcinomas were observed among 58 female Osborne-Mendel rats exposed 2 years to 7 mg/m^3 crocidolite asbestos fibres (6 h/day, 5 days/week), with follow-up for the life span. No tumours were found in the control group. (Smith et al., 1987)

When Davis et al. (1986) compared short and long amosite fibres, no tumours were seen in animals exposed to short fibres, whereas a tumour incidence of 33% (13/40) was reported for the long-fibre group. IARC (2012) considered that the milling process used to create short fibres may have affected the surface reactivity of amosite.

The study by Cullen et al. (2000) reported 7 lung carcinomas, 9 lung adenomas, and two mesotheliomas among 42 rats exposed to 1000 amosite fibres (> 5 µm)/cm^3, 7 h/day, 5 days/week during 12 months.

In a well-documented study, McConnell et al. (1994) exposed male Fischer rats to 10 mg/m^3) crocidolite dust (236 fibres/cm^3 >29 µm) 6 h/day, 5 days/week. The exposure ended at 10 months due to unexpected deaths. Lung tumours were found in 14/106 rats that survived the second year or longer. One of these was a mesothelioma and five were carcinomas. Lung adenomas were observed in 2/126 animals in the control group. Mc Connell et al. (1999) also exposed hamsters to amosite (0.8, 3.7, 7.1 mg/m^3, 6 h/day, 5 days/week, 78 weeks). Pleural mesotheliomas were found in 26% of those mid-dose animal that survived for at least 32 weeks, and 20 % of the high-dose animals. In the low-dose group 3/83 surviving animals had mesotheliomas. No lung tumours were observed in any of the groups.

A high incidence of pleural mesotheliomas was seen in Fischer rats exposed to erionite. The concentration was 10 mg/m^3 in Wagner et al. (1985), and unknown in Wagner et al. (1990; reviewed in IARC 2012). The exposure duration was 12 months (6 h/day, 5 days/week). 27/28 rats in the first study and 24/27 rats in the second study developed mesotheliomas. No control group was included in the later study.

One-year exposure to tremolite (10 mg/m^3, 7 h/day, 5 d/week) resulted in tumours in 16 out of 39 exposed rats (Davis et al., 1985).

Oral studies

Chrysotile, amosite or crocidolite fibres were administered to rats and hamsters in the diet (1% in pelleted food) for the whole lifetime in a series of studies by the National Toxicology Program (NTP, 1983, NTP, 1985, NTP, 1988, NTP, 1990a, NTP, 1990b). The dams of these animals had also been given the same fibre-containing diet. Altogether, there were no increases in the incidences of inflammatory, pre-neoplastic or neoplastic gastrointestinal lesions. Only in male rats exposed to chrysotile, there was a slightly increased incidence of adenomatous polyps in the large intestine, but the increase was not statistically significant. A slight increase (not statistically significant compared to concurrent controls) in adrenal cortical adenomas was observed in female and male hamsters exposed to chrysotile. No lesions were observed in other organs, including mesentheric lymph nodes, lungs, larynx and trachea.

Other routes of administration

A number of studies with intrapleural and intratracheal administration of asbestos fibres resulted in mesotheliomas and lung tumours in exposed rats or hamsters, particularly with fibres longer than 5 µm. Such studies are summarised in IARC (2012). Also studies with intraperitoneal administration have been performed, some of them presenting increased tumour incidences, but at lower rates than by intrapleural administration (IARC, 2012).

In the context of nanomaterial work, results from a rat peritoneal model indicated that fibre length was an important determinant of toxicity. Inflammation or fibrosis was not seen with the short (<5 µm) nanowires (Poland et al., 2012). However, direct application of such results from other substances and limited to peritoneum is not considered sufficient to set a fibre length cut-off for asbestos-related toxicity.

7.7.3 Summary

Human epidemiological studies have shown that all types of asbestos fibres cause cancer of the lung (all main histological subtypes), mesothelioma, cancer of the larynx and cancer of the ovaries. Animal studies support these findings. The human data is less consistent as regards other sites of cancer.

For amphibole asbestos, especially the most widely used ones, crocidolite and amosite, there is human evidence that they are more potent in causing mesothelioma than chrysotile. As regards lung cancer, there is also an indication that amphiboles are more potent. However, this evidence for lung cancer is not consistent across industries and is less pronounced when considering only the studies with highest quality (of the exposure assessment component). So, the difference in potency seems less pronounced than for mesothelioma. For cancers of the larynx and ovaries, there are insufficient data to conclude on fibre type specific potencies.

There is some limited indication that fibre dimensions may influence the risk of mesothelioma and lung cancer, with potency increasing with increasing length and decreasing width. However, based on human and animal data, it is not possible to exclude an asbestos associated risk of cancer for any fibre width or length category studied. These observations are nearly exclusively based on optical microscopy and thus concern fibres with dimensions detectable and countable with that method, i.e. fibres thicker than about 0.2 µm and longer than 5 µm. For cancers of the larynx and ovaries, there is insufficient data to conclude on fibre dimension specific potencies.

Smoking is not a risk factor for mesothelioma. The recent reviews and meta-analyses indicate that for lung cancer the overall data set is compatible either with a more than additive or a multiplicative joint effect between asbestos exposure and smoking. For practical reasons of performing the risk calculations, it can be assumed that the interaction of smoking and asbestos exposure is a multiplicative effect, i.e. that the relative risk from a given cumulative asbestos exposure multiplies the lower absolute background risk of a non-smoker with the same factor as it multiplies the higher absolute background risk of a smoker.

Numerous (meta-)analyses have quantitatively estimated the asbestos associated risk of mesothelioma and lung cancer. The EPA (1986) absolute risk model has been used for mesothelioma, while lung cancer risk has been modelled using relative risk models, either linear or non-linear. For lung cancer there is an indication that restricting the meta-analysis to studies with highest quality provides quantitative risk estimates that are higher than when all studies are used. This is consistent with the epidemiological theory that misclassification of exposure when random, results in flattening of the observed dose-response relationship in comparison of the true dose-response. There is also an indication that for lung cancer the exposure-response is not linear and the actual

risk at levels around and below the current EU OEL may be higher than the risk that would be calculated with linear extrapolation from the historical industrial cohorts with much higher exposures. This evidence is based on flexible regression type of analyses (using splines) and all individual data points across quantitative exposure response studies. For cancer of the larynx and cancer of the ovaries there are no reliable quantitative dose-response estimates. However, there is some indication that at the relatively low exposure levels, which are the main concern today, these cancers contribute only few excess cases when compared with lung cancer ad mesothelioma.

The epidemiological data does not allow identifying a threshold for asbestos-related risk of lung cancer or mesothelioma. The recent meta-regression analysis discussed earlier also do not give an indication of the existence of an exposure threshold.

The mode of action is further discussed in section 8.1.

The most recent meta-analyses calculating quantitative exposure-risk relationship slope factors for lung cancer and mesothelioma were published in 2010-2013 (van der Bij et al 2013, Lenters et al 2011, DECOS 2010). Some new studies providing quantitative exposure-response estimates for both lung cancer and mesothelioma have been published since. These concern extended cancer follow-ups of previously reported cohorts, some relatively small new cohorts and new case-control studies among which one very large multicentre case control study for lung cancer. Those new studies and their suitability for inclusion in an updated meta-analysis are further discussed in section 9.1.2 concerning Cancer risk assessment.

7.8 Reproductive toxicity

7.8.1 Human data

There are no human data on reproductive toxicity. However as explained in section 7.1 asbestos fibres have also been observed in placentas and various foetal tissues of stillborn infants and to lesser quantity in placentas of liveborn health infants.

7.8.2 Animal data

No inhalation studies focusing on reproductive effects of asbestos were found. Also the data by other routes of administration is very limited, but it is anyhow suggesting a potential for foetal exposure via the mother, as well as a potential for teratological effects.

In a study with administration of chrysotile asbestos fibres by oral gave to pregnant mice, transplacental transfer of fibres to the foetuses was observed. Two days before mating female mice were given two doses of 50 µg chrysotile (mean length 22.4 µm; range 2.3-70.0 µm), and additional doses were given on gestation days 7 and 12. The pups were sacrificed 8, 11, 19, or 20 days after birth. The presence of asbestos fibres was examined in lungs and liver of two pups from each of the 12 dams. In lungs, the mean fibre count was 780 fibres/g (mean fibre length 18.48 µm), and in liver 214 fibres/g (mean length 18.30 µm). No fibres were detected in lungs or liver of pups in the control group. There were no significant differences in foetal weight or postnatal mortality when comparing the exposed animals with the control group. (Haque et al., 2001). In a very limited mouse study (only five adult animals included), crocidolite suspension was injected into the tail vein of pregnant mice. When examining placental and foetal digests, transfer of fibres from the dam to the placenta and foetus was observed (Haque and Vrazel, 1998).

In the study by Fujitani et al. (2014), the teratogenic potential of 40 mg/kg bw of chrysotile, amosite, or crocidolite, administered by intraperitoneal injection on gestation day 9, was investigated in mice. Dams were euthanized on gestation day 18, and

foetuses were examined. No effects on maternal body weight were observed but the liver and spleen weights were statistically significantly increased in dams exposed to amosite or crocidolite. Furthermore, the numbers of neutrophils and total white blood cells were increased in those groups. The incidences of pup skeletal malformations (mainly fusion of vertebrae) were increased in all treatment groups. In addition, increased incidences of external malformations (mainly reduction deformity of limb) were observed in the group exposed to amosite. The number of dams with early dead foetuses was increased after exposure to chrysotile or amosite fibres.

Chrysotile, amosite or crocidolite fibres were administered to pregnant rats and hamsters in the diet (1% in pelleted food) in a series of studies by the National Toxicology Program (NTP, 1983, NTP, 1985, NTP, 1988, NTP, 1990a, NTP, 1990b). The focus of the study was on carcinogenicity of the offspring (life-long exposure). No fertility or developmental effects were reported.

7.8.3 Summary

The available data indicates that asbestos fibres may transfer from the mother to the foetus, and thus there is a potential for asbestos-induced foetal effects upon maternal asbestos exposure. Developmental effects were reported in one animal study with intraperitoneal administration of chrysotile, amosite or crocidolite fibres. The data set for reproductive toxicity is not very robust. However, it seems justifiable to base the OEL on the exposure-risk relationship observed for well-established cancer risks.

8. Other considerations

8.1 Mode of action (MoA) considerations

As described in section 7.7. there is significant toxicological and epidemiological evidence that asbestos fibres are carcinogens. Furthermore, the available data shows that exposure to asbestos fibres can result in mutagenic effects *in vivo*. In addition, there is some evidence indicating local genotoxic effects. No *in vivo* studies are available to demonstrate a threshold for genotoxicity, furthermore the epidemiological data does not indicate existence of a threshold for cancer risk. Therefore, asbestos fibres should be considered as non-threshold genotoxic carcinogens.

A similar interpretation was made by NFA (2019), who concluded: "[…] the current working group recommends that asbestos fibres are hazard assessed using a numerical risk assessment based on a linear approach and thus based on a notion that there is no threshold". Also Afsset (2009b) followed the same approach: "The OEL committee decided to maintain a carcinogenic mechanism of action without a threshold for asbestos fibres". The mechanisms involved were discussed by IARC (2012) and are summarised in Figure 1.

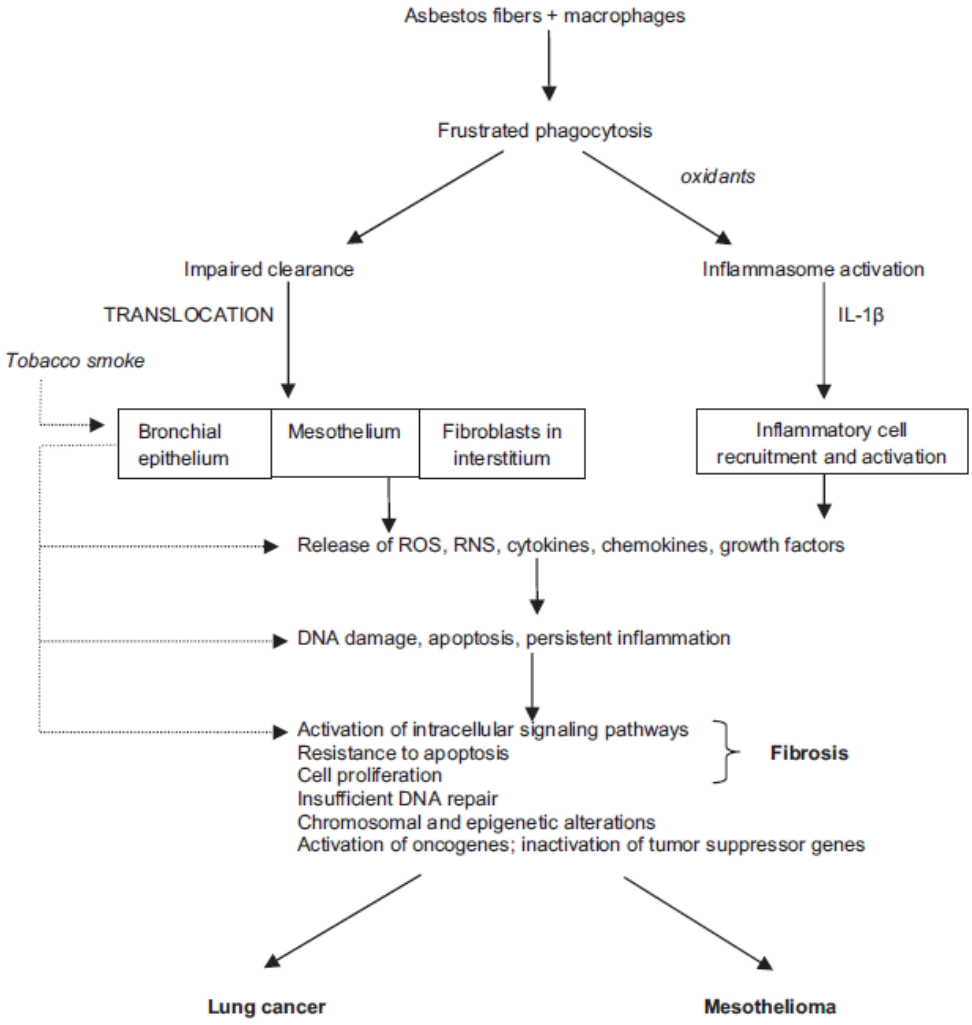

Figure 1. Proposed mechanisms for carcinogenicity of asbestos fibres (IARC 2012 based on Shukla et al. (2003), Kane (2006) and Nymark et al. (2008))

The toxicity of fibres is (partly) linked to their dimensions and biopersistence, and probably also surface reactivity (Donaldson and Tran, 2004). Hazardous effects resulting from repeated exposure to rigid fibres have often been considered to be the result of inability of macrophages to engulf the fibres, particularly if the fibre is longer than the diameter of a human alveolar macrophage (14-25 µm), leading to so called frustrated phagocytosis, later resulting in prolonged local inflammation. Reactive oxygen species and nitrogen species may be generated, causing tissue injury, activation of intracellular signalling pathways, (indirect) genotoxicity, and epigenetic changes (IARC, 2012; NFA, 2019) thought to be involved in the mutagenic/genotoxic mode of action of asbestos. Also, the needle-like shape of asbestos fibres may result in a widespread distribution of the fibres in various tissues. Furthermore, iron is an important constituent of some asbestos types, and genotoxic effects of iron (e.g. Fenton-type reactions resulting in increased production of reactive oxygen species) may thus be reflected upon exposure to asbestos. (NFA, 2019; Afsset, 2009a).

In the report of Afsset (2009a), the influence of fibre dimensions was discussed. Generally, long asbestos fibres (>5 µm) have been considered to show more proof of hazardous effects than short ones (<5 µm). The data on short or thin fibres is limited and fragmented. Afsset (2009a) concluded that "The existence of a non-zero but weak effect of SAFs (short asbestos fibres) thus seems to be a conservative hypothesis. Regarding TAFs (thin asbestos fibres), recent data, albeit few in number, confirms the

existence of a significant carcinogenic effect". These considerations are further discussed in section s 9.1.1. and 9.1.2.

As explained above the mode of action of asbestos fibres is complex, involving long-term processes, not only biological but also related to physico-chemical persistence with half times in human lungs being up to decades for some fibre types (section 7.1). Such properties may influence the risk differently for rats and humans due to the difference in lifespan. Species differences in the responses have been observed upon inhalation exposure of asbestos fibres. Differences in observed effects may be related to deposition and clearance from the lungs, in the translocation kinetics, or to antioxidant defence mechanisms (IARC, 2012). The relevance of rat studies versus observed carcinogenic effects in humans has been discussed in some publications. Muhle and Pott (2000) considered that humans are more sensitive than rats, and that the rat inhalation model is not sensitive enough for the prediction of cancer risk. Also Wardenbach et al. (2005) shared the view of humans being more sensitive than rats (up to a difference of orders of magnitude for amphiboles), whereas Maxim and McConnell (2001), as the conclusion of their literature review of studies on asbestos and synthetic vitreous fibres, expressed that "there is no reason to conclude that humans are more sensitive to fibres than rats with respect to the development of lung cancer".

It is noted that the above considerations have been made and are more relevant for using the rat model for man-made mineral (and other) fibres for which the human database is not as extensive as for asbestos, and where consequent predictions have to be made from animal studies. As regards asbestos it is noted, based on the above reviews, that part of the differences may be related to at least (1) differences in fibre dimensions in animal experiments with standard pure asbestos materials and real-life human exposures that deal with worker exposures after technical dimensional selection of fibres fit for each intended past commercial application (see section 5.2), and (2) for lung cancer, the enhancing interaction between smoking and asbestos in human studies not applicable in animal experiments. However, it is difficult to quantify the effect of these fundamental differences between standardised animal experiments and human observational studies.

In conclusion, the complex mode of action of asbestos does not allow identification of a threshold. It seems justified to conclude that for asbestos using the extensive human data are an appropriate approach to explore the exposure-response relationship even for low exposure levels where data points are sparse or lacking and extrapolation is needed. This is also supported by the human-rat sensitivity analyses recently performed by the Danish NFA (2019), see section 9.1.1.

8.2 Lack of specific scientific information

No information gaps were identified.

8.3 Groups at Extra Risk

Lifestyle factors may influence the risk caused by asbestos. As described in section 7.7.1 there is a joint effect between asbestos and smoking in the causation of lung cancer. Smoking and alcohol are established risk factors for laryngeal cancer (IARC, 2012), but there is no quantitative information on the joint effect between these and asbestos in the causation of laryngeal cancer. The same also applies to the other environmental risk factors of lung cancer or laryngeal cancer. Exposures to these are potential confounders in human epidemiological studies and their effect is aimed to be controlled in the analyses. The quantitative exposure-response relationships derived in section 9.1.2 describes the risk in an "average" working population without stratifying the relationship by concomitant other exposures the individual may have experienced. However, smoking asbestos exposed workers are at higher risk of lung cancer (but not mesothelioma) than are non-smoking asbestos exposed workers.

Attempts have been made to identify genetic susceptibility factors that influence the asbestos-associated risk of lung cancer or mesothelioma (see IARC 2012). However, no consistent associations have been found.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approaches for cancer risk assessment

France (Afsset)

In two separate documents French Agency for Environmental and Occupational Health Safety ((Afsset, 2009a), (Afsset, 2009b)) assessed the following main aspects (also described in Yamani et al. (2012):

1. the protective level of the that time 8-hour limit value for asbestos (0.1 fibres/cm^3)
2. the toxicity of thin (length > 5 µm, width < 0.2, length/width $\geq$ 3) and short (length < 5 µm, width < 3 µm, length/width $\geq$ 3) asbestos fibres
3. the possibilities and limitations offered by Transmission Electron Microscopy (TEM) in comparison with Phase Contrast Microscopy (PCM)

Afsset concluded that given the fact that all known and commercialised mineral varieties of asbestos fibres have the potential to induce cancer in humans through inhalation, it was not necessary to differentiate between them when making a recommendation for an OEL. Afsset further concluded that the carcinogenicity of asbestos fibres in humans, acts via a mechanism of action without a threshold and that the available data were sufficient to derive a dose effect relationship at low doses and to calculate a single risk excess taking into account lung cancer and mesothelioma.

After analysing the excess health risk models available, especially the INSERM (1997) model that is based on EPA (1986) linear model and the one performed by Hodgson and Darnton (2000), Afsset retained the Inserm model as it was based on French mortality data and as the superiority of other models could not be demonstrated with regards to the limitations and uncertainties associated with derivation methods at low doses.

The Inserm model was applied to male workers, aged between 20 and 65, and a majority exposure to a variety of chrysotile fibres, under a continuous asbestos exposure (40 hours per week and 48 weeks per year or 1920 hours per year). The following excess risk of death from mesothelioma and lung cancer combined were calculated (based on fibre counting with PCM):

- 10^{-4} for an exposure concentration of 0.003 fibres/cm^3
- 10^{-5} for an exposure concentration of 0.0003 fibres/cm^3
- 10^{-6} for an exposure concentration of 0.00003 fibres/cm^3

Afsset noted that the lowest 8-hour OEL for asbestos fibres in Europe was 0.01 fibres/cm^3 (in Germany, Switzerland and the Netherlands), corresponding to an estimated excess risk of 3.3 x 10^{-4} with the above model. Afsset considered that 0.01 fibres/cm^3 can constitute a relevant step in the progress towards a reduction in the risk of asbestos exposure in France. However, Afsset recommended retaining a target value of 0.00003 fibres/cm^3, which corresponds to a level of risk of 10^{-6}.

Finally, Afsset considered it important to remember that the ALARA (As Low As Reasonably Achievable) principle must be applied for a carcinogenic substance that does not have a threshold.

Afsset did not propose a skin notation and noted that as there is no particular evidence of short term effects to base a STEL, the national standard practice is that the concentration corresponding to 5 times the 8-hour OEL over a 15-minute period should not be exceeded.

As regards uncertainties, Afsset discussed for the linear extrapolation to low exposures that some recent case-control studies (e.g. Gustavsson et al. (2002)) indicate that such an extrapolation may underestimate the risk of lung cancer at low exposures. Afsset also considered the Hodgson and Darnton (2000) non-linear approach for lung cancer as well as the approach to assess differently the excess risk by asbestos fibre type. But as the Inserm model was based on French mortality data and used simple hypotheses, due to the associated limits, especially in terms of the "major" / "unique" exposure to chrysotile (due to a lack of specific data on amphiboles), Afsset preferred to retain the Inserm model.

For thin asbestos fibres Afsset concluded that given the carcinogenic potential, this dimensional class is to be included when measuring dust levels in the workplace. For short fibres Afsset noted that the limit of 5 µm in length that is used to differentiate between a "short" and "long" fibre, does not correspond to demonstrated scientific safety data and the carcinogenicity of short fibres, even if it remains difficult to assess, cannot be excluded. However, Afsset concluded that due to the systematic presence of asbestos fibres with a length above 5 µm in occupational activities linked to asbestos in the workplace, the (national) OEL that will be suggested will indirectly cover a possible health risk linked to short fibres.

Concerning the exposure measurement methods, Afsset considered that no method currently available (PCM, scanning electron microscopy (SEM), indirect TEM and direct TEM) was considered ideal for measuring occupational exposure to asbestos fibres, especially exposure to the finest of these fibres. Adaption of the TEM methods, using the indirect route (in order to alleviate the risk of fibre loss and changes in their particle size distribution during the preparation phase) or direct TEM (to obtain optimal splitting of the deposit on the filter during sampling), should eventually allow these methods to become valid for use in the occupational environment so that the exposure of operators to asbestos fibres, whatever their dimensional characteristics, can be assessed. Afsset recommended to adapt the TEM method (direct or indirect) so that it can be used as an application in the occupational environment. Since the above-reported expertise of AFSSET, more recent work has been carried out to adapt the TEM methods to the occupational environment and the regulation has been modified with reference to the developed French standards (see section 6).

In a separate subsequent assessment ANSES (2014) addressed the following questions:

1. To review the toxicological and epidemiological evidence relating to cleavage fragments of minerals with non-asbestiform profiles: actinolite, anthophyllite, tremolite, grunerite and riebeckite. What conclusions can be reached about their effects on health?
2. What current data are available regarding the specific exposures to cleavage fragments of the minerals cited above? (This was restricted to occupational exposure)
3. Are there routine analytical methods capable of distinguishing the fibres of actinolite-asbestos, anthophyllite-asbestos, tremolite-asbestos, amosite and crocidolite on the one hand, from cleavage fragments from five (non-asbestiform) amphiboles, actinolite, tremolite, anthophyllite, grunerite and riebeckite on the other? (This was restricted to sampling and analysis in bulk materials and air)

As regards epidemiological studies on the general population and on workers exposed to amphiboles elongated mineral particles (EMPs) ANSES noted that excessive incidence and/or mortality had been observed for mesothelioma and/or lung cancer and/or other respiratory pathologies, and/or excessive pleural and parenchymal anomalies. However, these studies were unable to attribute the health effects observed to cleavage fragments alone, as the populations studied had been exposed to complex mixtures of particles, including asbestiform particles or crystalline silica. In the light of the data analysed, ANSES concludes that it is not possible to rule out a risk to health linked to exposure to cleavage fragments of actinolite, anthophyllite, tremolite, grunerite and riebeckite.

As regards toxicological studies, ANSES noted that several reviews have concluded that 'cleavage fragments' are less toxic than asbestiform fibres, but an analysis of the articles cited in these reviews, apart from the three articles, indicates that the cleavage fragments studied did not have the dimensions of a "WHO" fibre and are in fact non-elongated mineral particles. These reviews confirm that non-elongated mineral particles are not toxic or are less toxic than asbestiform fibres, but provide no information on the toxicity of cleavage fragments as defined with the dimensions of a "WHO" fibre (L > 5 µm; D < 3 µm; L:D > 3:1). The three more informative studies focused on the toxicological effects of cleavage fragments of tremolite and ferro-actinolite corresponding to the definition of a "WHO" fibre. The results of these studies showed that samples composed "mostly of cleavage fragments" induced mesotheliomas in rats by intra-peritoneal injection and can induce an inflammatory reaction in rats by intra-tracheal injection. Studies on Libby amphibole (corresponding to a mixture of cleavage fragments and asbestiform fibres) tend to demonstrate that these amphiboles are less toxic than asbestos but, when adjusted on the number of particles injected or to the dimensions of those particles, the differences in toxicity are not significant. ANSES noted that other parameters modulating the toxicity (biopersistence, contaminants, surface reactivity, etc.) are not discussed in these studies.

No exposure data specifically on the cleavage fragments of the amphiboles were identified in the literature.

ANSES (2014) concluded the following:

1. In the current state of knowledge concerning their health effects, cleavage fragments from non-asbestiform amphiboles of actinolite, anthophyllite, tremolite, grunerite and riebeckite meeting the WHO's dimensional criteria for fibres (L > 5 µm; D < 3 µm and L:D > 3:1) should not be distinguished from their asbestiform counterparts (actinolite-asbestos, anthophyllite-asbestos, tremolite-asbestos, amosite and crocidolite);
2. Health effects similar to those of asbestos are demonstrated for other calcic and sodic-calcic elongated mineral particles (EMPs), present in the form of a mix of asbestiform and non-asbestiform particles: fluoro-edenite, and winchite and richterite, which are the major components of Libby amphiboles;
3. There are currently no specific data on the health effects of the other calcic and sodic-calcic EMPs;
4. There is no reason to make a distinction between the cleavage fragments meeting the "WHO" dimensional criteria for fibres (L > 5 µm; D < 3 µm and L:D > 3:1) and asbestiform fibres of calcic and sodic-calcic EMPs, in particular due to the uncertainties and difficulties related to their characterisation and to their differentiation by routine analytical methods.

ANSES (2014) made also a number of recommendations e.g. for adopting harmonised definitions for the terminology, for using the term "elongated mineral particle" (EMP) to describe any mineral particle with an aspect ratio (L:D) greater than 3:1, irrespective of whether its origin is asbestiform or non-asbestiform (EMPs of interest are those capable

of being inhaled (D < 3 µm)). ANSES also recommended using TEM for the characterisation of EMPs in the air.

Germany (AGS)

In the German system the limit values for carcinogens are based on the tolerable risk (nominal risk of 4 x 10^{-3}) and acceptable risk (4 x 10^{-4} , and at the latest 2018, 4 x 10^{-5}) excess risk levels (AGS, 2014).

Committee on Hazardous Substances (AGS, 2008) used the EPA (1986) models (lung cancer and mesothelioma) to calculate the workplace air concentrations (8-hour TWA) that correspond to these risk levels. As the unit risk from EPA model was based on risks related to an exposure of 24 hours per day for 70 years and a respiratory volume of 20 m³ per day, the AGS converted it to correspond to workplace setting (40 years; 240 working days per year; 8 hours per day; respiratory volume 10 m³ / 8 hours). The following concentration – risk level values were generated:

- 4 x 10^{-3} for an exposure concentration of 0.1 fibres/cm^3
- 4 x 10^{-4} for an exposure concentration of 0.01 fibres/cm^3
- 4 x 10^{-5} for an exposure concentration of 0.001 fibres/cm^3

The counting method to be applied is scanning electron microscopy according to method BGI 505-46 (DGUV, 2004).

In view of the differences in the risk level and the lack of uniformity of results for lung cancer and mesothelioma, AGS considered that no distinction is made between amphiboles and chrysotile, and no correction factor is applied to take account of different methods of fibre detection (optical or electron microscope). Since no data were available which might provide sufficiently reliable justification of a different approach, linear extrapolation was applied to different cumulative exposures.

The Netherlands (DECOS)

The Dutch Expert Committee on Occupational Safety (DECOS, 2010), derived occupational exposure reference levels corresponding to the nationally established benchmark excess risk levels of 4 x 10^{-3} and 4 x 10^{-5}. These reference levels were calculated combining excess risk of lung cancer and excess risk of mesothelioma. Meta slope factors for lung cancer and mesothelioma were first calculated from existing epidemiological studies and then applied to the Dutch population with a life table method; i.e. taking into account the shrinking of the population due to competing causes of death. Start of exposure at the age of 20 and cease of exposure at 60 years were assumed and risk was calculated until 100 years of age. DECOS calculated the reference levels assuming transmission electron microscopy (TEM) as the analytical method. DECOS used a pragmatic conversion factor of 2 between TEM fibre counts and the phase contrast microscopy (PCM) fibre counts that were the basis of the risk estimates available in the epidemiological studies; i.e. that TEM, with higher resolution due to its higher magnification, would detect on average 2 times more fibres in a given air sample than would PCM.

For lung cancer, DECOS reviewed 17 cohort studies and 1 case-control study that provided quantitative estimates of risk by cumulative asbestos exposure. These were the same as those used by Lenters et al. (2011) except one that was not yet published at the time of the DECOS analysis. DECOS also assessed the studies based on the quality and documentation of the exposure assessment (described in greater detail in Lenters et al. 2011) and finally used the meta slope calculated using the four highest quality studies. These were the South Carolina chrysotile textile factory cohort, Libby vermiculate miners exposed to tremolite, UK asbestos textile cohort with mixed exposure and a population-based case-control study in Stockholm, Sweden with mixed exposure. DECOS assumed (1) a minimum latency time of 10 years, (2) a linear exposure-

response relationship and (3) a multiplicative effect for smoking and asbestos as a pragmatic approach (i.e. applying the asbestos-related excess risk to the general population rates that for lung cancer are driven by smoking). DECOS made no distinction based on fibre types as the final data set of 4 highest quality studies did not allow doing that and because DECOS considered the data on fibre potency difference less convincing for lung cancer (compared to mesothelioma). The lung cancer meta slope K_L used was 1.64×10^{-2}. I.e. the relative risk of lung cancer would follow the formula RR = 1 + 0.0164 x cumulative exposure (in f–y/cm^3).

For mesothelioma DECOS reviewed 14 cohort studies and used 12 of them. One was excluded as it was based only on one case and the other because a more recent study from the same population was used. DECOS assumed that the mesothelioma risk follows the EPA (1986) model. DECOS acknowledged that for mesothelioma there is convincing evidence for a potency difference between chrysotile and amphiboles. None of the studies fulfilled all the quality criteria used. For chrysotile exposure and mixed exposure there was one study each that fulfilled all but one of the quality criteria and those studies were used. For amphiboles all available studies were used although this was not an optimal situation from the quality point of view. The following mesothelioma slope factors K_M ($x10^8$) were calculated: 0.017 for chrysotile, 2.46 for mixed exposure (either amphiboles alone or a mixed exposure upto 20% of amphiboles), 7.95 for amphiboles and 0.34 when all asbestos cohorts were pooled.

The exposure concentrations corresponding to the excess risk levels of 4×10^{-3} and 4×10^{-5} of lung cancer and mesothelioma collectively are given in Table 7.

Table 7. Exposure concentrations of various types of asbestos corresponding to the reference risk levels of 4×10^{-3} and 4×10^{-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/cm^3 as measured by TEM. DECOS (2010)

Excess risk level	Concentration corresponding to the excess risk level (fibres/cm^3, TEM)		
	Chrysotile	Mixed, up to 20% amphiboles	Amphiboles
4×10^{-3}	0.2	0.13	0.042
4×10^{-5}	0.002	0.0013	0.00042

DECOS considered that the asbestos-related risk is much higher for lung cancer and mesothelioma than for the other cancers, including ovarian and laryngeal cancer and therefore lung cancer and mesothelioma risks were used to define the exposure standards. DECOS further noted that asbestosis occurs only in association with exposure to concentrations 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 the standard setting process.

Based on the DECOS assessment, the current OEL in the Netherlands is 0.002 fibres/cm^3 (see Chapter 4), i.e. it corresponds to the above chrysotile-related exposure level derived for excess risk level of $4x10^{-5}$, but concerns all asbestos fibre types The legislation does not prescribe which analytical method to use for the analysis of asbestos samples, as it is stated that the measurement shall be carried out in accordance with a standardized method suitable for the purpose, or another method, if it gives equivalent results. However, as the OEL is quite low there is preference to apply a method that is specific for asbestos fibres, the general agreement is to use SEM/EDX as analytical

method. Analysis of asbestos air samples to be compared with the OEL are generally performed according to the ISO 14966.

Denmark (NFA/AT)

The Danish Working Environment Authority asked the National Research Centre for the Working Environment (NFA) to review the scientific evidence underlying a health-based occupational exposure limit for asbestos. The NFA recommended (NFA, 2019), after reviewing both animal and human data as well as the above DECOS and Afsset assessments, to consider the slope factors for lung cancer and mesothelioma from the DECOS meta-analyses the most appropriate starting points for deriving the exposure-response relationship combining these two cancers. NFA used the most conservative K_L and K_M slope factors, i.e. for mesothelioma the one for amphibole asbestos, to calculate the exposure-response relationship for all asbestos. The following concentration – risk level values were generated:

- 1×10^{-3} for an exposure concentration of 0.01 fibres/cm^3
- 1×10^{-4} for an exposure concentration of 0.001 fibres/ cm^3
- 1×10^{-5} for an exposure concentration of 0.0001 fibres/ cm^3

As national background rates of lung cancer depend on national smoking habits, the NFA performed own risk calculations using the national life-time (0-74 years) lung cancer rates (4.9% men, 4.5% women) and the DECOS K_L values. The calculations did not differ significantly from the DECOS values. For mesothelioma, NFA noted that the only well-established risk factor is asbestos exposure. Consequently, NFA proposed to use the risk estimates provided by DECOS, as there was no reason to suspect that the background incidence of mesothelioma or the ambient air levels of asbestos differ between Denmark and the Netherlands. Finally, NFA performed sensitivity analyses using three animal assays: the two chrysotile studies that had applied the lowest inhalation exposure and the amosite study that had applied the lowest inhalation exposure. As those data associated given excess risk levels to higher airborne asbestos concentrations than when using human data, NFA proposed to use the above excess risk associations calculated from human data.

The NFA report recently underwent a review of a quality committee of the Danish Working Environment Authority (Arbejdstilsynet AT). The quality committee (AT, 2019) noted that the most common asbestos type used in Denmark was chrysotile and assumed that the vast majority of workers in Denmark are only exposed to chrysotile, and further assumed that the level of amphibole contamination in chrysotile in Denmark is similar as the amphibole contamination in studies on chrysotile included in the DECOS calculations. Consequently, the quality committee recommended to use the DECOS slope factors for chrysotile. The quality committee also recommended that as lung cancer background rates are higher in Denmark than in the Netherlands, also the excess risk for lung cancer is presumably higher and the calculations should be adjusted for that. The AT (2019) recommendation would result in the following adjusted risk levels:

- 1×10^{-3} for an exposure concentration of 0.027 fibres/cm^3
- 1×10^{-4} for an exposure concentration of 0.0027 fibres/cm^3
- 1×10^{-5} for an exposure concentration of 0.00027 fibres/cm^3

As regards monitoring methods NFA referred to the WHO (1997) phase contrast microscopic (PCM) analytical method as the monitoring tool defined by the respective Directive 2009/148/EC and the fibre dimensions of length >5 µm, a diameter of less than 3 µm and a length-to-diameter (L/D) ratio of ≥3. NFA further noted the above Afsset assessment concerning thin asbestos fibres (L≥ 5 µm, d<0.2 µm and L/D≥3). NFA reiterated the conclusion by Afsset that if thin fibres were also to be measured then

novel distinct methods would have to be used. However, NFA, did not explicitly state which monitoring method should be used.

It is noted that NFA used the DECOS risk calculations. These DECOS calculations were performed with the assumption that TEM would be used as monitoring method and that TEM would detect 2 times higher air concentrations than PCM that had been used in historical epidemiological publications. NFA did not apply any monitoring method related modification factor for those DECOS risk values.

Comparison of AGS, AFSSET, DECOS and NFA/AT

Table 8 compares the fibre concentrations associated to given excess risk levels (combining lung cancer and mesothelioma) calculated by Afsset, AGS, DECOS and NFA/AT. All bodies calculated excess risk over lifetime. When comparing working life occupational exposure levels associated with a certain lifetime risk it should be considered that differences exist in the way lifetime risks have been calculated (see also the uncertainty analysis summarised in section 9.1.2). For instance by using fundamentally different methods (conditional on survival or unconditional (life-table method)). Unconditional methods are the preferred methodology because these estimate an unbiased risk, adjusted for mortality due to other causes of death). And also by choosing for instance a different exposure scenario (duration of exposure) or different input parameter. With regard to the latter for instance, for lung cancer, country specific mortality rates have been used that differ between countries, or rates for males were used, or alternatively male and female rates were combined. These differences can lead to considerable differences in the estimated risk at a certain working life exposure.

It is noteworthy that each body assumed a different monitoring method as basis of their excess risk estimates. Either PCM (Afsset), SEM (AGS) or TEM (DECOS) or did not specify the method (DK NFA/AT). These have different sensitivities to detect thin fibres and therefore the values should be compared with caution. AGS and Afsset used the EPA (1986) model data applied to the national population and consequently have close to identical fibre levels (the original reports presented slightly different risk levels that needed to be converted to the risk levels of table 6 and as the original reports were showing only one digit precision there is some rounding error in table 8). DECOS performed an updated meta-analysis. DECOS air concentrations for a given excess risk level are lower, especially for amphiboles, when compared to Afsset and AGS values that apply for all asbestos.

Table 8. Comparison of excess risk levels (lung cancer and mesothelioma combined) associated to given fibre concentrations as estimated by Afsset (2009b), AGS (2008), DECOS (2010), Danish NFA (2019) and Danish AT (2019)

	Excess life-time cancer risk (cases per 100 000 exposed) associated with given fibre concentrations (fibres/cm^3)		
Fibre concentration	**0.001**	**0.01**	**0.1**
Afsset, all asbestos	3.3	33	330
AGS, all asbestos	4.0	40	400
DECOS, chrysotile	2.0	20	200
DECOS, mixed	3.1	31	310
DECOS, amphiboles	9.5	95	950
DK NFA (based on	10	100	1000

Fibre concentration	Excess life-time cancer risk (cases per 100 000 exposed) associated with given fibre concentrations (fibres/cm^3) 0.001	0.01	0.1
DECOS amphiboles)			
DK AT (based on DECOS mixed)	3.7	37	370

US OELs

The EPA (1986) model and assessment is usually the basis of the various exposure standards set for asbestos in the US. The OELs are just listed here for reference without further describing the use of EPA (1986) model.

US OSHA (1998) Permissible Exposure Limit (PEL) for asbestos is 0.1 fibres/cm^3 of air as an 8-hour time-weighted average (TWA), with an excursion limit (EL) of 1.0 asbestos fibres/cm^3 over a 30-minute period. OSHA (1994) estimated that the limit of 0.1 fibres/cm^3 would reduce excess cancer risk to 3.4/1000 workers.

NIOSH (2015) recommended exposure limit (REL) for asbestos is 0.1 fibres/cm^3 and ACGIH (2015) TLV for asbestos is also 0.1 fibres/cm^3. The Mine Safety and Health Administration MSHA (2008) has set regulatory exposure limits of 0.1 fibres/cm^3 (reference period of 8 hours) and 1 fibres/cm^3 (reference period of 30 minutes)

9.1.2 ECHA Cancer risk assessment

Unless indicated otherwise, the workplace air monitoring results referred to in this Section have been conducted with WHO phase contrast microscopy method (PCM) or equivalent (see Section 6) or have been converted to such metrics from earlier measurement techniques.

As described in section 7.7 human epidemiological studies have shown that asbestos fibres cause cancer of the lung, mesothelioma, cancer of the larynx and cancer of the ovaries. As described in section 8.1. the data on Mode of action indicate that asbestos fibres should be considered a non-threshold carcinogen and the data on species differences indicate that it is preferred to use human data for exposure-response analysis and risk assessment.

The epidemiological evidence base contains numerous studies in which asbestos associated risk of mesothelioma and lung cancer has been estimated by level of (cumulative) exposure. For cancer of the larynx and cancer of the ovaries there are no such robust quantitative exposure-response estimates. However, indications exist that these cancers contribute only few excess cases when compared with lung cancer and mesothelioma, at relatively low exposure levels that are of concern today. Even in populations with heavy exposure the asbestos-related excess cases from these cancers would be 10% or less of excess cases resulting from lung cancer and mesothelioma (see sensitivity analysis at the end of Appendix 4).

For mesothelioma the human data indicate a clear potency difference between amphibole and chrysotile asbestos, while for lung cancer a potency difference is less pronounced. Also, clear indications exist that for lung cancer the exposure-response relationship is not linear; actual risk at levels around and below the current EU OEL may be higher than the risk as calculated using linear extrapolation from higher exposures experienced by historical industrial cohorts.

The most recent meta-analyses or meta-regression analyses calculating quantitative exposure-response slope factors for lung cancer and mesothelioma were published between 2010-2013. Some new studies have been published since, providing quantitative exposure-response estimates for both lung cancer and mesothelioma. Those studies were reviewed for their suitability for inclusion in a refined analysis and an exposure-response relationship expressing the excess risk of lung cancer and mesothelioma (combined) by level of exposure was consequently derived based on all suitable studies available. This is summarised in the below paragraphs and further described in Appendixes 3 and 4.

The EPA mesothelioma model was used to estimate lifetime mesothelioma risk after a working life asbestos exposure, with a meta-K_M value as input. The lifetime lung cancer risk was calculated in a lifetable analysis using a meta-exposure response relation as input. For estimation of lung cancer relative risk by level of cumulative exposure, both linear and non-linear (natural spline) models, with and without intercept The Akaike information criterion (AIC) was calculated for each model and compared across models. The AIC is a measure for sample prediction error and the relative quality of model for a given dataset and thus provides a means for model selection. A lower AIC score is better.

It is noted that the use of the absolute risk model of EPA for mesothelioma is well-established in asbestos risk assessment and has consistently been used by the EPA, WHO and other organisations in their risk assessment. Asbestos and some asbestos-like fibres are the only known causative agents for mesothelioma. The background risk of mesothelioma is extremely low and estimated to be 1 case per million in absence of (occupational) asbestos exposure. Therefore, using a relative risk model, as is common for more regularly occurring cancers with multiple causes, would be problematic. When comparing an asbestos exposed population to an unexposed population, the rate in the latter group would be very low and be based on very small numbers even in a large comparison group and thus leading to very imprecise relative risk estimates. Using standardised mortality or incidence rates comparing exposed populations with the general population would result in underestimation of the true asbestos effect because the (mortality or incidence) rate in the comparison group would also be almost exclusively result from asbestos exposure in that population. Adjusting mortality or incidence rates in the general population is not a commonly applied procedure because it also introduces uncertainties and imprecision. Therefore, absolute risk models are considered the appropriate approach in case of risk assessments for mesothelioma.

For lung cancer there were 22 suitable studies (see Table 11, Appendix 4). They provided 124 risk estimates (i.e., study points of the RR for lung cancer at a given exposure level) over a cumulative exposure range of 0.11–4710 f–y/cm^3. In comparison to van der Bij et al. (2013) (and Lenters et al. (2011)), the lung cancer analysis used a more recent follow-up study of Pira et al. (2017) instead of Pira et al. (2009) for the Italian Balangero chrysotile mine cohort and a more recent follow-up of Larson (2010) instead of the study of Sullivan (2007) for the Libby vermiculate miner cohort. The analysis also included three cohorts for which the data were not yet available at the time of the previous meta-analyses. Notably, the French asbestos textile and friction material plant cohort of Clin et al. (2011a) with mixed exposure, the Chinese chrysotile mine cohort of Wang et al. (2013b) and the Chinese asbestos factory (textiles, rubber products and asbestos cement) cohort exposed to chrysotile (Courtice et al., 2016). The Swedish case-control study of Gustavsson et al. (2002) was replaced by the pooled case-control study of Olsson et al. (2017) which also includes the Gustavsson study data.

The spline models had a considerably better fit than the linear models (see Table 12 and Figure 2, Appendix 4). The best fitting model (the one with the smallest AIC value), i.e. spline with intercept, was used for further risk calculations, adjusting the exposure response relation for the elevated risk at zero exposure (adjustment for intercept).

For mesothelioma there were 13 suitable studies to estimate the potency or meta-slope factor K_M (see Table 13, Appendix 4). In comparison to the DECOS (2010) meta-analysis, one more study was available and was included. This study, by Loomis et al. (2019), involves the NC asbestos textile cohort exposed to chrysotile. The pooled K_M value combining all studies, regardless of asbestos fibre type ($x10^8$ in $(f–y/cm^3)^{-1}$) was 0.337, i.e. very similar to the 0.34 calculated by DECOS (2010). There is clear evidence that the mesothelioma potency differs between asbestos types, amphiboles being more potent that chrysotile. Under the current EU situation with all asbestos types being already banned, potential exposure can be assumed mixed to all types of asbestos. The rationale for this assumption is that while handling asbestos products during removal or maintenance work on a given day may concern only a certain asbestos type, e.g. amphiboles, in the long run the exposure potential is expected to reflect the share of past use of different types of asbestos. Thus, either using excess risk calculations integrating all asbestos types combined or those coming from populations with mixed exposure to various asbestos types seem most relevant.

The meta-K_M value based on all available cohort studies is almost three times lower than the K_M value for cohorts with mixed asbestos exposure (see Appendix 4 for details). This raised the question whether the overall K_M is a justified estimate of mixed asbestos exposure as it occurs at present. Therefore, alternatively, a meta K_M was also estimated by using global production data for chrysotile and amphiboles (estimated between 94% and 96% of all asbestos produced respectively), and calculating a meta K_M value by taking the production weighted average of the K_M values of chrysotile (0.017 ($x10^8$ in $(f–y/cm^3)^{-1}$)) and amphiboles (7.95 ($x10^8$ in $(f–y/cm^3)^{-1}$)). This led to K_M values between 0.33 and 0.49 ($x10^8$ in $(f–y/cm^3)^{-1}$). These values are close to the overall meta-K_M value based on all cohort studies, considerably lower than the K_M value for cohorts with mixed exposure. The high K_M value for cohorts with mixed exposure only is explained by the fact that the share of amphibole exposure wat relatively high in these cohorts, up to 20% of the asbestos used. A more detailed analysis of the uncertainties can be found in Appendix 4.

The meta exposure response spline for lung cancer and meta-K_M value for mesothelioma combined were used to calculate the combined risk for lung cancer and mesothelioma mortality after a working life of exposure at several exposure levels for 8 hours per day and 5 days per week over a 40 years working life period (starting at 20 years). For lung cancer this was done using the so called life table analysis to adjust for the fact that at higher age mortality from other causes reduces the population at risk compared to the original population initially exposed, which influences excess risk estimates when not adjusted for.

The input for the life-table analysis (lung cancer and total mortality) were mortality rates, per January 2021, averaged across all EU countries for the years 2011-2016 from the Eurostat database. For this purpose, the average male and female mortality rates were calculated by age. The excess risk was calculated until 89 years of age. The analyses focused on exposure levels at and below the current EU OEL. The resulting excess risk of lung cancer and mesothelioma (combined) by level of exposure is described in Table 9 and expressed per 100 000 exposed individuals. Lung cancer and mesothelioma appeared to contribute almost equally to the estimated number of cases per 100 000 exposed individuals.

Table 9. Cancer exposure-risk relationship (lung cancer and mesothelioma combined) after working life exposure to given 8-hour air concentration for five working days a week as measured by PCM

Air concentration of mixed asbestos as measured by PCM		Excess life-time cancer risk (cases per 100 000 exposed)
Fibres/cm^3	Fibres/m^3	
0.001	1000	1.2
0.002	2000	2.5
0.005	5000	6.2
0.01	10000	12
0.02	20000	25
0.05	50000	62
0.1	100000	125

Uncertainties in the risk estimates

A few issues are expected to contribute most to the uncertainties in the risk estimates presented. These are extensively described in Appendixes 4, 5 and 6 and only summarised below:

- **Statistical estimation error and model assumptions.** Exposure response relations have been estimated on the basis of 22 studies on lung cancer and 13 studies on mesothelioma. Uncertainties arise because of limited statistical precision in the risk estimates due to limited quality of the exposure estimates, differences in design, conduct and analysis of the studies, leading to heterogeneity between studies. Some studies have a small sample size contributing to random estimation error. All these factors together lead to uncertainty in the meta-exposure-response relation and risk calculations. In all risk calculations, point estimates for the exposure response slope (lung cancer) or potency factors (K_M in case of mesothelioma) have been used. The confidence intervals around these point estimates indicate that for both lung cancer and mesothelioma, variation around these point estimates can be up to a factor 1.5-2. When considering specific types of asbestos, statistical uncertainties increase considerably, because inferences about potency differences are based on a very limited number of studies (for mesothelioma and amphiboles, only two studies are available and five study are available with chrysotile exposure only). Choices made in modelling of exposure-response relations, used to calculate lifetime risks may contribute to larger differences in risk estimates. A spline model described the exposure response relation for lung cancer best. Use of a more conventional linear model led to a shallower exposure response relation at low exposure levels, and this would have led to 35% lower lifetime risk estimates for lung cancer and mesothelioma combined. Further sensitivity analyses indicated that the spline gave a robust description of the available data for lung cancer and exposure. Changes in the spline modelling approach (knot placement) changed the exposure response slope at exposure levels to a limited extent (10% maximally).

- **Exposure assessment methodology**. In all quantitative exposure response studies, asbestos exposure of individual workers has been estimated by combining data from measurement surveys on the level of job titles, with worker job title information and job tenure (duration of exposure). Poor quality of exposure estimates may lead to exposure misclassification and underestimation of exposure–response relationships in epidemiological studies. The magnitude of underestimation is study specific. Overall, the exposure response slope is steeper in studies on asbestos with higher quality exposure assessment as has been shown for lung cancer. Limiting exposure response modelling for lung cancer to studies with higher quality results in a exposure response slope that is 1.5-2 times higher compared to using all studies.

- **Fibre analysis.** In all the used epidemiological studies with quantitative exposure data fibre concentrations have been measured using PCM or converted to PCM from earlier methods. With PCM, exposure to long but thin fibres is underestimated leading to an overall underestimation of exposure. As a result, the risk from asbestos exposure in these studies is associated with exposure levels that have been underestimated leading to a higher risk per unit of exposure. This only becomes an issue of concern when, for instance in the context of compliance testing, exposure is assessed using other, more modern, techniques to assess fibre concentrations which do measure thinner fibres as well.

- **Other cancers associated with asbestos exposure.** Asbestos exposure is causally related to the occurrence of larynx and ovary cancer. These cancers have not been considered in the quantitative risk assessment and excess risk calculations. The reason for this omission is simple; no quantitative exposure-response-relations have been published that can be used in risk assessment procedures. As a result, the calculated excess risk underestimate the true risk for developing cancer resulting from asbestos exposure. It can be argued that the underestimation is relatively modest because of two reasons. First, larynx and ovary cancer are relatively rare and occur less frequently than lung cancer and mesothelioma in asbestos exposed populations. In addition, an exploratory analysis shows that not all larynx and ovary cancers can be attributed to asbestos exposure because other causes do play a role as well. It was estimated that these two cancers may maximally contribute another 10% additional cases in comparison with the ones observed for lung cancer and mesothelioma together in the excess risk calculations. It has been suggested that asbestos exposure may also lead to stomach cancer, colorectal cancer and cancer of the pharynx. Potential underestimation resulting from these cancers is expected to be in the same order of magnitude, related to asbestos exposure, but has not been considered extensively because there is still doubt whether the increased risks observed in some studies for these cancers are the result of a causal association between asbestos exposure and these cancers.

- **Estimation of the exposure response slope for mixed asbestos.** In the risk assessment process, it is assumed that at present, workers are mainly exposed to mixed asbestos. Because potential potency differences between different fibre types for lung cancer seems relatively small, the meta-estimate of the exposure response relation for lung cancer, taking all studies together, is expected to yield an acceptable meta-estimate for mixed asbestos. Differences in relative risk between the meta-exposure response estimate and the estimate for mixed asbestos types only were

below 10%, using the spline model adjusted for intercept. As regards mesothelioma, the question arises what an adequate potency estimate is for mixed asbestos, against the background that clear potency differences exist between different types of asbestos for developing mesothelioma. Point estimates for the K_M value used in the risk assessment were calculated in different ways. First, the average value of K_M values for all available studies were calculated. In addition, an asbestos use weighted average of chrysotile and amphibole asbestos was calculated. These two estimates of the K_M factor were very similar. However, the agreement depends to some extent on the assumed ratio of chrysotile:amphibole asbestos use over the second half of the previous century, which plausibly ranges between 94% and 96%. A lower contribution of chrysotile to mixed asbestos exposure, will lead to an increased risk of developing mesothelioma in case of mixed asbestos exposure. This underestimation can be as high as almost 50% for mesothelioma. These potency differences have played a considerably less important role in case of lung cancer.

- **Differences in lifetime risk related to choices in risk calculations.** Some differences in risk outcomes relate to assumptions and choices in the risk calculations for which there is no default approach agreed upon. These choices are related to using conditional (life table analysis) or simple unconditional risk calculation methods, but also the cut-off age for the lifetime risk, choice of background rates (e.g. country specific rates, EU averaged rates, both genders combined or men only), time period of reference rates (which have changed for lung cancer because of changes in smoking habits), etc., all influence the estimated risks. Some of these have been explored in the literature or in sensitivity analyses in Annex 1. The use of conditional (life table methods) leads to unbiased estimates but these can be up to a factor 2 lower than unconditional risk estimates (not adjusted for other causes of death). Calculating lifetime risk until age >100 instead of 89 (as in this opinion) leads to a 10% higher risk. The average of male and female lung cancer rates has been used for calculations. Lung cancer rates are higher for males. Use of male rates only, led to a 30% higher lifetime risk in comparison to the figures presented in the tables. It should be noted that the choice of mortality rates is only relevant for lung cancer. Mesothelioma risk has been estimated using an absolute risk model which does not require input of background mesothelioma rates.

  As indicated in the previous section, in particular this category of choices, arising from the lifetime excess calculations, may contribute to the explanation of differences with other risk assessments because other mortality rates or lifetime risk periods have been used.

Comparison of exposure measurements in historical epidemiological data and current monitoring methods

The above exposure-risk relations are based on studies which used fibre counting protocols which were based on phase contrast optical microscopy (PCM) or converted to PCM from earlier methods (see also Appendixes 3 and 5). As explained in Chapter 6, that method uses a dimensional fibre definition without further fibre type characterisation; i.e. all fibres that conform to the dimensional definition are counted regardless of their mineralogical composition. In historical settings, e.g. asbestos product factories, it is likely that asbestos fibres accounted for most, if not all airborne fibres. More recently,

measurement techniques based on electron microscopy (EM) have been introduced. These methods (1) can detect much thinner and shorter fibres than PCM and (2) are also equipped with analysers able to characterise the elemental composition or crystal structure of the fibres (see Chapter 6). Any transferring of the relationship between epidemiologically established PCM-based exposure-risk relationship into electron microscopic exposure metrics can only be based on aggregate level comparison of the methods as it is not possible to transfer the underlying individual level historical epidemiological data based on PCM exposure metrics to the modern EM methods. The inherent uncertainties are further discussed in Appendix 5 and summarised below.

The ratio of fibre concentration measured by EM and PCM depends, among others, on the fibre dimensions in the sample and type of asbestos (see Appendix 5). In a recent French analysis (Eypert-Blaison et al. (2018b) and Eypert-Blaison et al. (2018a)) of samples from asbestos removal work sites, when restricting the counting to fibres that conform to WHO definition (i.e. excluding short fibres and thin fibres not detectable with PCM), the arithmetic mean TEM/PCM ratio was 4.6 when combining all asbestos fibre and material types, but it ranged from 0.1 to 19 depending on the type of asbestos material removed. When including all fibre widths (i.e. also thin asbestos fibres not detectable with PCM) the arithmetic mean was 15 and range by type of material from 0.2 to 95. In addition to the type of material, also type of asbestos fibre (the difference was smaller for amphiboles) and method of removal (highest ratio in hydroblasting) influenced the ratio. To be noted that the (rare) ratios below 1 above reflect situations where non-asbestos fibres were abundant and were counted by PCM but not by TEM. The results of these more recent comparisons are similar to those observed earlier by Verma and Clark (1995) who studied somewhat thicker fibres (width > 0.3 µm) and consequently established somewhat lower PCM to TEM conversion factors for fibres longer than 5 µm of between 1.2 and 10.4, but usually between 1.4 and 3.2. Overall, it is obvious that the TEM/PCM ratios are always context (exposure situation) dependent and should not be generalised.

As described in section 7.7.1 there is indication that the carcinogenic potency of asbestos fibres increases with increasing fibre length and decreasing fibre width. However, the exposure in each of the historical cohorts covered a very variable size distribution not allowing very exact estimates concerning given a fibre length or width and accounting for the effect of fibres with other fibre dimensions. Furthermore, the data available is very much driven by the WHO fibre definition (especially the fact that fibres shorter than 5 µm were not considered at all) and the PCM method (fibres thinner than about 0.2 µm could not be detected). However, based on human and animal data, it is not possible to exclude an asbestos associated risk of cancer for any fibre width or length category studied (within the above limitation of the existing studies dealing only with fibres fulfilling the WHO definition).

For fibres thinner than those detected by PCM, the so called thin fibres (width < 0.2 µm, length > 5 µm, length/width $\geq$ 3), Afsset (2009a,b) concluded that given the carcinogenic potential, this dimensional class is to be included when measuring dust levels in the workplace (See section 9.1.1). The observations made in ECHA review in chapters 7 and 8 concerning human data, animal data and mode of action data (especially the role of frustrated phagocytosis) concur with this conclusion. However, as explained, the inclusion of such fibres has important repercussions concerning the choice of analytical method that call for more methodological harmonisation (see Chapter 6) and are also related to the conversion factor that is needed to convert the PCM based epidemiological risk estimates to EM based counting methods.

For the so-called short fibres (length < 5 µm, width < 3 µm, length/width $\geq$ 3), i.e. fibres shorter than the WHO PCM definition the data base is less robust as reviewed by ANSES (section 9.1.1). Mainly because these fibres were not at all assessed when using WHO PCM method while they were most likely present in the exposures of the historical cohorts together with the so called WHO fibres. Afsset noted that the limit of 5 µm in

length used to differentiate between a "short" and “long” fibre does not correspond to demonstrated scientific safety data and the carcinogenicity of short fibres, even if it remains difficult to assess, cannot be excluded. However, Afsset concluded that due to the systematic presence of asbestos fibres with a length above 5 µm in occupational activities linked to asbestos in the workplace, the (national) OEL that was suggested will indirectly cover a possible health risk linked to short fibres. Based on ECHA review of more recent studies, there is still no human risk data for exposures consisting solely of short asbestos fibres. There is also little animal data specifically on such fibres and the existing mode of action data of asbestos fibres is largely driven by studies based on the WHO fibre definition. Inclusion of short fibres in EM counting would influence overall concentration even more than the inclusion of thin fibres (see the recent French data above, in Chapter 5 and in Appendix 5) and thus result in even higher and more variable conversion factors by type of material and type of removal technique. Similar considerations apply to the elongated cleavage fragments (see ANSES review in section 9.1.1). ECHA concludes that justifying inclusion of short fibres and cleavage fragments in the fibre counts used to monitor the compliance with the OEL would require more accurate scientific understanding concerning their toxic properties. It is to be noted that the root problem for changing the fibre dimension definition is that the human data set available can associate the excess risk only to exposure levels conforming to the WHO fibre definition of the PCM method that has been the measurement standard so far.

Regulatory bodies have taken pragmatic approaches to overcome the above methodological uncertainties concerning the conversion between PCM and EM fibre counts. RIVM (1987) and WHO (1987) used a pragmatic factor of 2 between TEM and PCM in their assessments of environmental exposure. It is noteworthy that fibre dimension distribution may differ between the environmental and occupational setting due to selection of fibre characteristics (especially length) to fit the technical needs of the commercial application in question. EPA concluded factors between 2 and 4 (for fibres more than 5 µm long with a diameter greater than 0.4 µm, see Appendix 5).

Approaches used in OEL setting context are further described in section 9.1.1. In brief, DECOS (2010) used a factor of 2 when deriving an exposure-risk relationship for occupational setting to be monitored by TEM but based on epidemiological data expressed as PCM measurements. AGS (2008) did not consider it necessary to introduce a correction factor to take account of different methods of fibre detection (optical or electron microscope) while setting standards to be monitored by SEM but based on EPA (1986) exposure-risk relationship relying on PCM. Afsset (2009b) acknowledged the higher sensitivity of TEM but based its recommendation on PCM while calling for development of a TEM method. Danish NFA (2019) did not consider a modification factor in its recommendation to adapt the DECOS (2010) approach to the national setting and also did not recommend a specific analytical method.

Currently there is no uniformly accepted and used international EM method to count asbestos fibres at workplace and national bodies have set national standards. The fibre dimension aspects of the national SEM and TEM methods are described in Chapter 6. While an aspect ratio of $\geq$3 is assumed in all methods and most methods also require a fibre length of $\geq$5µm, there is much variation as regards the minimum thickness of fibres that are detected and counted.

As described above there is no science-based single conversion factor between PCM and EM measurements. And there is also no uniformly used international EM method. The historical epidemiological data available for exposure-risk assessment are based on PCM. However, this method does not differentiate between asbestos fibres and other fibres which indeed would be preferable. The pragmatic solutions taken at national level involve the following choices:

1. Using a uniform pragmatic conversion factor to transfer the extra risk levels identified based on PCM into EM based values accounting for the higher sensitivity of EM as suggested by DECOS. Those regulatory bodies that have used

conversion factors, have typically used factors between 2 and 4 thus compromising for pragmatic reasons the fact the in real life situations the ratio between the results by two measurements are context related and subject to a relatively wide variation. These conversion factors are based on restricting the EM counting to fibres with widths detectable also with PCM. As pointed out above there is little scientific reason for excluding the thin fibres in EM counts where they can easily be detected. Such an approach resulted in an average EM/PCM ratio of 15 in a recent French study.

2. Using a PCM based limit value that, when necessary (e.g. a presumed high fraction of non-asbestos fibres), can be complemented by EM measurements, still applying the same limit value. It is noted that when applying EM, this limit value would follow a precautionary approach as EM would detect also thin asbestos fibres not detectable by PCM which was the method used in studies forming the basis of the ERR. I.e. if EM had been used in those cohorts, a given excess risk would have been associated to higher fibre asbestos counts than the PCM all fibre count. It is noteworthy that very likely the share of non-asbestos fibres in these historical asbestos manufacturing etc cohorts was small and thus PCM counting all types of fibres would not have overestimated the asbestos fibre count importantly. This would follow the German and French approach where no conversion factor is applied. While there are other differences, i.e. Germany using SEM and counting only WHO fibres and France using TEM and counting also thin fibres (<0.2 μm).

As explained in Chapter 6 harmonisation work is required at EU level concerning the different EM methods currently used. That harmonisation concerns also the dimensional fibre definitions, counting rules and other factors that influence the EM asbestos fibre counts. Consequently, it is not possible to recommend a precise conversion factor. Transitional provisions seem necessary before that harmonisation work has come to a conclusion.

9.2 Derived Occupational Exposure Limit (OEL) Values

9.2.1 Published approaches to establishing OELs

The recent national approaches have assumed a non-threshold mode of actions and derived an exposure-risk relationship that was then used to establish an OEL based on national conventions concerning an acceptable excess risk. Those are described in section 9.1.1.

9.2.2 Occupational Exposure Limits (OELs) - 8h TWA

It is concluded that asbestos is a non-threshold carcinogen and consequently an exposure-risk relationship is derived in section 9.1.2.

9.2.3 Short Term Exposure Limits (STELs)

Asbestos is considered to be a non-threshold carcinogen and an exposure-risk relation is derived for these effects in section 9.1.2. Asbestos also causes non-malignant pulmonary and pleural diseases following long-term exposure. There is no particular evidence of short-term threshold effects of asbestos to base a STEL. ECHA notes that while some Member States use a fixed ratio between an 8-hour time-weighted average (TWA) and STEL value in absence of specific acute effects, no such convention exists at the EU level.

9.2.4 Biological Limit Value (BLV)

There is no biomonitoring method currently available and no BLV is proposed for asbestos.

9.2.5 Biological Guidance Value (BGV)

There is no biomonitoring method currently available and no BGV is proposed for asbestos.

9.3 Notations

Asbestos fibres are not absorbed via the dermal route. There is no reported evidence of asbestos being a skin sensitiser or respiratory sensitiser.

Therefore, no notation for 'Skin', 'Skin sensitisation' or 'Respiratory sensitisation' is warranted.

9.4 Other related considerations

Current health surveillance –related provisions of Directive 2009/148/EC

It is noted that Article 18 sections 2-5 of Directive 2009/148/EC set the health surveillance related measures for asbestos work and Annex I of the Directive gives practical recommendations to which the Member States may refer for the clinical surveillance of asbestos workers.

Health surveillance –related observations during ECHA's review

As stipulated by Article 18 and Annex I of Directive 2009/148/EC the health surveillance includes aspects that fall under the competencies of the doctor or respective national authorities mandated by the national laws and practices. Such aspects were not under the mandate of ECHA's task. However, during the review of the scientific literature, the following new developments as regards current health surveillance related provisions of Directive 2009/148/EC were identified;

Article 18: No new scientific evidence directly linked to these provisions was identified.

Annex I: The following aspects were identified:

- Paragraph 1 does not list carcinoma of the larynx and carcinoma of the ovary as diseases for which the current knowledge indicates that exposure to free asbestos fibres can give rise to. As explained in section 7.7 the current human evidence concerning causal role of asbestos exposure is considered convincing for carcinoma of the larynx and carcinoma of the ovary. Paragraph 1 also does not mention any of those non-malignant pleural diseases for which asbestos exposure is a causal factor as explained in section 7.3.
- Last sentence of paragraph 3 mentions tomodensitometry. This refers to a radiological imaging method that in the current English medical literature is called computed tomography (see section 7.3.1). It covers both conventional computed tomography and high resolution computed tomography that is a method commonly used today in diagnosis of asbestos-related diseases. Consequently, it would seem more accurate to formulate the last sentence in Annex I "…or a chest X-ray or computed tomography…". It is considered that the choice of method should still be done "in the light of the latest occupational health knowledge available" as already stated in Annex I

Safety of asbestos-removal work

It is noted that in certain settings, the concentration of asbestos fibres inside the isolated work area during asbestos removal work can be very high, tens or in extreme cases hundreds of fibres/cm^3 (see section 5.3.3). The safety of workers in such settings relies heavily on personal protective equipment. Very high effectiveness of respirator and other personal protective measures are required to ensure that the actual exposure of the worker does not exceed the OEL. As described in section 5.3.3 it is further noted that the actual concentration inside the isolated work area depends not only on the type of asbestos material removed but is quite much influenced also by the removal technique

used. The prevention of exposure in such settings thus requires a comprehensive preventive approach combining work organisational, technical, and individual protection related aspects. Such measures include safe systems of work, the correct use of decontamination and changing facilities together with the training and supervision of workers.

Additionally, given how many applications of asbestos there were in the past, an adequate assessment to determine the presence and dentification of asbestos products and their physical condition (state of repair) before starting renovation or demolition work remains a continuing challenge (See Chapter 5).

As described in section 5.3.1 the latest EU guidance on asbestos work is from 2012 while some national authorities have further developed their approaches, including standards and guidance documents. The revision of the OEL may necessitate the need to update some of the existing guidance, at both EU and national levels, so that it continues to provide recommendations on safe ways of working that can ensure compliance with the revised OEL.

Appendix 1. REFERENCES

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Appendix 2. Tabulated Summaries for Substance identification and Physico-chemical properties of asbestos

Table 10. Substance identification and physico-chemical properties of asbestos (adapted from IARC 2012 and DECOS 2010)

Mineral	CAS number	Idealised chemical formula *	Colour	Melting point, decomposition temperature (°C)	Other properties
Serpentines					
Chrysotile (white asbestos)	12001-29-5	$[Mg_3Si_2O_5(OH)_4]_n$	White, grey, green, yellowish	800-850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
Amphiboles					
Crocidolite (blue asbestos)	12001-28-4	$[NaFe^{2+}{}_3Fe^{3+}{}_2Si_8O_{22}(OH)_2]_n$	Lavender, blue, green	800	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite (brown asbestos)	12172-73-5	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]n$	Brown, grey, greenish	600-900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Anthophyllite	77536-67-5	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Grey, white, brownish-grey, green	950	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Tremolite	77536-68-6	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	White to pale green	1040	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water

Mineral	CAS number	Idealised chemical formula *	Colour	Melting point, decomposition temperature (°C)	Other properties
Acitonolite	77536-66-4	$[Ca_2(Mg,Fe^{2+})_5Si_8O_{22}(OH)_2]_n$	Green	unknown	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrysotile and talc deposits; negative surface charge in water

* The chemical formulas of asbestos minerals are idealized. In natural samples, the composition varies with respect to major and trace elements

Appendix 3. Analysis of the more recent studies assessing asbestos-related exposure response for lung cancer and mesothelioma

As described in section 7.7.1, lung cancer and mesothelioma are the cancer sites for which robust quantitative exposure-response relationships have been identified in human epidemiological data. As further described in section 7.7.1 the most recent meta-analyses calculating quantitative exposure-response slope factors for lung cancer were van der Bij et al. (2013) and Lenters et al. (2011) and for mesothelioma DECOS (2010). The DECOS (2010) meta-analysis is also further described in section 9.1.1.

In order to support the Cancer risk assessment presented in section 9.1.2 the studies published more recently and not used in the above meta-analyses were identified with a literature search. These included (1) updates of the existing cohorts, (2) new cohort studies and (3) new case-control studies. The quality of the new studies was reviewed using the criteria used by van der Bij et al. (2013) further described in Lenters et al. (2011) and its supplementary material. Studies that qualified the set criteria were added to the data used by van der Bij or DECOS. For updates or overlapping studies the most informative one was used. It is noted that for existing cohorts used in earlier meta-analyses, the analysis of the exposure assessment quality performed already then, was not repeated.

The review of the new studies, rationale for including/excluding a given study are described this Appendix separately for lung cancer and mesothelioma. Special emphasis was on quality of the quantitative exposure assessment, especially if older gravimetric exposure measurements were converted into PCM fibre counts based on company or department level double samples analysed with both methods, or only based on coarse external conversion factors. Furthermore, it was checked if the published data on the study provides the information on parameters needed for the lung cancer or mesothelioma modelling.

It is to be noted that for open-ended, uppermost exposure categories, the midpoint was calculated as 5/3 times the lower bound of those categories (as proposed by the asbestos advisory committee of the Unites States Environmental Protection Agency in 2008 (EPA, 2008) and used in the previous meta-analyses). For example, midpoint estimate for an open-ended category of > 100 f–y/cm^3 was calculated as 5/3 * 100 = 167.

1. Lung cancer

1.1 Updates of previously published cohorts

Balangero mine

In the recent cohort update from the Italian Balangero chrysotile mine and mill Pira et al. (2017) reported 53 deaths from lung cancer among 1056 men. Details of jobs held by cohort members were obtained from factory records and co-workers as already described in Pira et al. (2009) that was used in the earlier meta-analyses. Jobs were classified as mining, crushing, waste dumping, screening and fibre separation, bagging and storage and maintenance. For each worker, cumulative exposure was calculated by summing across all jobs the products of estimated exposure and duration of employment in that job. Fibre counts at the plant were first

carried out in 1969. In order to categorise jobs by dust exposure levels before 1969, exposure circumstances occurring between 1946 and 1969 were simulated at the plant. Factory files were examined for information on daily production, equipment used, characteristics of the job and number of hours worked per day, and workers employed since 1935 helped to reconstruct the appropriate conditions.

Ferrante et al. (2020) followed a slightly smaller number (972) of mine workers of the same Balangero chrysotile mine who had been employed at least 6 months. There were 41 incident cases of lung cancer.

It is noted that the studies of Pira et al. (2017) and Ferrante et al. (2020) used the same original exposure data set in their assessment of exposure. However, slightly different assumptions were made. The previous meta-analyses (Lenters et al. (2011) and van de Bij et al. (2013) used the earlier publication according to the Pira study methodology. It is also noted that the cohort followed by Pira et al (2017) is slightly larger than the one by Ferrante at al. (2020).

The update by Pira et al. (2017) was used in the meta-analysis.

Data from Pira et al. (2017) Table 3.

CE (f–y/cm^3)	CE midpoint	SMR	Obs	Exp[a]
< 100	50	0.82	13	15.85
100-400	250	1.46	20	13.70
≥ 400	666.7	1.25	20	16.00

[a] calculated as Obs/SMR

Libby vermiculite mine

Larson et al. (2010) extended the follow-up of the Libby MT vermiculite mining cohort that was exposed to what is called "Libby amphibole" consisting of tremolite and related fibrous amphiboles. Compared to the previous mortality study by Sullivan (2007), five more years of follow-up were added, also the female workers were included and multiple causes of death were considered. The cohort consisted of 1862 workers (vs 1672 used in Lenters and DECOS). There were 98 deaths of lung cancer. The previously generated NIOSH exposure estimates were used to calculate cumulative fibre exposure. However, cumulative exposures were lagged 20 years. RRs of lung cancer were calculated in comparison to the lowest quartile (< 1.4 f–y/cm^3) for the following quartiles of cumulative fibre exposure: 1.4 – 8.5, 8.6 – 43 and > 44 f–y/cm^3. The lagging of cumulative exposure with 20 years resulted thus in exposure quartiles lower than those used by the earlier analyses (< 4.5, 4.5 – 23, 23 - 100, > 100) f–y/cm^3.

The use of cumulative exposure lagged 20 years is slightly at odds with the original EPA model and those used later. However, the new update with extended follow-up was included in the meta-analysis replacing the study of Sullivan (2007).

Data from Larson et al. (2010) Table 5.

CE20 (f–y/cm^3)	CE20 midpoint	Obs	RR	95% CI
< 1.4	0.7	19	1.0	Ref.
1.4-8.6	5.0	21	1.1	0.6-2.1
8.6-44.0	26.3	20	1.7	1.0-3.0
≥ 44.0	73.33	38	3.2	1.8-5.3

North Carolina (NC) and South Carolina (SC) plants

Elliott et al. (2012) followed 6136 workers of the NC and SC asbestos textile factories for lung cancer mortality. Chrysotile exposure concentrations were estimated independently for each cohort using job exposure matrices based on detailed employment histories and industrial hygiene sampling measurements. There were altogether 361 deaths of lung cancer. RRs for lung cancer were calculated for cumulative exposure of 100 f–y/cm^3 vs 0 f–y/cm^3 using both an exponential rate model and an excess relative rate model for the pooled data and separately for SC and NC cohorts and the three NC plants. The follow-up period and method of exposure assessment were the same as those used by Hein et al. (2007) for SC cohort and Loomis et al. (2009) for the NC cohorts which were already included in the meta-analysis of Lenters et al. (2011). So, the study adds no further follow-up experience to the cohorts, it rather analyses methodological aspects that might explain the differences in risk between the two cohorts.

In a further analysis of three of the plants of the NC asbestos textile cohort of 5397 workers Loomis et al. (2019) analysed pleural cancer and mesothelioma mortality by cumulative exposure to chrysotile asbestos fibres. The study does not report analyses for lung cancer.

For the reasons explained above these studies were not included in the lung cancer analysis.

It is further noted that Levin et al. (2016) extended the cancer follow-up of the 1130 amosite exposed Tyler TX asbestos factory workers, Larson et al. (2020) further extended the follow-up of the above-mentioned Libby MT vermiculite mining cohort and Finkelstein (2010) continued the mortality follow-up of 156 Ontario asbestos cement plant workers. Berry et al (2012) extended by 8 years the follow-up of Berry et al. (2004) of the Australian crocidolite miner cohort. However, these studies did not report lung cancer risk estimates by cumulative exposure and are therefore not considered further.

1.2 New cohort studies

French asbestos textile and friction study

Clin et al. (2011a) followed 2024 workers of a French asbestos textile and friction material plant with exposure to crocidolite and chrysotile and observed 42 incident cases of lung cancer in a follow-up until end of 2004. The vital status in 2004 could not be verified for 5.3% of the cohort. Cumulative exposure index (CEI), lagged 10 years, for asbestos at career end expressed in f–y/cm^3 were calculated according to the company's own employment exposure matrix.

Job history and exposure assessment: Detailed information on the professional history and occupational exposure of each subject in the cohort was available in files held by the company occupational health department. Data on occupational exposure to asbestos included the following information: date of first employment, date of departure from the company, exposure sector (textile/friction), type of asbestos handled (chrysotile alone or mixed chrysotile/amphibole), duration of asbestos exposure. Dust concentration measurement data collected by the company was available since 1959 and double measurements done in 1974 were used to convert the earlier gravimetric results to fibre concentrations.

The exposure assessment and completeness of follow-up were of comparable quality compared to the other available studies and this study was therefore included in the

quantitative exposure-response meta-analysis. Document on details of the exposure assessment strategy and exposure data analysis was relatively limited.

Data from Clin et al. (2011) Table 1.

CE10 (f–y/cm^3)	CE10 midpoint	Obs	HR	95% CI
< 40	20	5	1.0	Ref.
40-140	90	14	1.05	0.42-2.62
140-853	496.5	23	1.89	0.74-4.84

Chinese asbestos products factory

Courtice et al. (2016) followed a cohort of 577 workers from an asbestos factory (textiles, rubber products and asbestos cement) in China from 1972 to 2008. Eligible cohort included 586 workers; thus follow-up was relatively complete. Individual cumulative fibre exposures in f–y/cm^3 were calculated as the product of the estimated fibre concentration for a specific exposure area and the duration of employment in each exposure area during the appropriate calendar time period, lagged 10 years. Paired samples were collected to generate fibre concentrations from the existing dust concentration data.

Job history and exposure assessment: Baseline information about each worker was obtained from factory personnel records and interviews. Information included date of hire, job type, and exposure duration. There were nine job types: raw materials workers, carders, spinners, weavers, rubber workers, cement workers, maintenance workers, administration workers, and rear service workers. Administration workers included managers and other office workers such as clerks, accountants, etc., and rear service workers included cooks and other miscellaneous staff. Periodic total dust measurements in mg/m^3 were available every 5 years from 1955 until 1990, then once in 1994. In 1999 and 2002, membrane filter samples for gravimetric analysis were collected in parallel with filters for phase contrast microscope analysis. One hundred and twenty pairs of fibre/dust measurements were available, or a total of 240 samples. These data were used to establish the association between gravimetric dust and fibre concentrations, which was subsequently used to convert gravimetric dust measurements into fibre concentrations.

The exposure assessment and completeness of follow-up were of comparable quality compared to the other available studies and this study was therefore included in the quantitative exposure-response meta-analysis. Document on details of the exposure assessment strategy and exposure data analysis was relatively limited.

Data from Courtice et al. (2016) Table V.

CE10 (f–y/cm^3)	CE10 midpoint	Obs [a]	RR	95% CI
< 89	44.5	10	1.0	Ref.
89-133	111	9	1.93	1.07-2.32
133-548	340.5	13	2.59	2.18-3.09
≥ 548	913.33	23	5.59	4.77-6.56

[a] from Table II of Courtice et al. (2016)

Deng et al. (2012) followed a cohort of 586 male asbestos factory workers (textile, rubber and asbestos cement products) for 35 years. There were 51 deaths from lung cancer. Cumulative exposure was estimated based on employment histories from

company records and a questionnaire and historical dust and fibre measurements available for the different workshops of the plant and pairwise samples to correlate the old dust concentrations to fibre concentrations. The cumulative exposure was modelled as a continuous variable from the midpoint of each of the ten exposure categories (lowest 8.8 – 36, highest > 462 f–y/cm^3). The analyses were adjusted for age, smoking and calendar time.

As the study by Courtice et al. (2016) above concerns a longer follow-up of the same cohort, that study was given preference and the study by Deng et al. (2012) was not included.

Chinese chrysotile mine study

Wang et al. (2013b) followed a cohort of 1539 male workers from a chrysotile mine in China for 26 years. It was reported that none of the cohort members was lost for follow-up. Individual cumulative fibre exposures (f–y/cm^3) were estimated based on converted dust measurements and working years at specific workshops. There were 56 cases of lung cancer and SMRs were calculated for four categories of cumulative exposure (< 20, 20 – 99, 100 – 449, > 450 f–y/cm^3, lagged 10 years. There was a significant ($p<0.001$) trend of increasing SMR for lung cancer by cumulative exposure category.

Job history and exposure. Data were collected on each worker's job type, when they first started working in the mine; number of years working at different workshops/departments, from the personnel department of the mine. Periodic data of total dust concentrations of different workshops were available from 1984 to 1995 and in 2006. Conversion from gravimetric results to fibre concentrations was based on correlations observed in 35 paired samples measured in 1991 in main workshops in chrysotile mine. However, dust exposure estimates were based on static sampling underestimating personal cumulative exposure.

The exposure assessment and completeness of follow-up were of comparable quality compared to the other available studies and this study was therefore included in the quantitative exposure-response meta-analysis. Document on details of the exposure assessment strategy and exposure data analysis was relatively limited. However, this cohort is expected to influence the meta-analysis to a very limited extent because of the high exposure levels and the limited number of lung cancer cases (n=53) resulting in a limited precision of the point estimates.

Data from Wang et al. (2013b) Table 5.

CE (f–y/cm^3)	CE midpoint	SMR	Obs	Exp[a]
< 20	10	1.10	5	4.55
20-99	59.5	4.41	12	2.72
100-449	274.5	10.88	16	1.47
≥ 450	750	18.69	20	1.07

[a] calculated as Obs/SMR

Wang et al. (2014) followed 1539 male chrysotile mining workers and 464 male chrysotile textile workers and 424 control workers. The miner cohort is the same as the one by Wang et al. (2013b) above and the textile worker cohort is a subset of the cohort published by Courtice et al. (2016) and Deng et al. (2012). Cumulative exposure to asbestos fibres was estimated from dust measurements based on paired samples comparing dust and asbestos fibre results. There were 46 deaths from lung cancer among the textile workers, 56 among the miners and 7 among the control workers. Hazard ratios were calculated for four categories of cumulative exposure both in textile (< 122, 122 – 274, 275 – 1316, > 1317 f–y/cm^3) and in mine (< 241, 241 – 342, 343 – 759, > 760 f–y/cm^3) workers in comparison to the control workers adjusting for either

age or for age and smoking. There was a difference in risk between the textile and mine workers only in the lowest cumulative exposure category.

Preference was given to Courtice et al. (2016) for the textile cohort as the Wang et al. (2014) uses only a subset of the cohort. Preference was also given to Wang et al. (2013b) for the miner cohort as Wang et al (2014) uses a smaller cumulative exposure gradient in order to allow comparison with the textile cohort. Consequently Wang et al. (2014) was not included.

Luberto et al. (2019) pooled 21 Italian asbestos cement manufacturing cohorts with 12 578 workers and calculated SMRs based on about 390 000 person-years of follow-up. There were 810 lung cancers in males and 38 in females. For cases lost for follow-up the last date of contact was used in calculation of person-years. The number of cases lost for follow-up is not reported but is not expected to be high. Exposure was mixed to amphiboles and chrysotile. For each plant and period, the experts estimated the proportion of workers exposed, the percentage of typical working time in tasks with asbestos exposure and the range of minimum and maximum concentration of asbestos airborne fibres (fibres/cm^3), separately for direct and indirect exposure. Tasks and jobs of individual workers were not known; therefore plant and period-specific data were used to compute for each plant and year an Average Exposure Index (AEI) to be applied to all members of a given cohort. From the AEI a Cumulative Average Exposure Index (CEI) was computed for the occupational history of each worker summing the contribution of all periods of activity. SMRs for lung cancer were calculated for tertiles of CEI (< 54, 54 – 620, > 620 f–y/cm^3), no lag time was applied.

Job history and exposure assessment: Tasks and jobs of individual workers were not known; therefore plant and period-specific data were used to compute for each plant and year an Average Exposure Index (AEI) to be applied to all members of a given cohort. The cumulative average exposure index was calculated both crude and fibre-type-weighted. In the latter the weights were the malignant mesothelioma potency factors for chrysotile, amosite and crocidolite (respective 1:14:71) as estimated by Hodgson and Darnton (2010) resulting in the fibre-type-weighted CEI being expressed as "chrysotile equivalent" taking into account differences in the use of amphibole and chrysotile asbestos by plant and period. The same weighted CEI was also used for analyses of lung cancer and other studied cancers. The detailed results were presented only for the fibre-type-weighted CEI, while it was stated that "none of the other analyses showed relevant differences with the analyses presented for fibre-type-weighted CEI and all confirmed the exposure-response trends with increasing exposure."

The follow-up is methodologically well-conducted. However, only plant- and period-specific exposure estimates could be produced, assuming all workers at a given plant a given time had the same exposure. Furthermore, the calculation of chrysotile weighted cumulative exposure indices, combining all fibre types, does not allow to compare the results with other studies reporting non-weighted cumulative exposures either for chrysotile, amphibole or mixed exposure, nor for simply considering all asbestos non-weighted for fibre type.

Dutch open population study

Offermans et al. (2014) followed 58 888 male general population participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17 years (1986-2003). The number of cases lost for follow-up is not reported but is not expected to be high. Semi-quantitative cumulative exposure estimates were generated using both the Dutch (DOMJEM) and the Finnish job exposure matrixes (FINJEM). The cumulative exposure was expressed as non-dimensional "unit-years" in DOMJEM and as f–y/cm^3 in FINJEM. There were 2324 cases of lung cancer. Hazard ratios were calculated in

comparison to the unexposed for the three tertile categories of the exposed subjects (medians 0.20, 1.58 and 6.57 f–y/cm^3, according to FINJEM), no lag time was applied.

Job history and exposure assessment: Information on lifetime occupational history until 1986 was obtained from the questionnaire completed at study enrolment. Questions concerned the job title, name and type of the company, products made in the department, and period of employment. On the basis of these questions, occupations were coded according to the Standard Occupational Classification of 1984 of the Dutch Central Bureau of Statistics. Subjects could enter a maximum of five occupations, which was generally sufficient to cover the lifetime occupational history for the large majority of the cohort, because cohort subjects held on average 1.9 job codes during their working life up to 1986. For all subjects, the job code was assessed for each of the maximally five occupations held between starting work and 1986. Although FINJEM was constructed for Finland, exposure estimates were not adapted to Dutch occupational circumstances. The occupational information was used to semi-quantitatively estimate the cumulative exposure based on the FINJEM which gives mean group exposure (proportion of exposed and level of exposure) for carcinogenic agents by occupation for four time periods (1945-59, 1960-74, 1975-84 and 1985-94). There was no individual-level information on exposure. The cumulative exposure was estimated as proportion x level x time summing the information for each of the maximum five occupation held by the individual. For those workers who started working before 1945, exposure was set to zero, because there was hardly any asbestos industry in the Netherlands in the period before 1945. Based on DOMJEM, only non-dimensional "unit-years" were calculated.

The follow-up is methodologically well-conducted. However, due to the nature of a follow-up study in the general population cohort, the exposure estimates are based on population level aggregate estimates of level of exposure. Such an approach involves also the introduction of an element of semi-quantitative probability of exposure (based on estimates of proportion of workers exposed in a given occupation/industry during a certain period of time). It is considered that such semi-quantitative estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

It is ECHA further noted that Wang et al. (2013a), Wang et al. (2012) and Lin et al. (2012) have published cancer follow-ups of Chinese asbestos factory cohorts. Ferrante et al. (2017) pooled data from 43 Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding). However, these studies did not report lung cancer risk estimates by cumulative exposure and are therefore not considered further. Furthermore Magnani et al. (2020) reported lung cancer risk estimates for the same Italian asbestos cohort pool as Ferrante et al. (2017) and using the same exposure assessment method as Luberto et al. (2019) above. This study was considered not suitable for inclusion in the meta-regression analysis for the same reasons as the study by Luberto et al. (2019).

1.3 New case-control studies

Pooled multi centre case-control study

Olsson et al. (2017) pooled 14 lung cancer case-control studies conducted in 1985-2010 in Europe and Canada, including 17 705 cases and 21 813 controls with detailed information on smoking habits as well as estimated cumulative asbestos exposure based on quantitative job-exposure-matrices. Participation rates were 62%–98% (mean, 83%) among cases and 41%–100% (mean, 70%) among controls. ORs for lung cancer were calculated compared to the unexposed for four categories of cumulative exposure (< 0.5, 0.5. – 1.1, 1.2 – 2.7, > 2.8 f–y/cm^3). Lagging of cumulative exposure was applied, in which exposure in the 5, 10, 15, or 20 years before diagnosis/interview was disregarded. As results did not differ by lag-times, the unlagged models were used in the

main analyses. The authors discussed that a possible explanation for no effect of lagging is that the relative exposure distribution remained the same because most exposed subjects were exposed to no or low exposure levels in recent decades, particularly after the implementation of asbestos bans in the different countries. The ORs by cumulative exposure increased significantly among men (p for trend < 0.01) but not among women (p for trend 0.17). The study includes also the Swedish case-control study of Gustavsson et al (2002) that was already included in the previous meta-analyses on lung cancer.

Job history, exposure assessment: Occupational data consisted of a list of employment periods for every study subject. For every period, job and industrial activity had been recorded and coded according standard international classifications. Quantitative measurements of fibres (71,816) from 14 countries (mainly Germany, the UK, Canada, Italy, France, and Norway) were entered into the project-specific exposure database ExpoSYN according to a standardized protocol. Most data points were determined by phase-contrast microscopy (>95%), most data represented chrysotile (67%). Regarding measurement strategies, 53% of the measurements were considered "representative," 9% "worst case," and 38% "unknown." All measurements were linked to a standardised job title. Statistical models were applied to the personal measurements (27,958) collected in 1971–2009 to develop a project-specific quantitative job-exposure-matrix (SYN-JEM) for occupational asbestos exposure. When there were < 5 measurements for a specific job, the geometric mean estimate of all jobs within the same unit or major job group was applied, so the job estimate was based on information from the most similar Jobs. Very few measurements were available before 1975. For all countries and occupations together, a linear historical trend with an annual decrease of fibre concentrations of −10.7% before ban implementation and no further downward trend after ban implementation, and an exposure ceiling before 1975 to avoid unrealistically high estimates due to unrestrained back-extrapolation to periods when actual measurements were not carried out. Linking the occupational histories of the participants to SYN-JEM generated individual job-, region-, and year-specific estimates of the average intensity of asbestos exposure during a standard 8-hour working day in fibre/cm^3. Cumulative asbestos exposure (expressed as f–y/cm^3) was defined as the average exposure intensity in a particular job multiplied by the years of employment, and totalled over the working life of the participants. Some measurements in the data base were attributed to jobs clearly unrelated to asbestos exposure, like teachers; it was assumed these to represent exceptional situations, which should not be generalized to all individuals in that job. Therefore, a semi-quantitative general population job-exposure matrix based on job codes (DOM-JEM) was used in the model, where every job was rated as non-exposed (=0), low exposed with regard to exposure intensity or high exposed with low exposure probability (=1), or high exposed with high-exposure probability (=2). Jobs considered to be non-exposed in DOMJEM were set to 0 fibre/cm^3 in SYN-JEM, disregarding actual measurements, if any.

It is also noted that about 90% of the pooled data are from Europe, either from individual studies conducted in Germany, Italy, France, Netherlands, Spain and Sweden or from a multicentre study that included data from Czech Republic, Hungary, Poland, Romania, Slovakia and United Kingdom. The exposed individuals in the data also mostly include downstream users rather than more heavily exposed asbestos miners, millers or asbestos product manufacturers. The range of exposure (0.0023–64.6 f–y/cm^3) in this pooled analysis was lower than in the Lenters et al. 2011 or Van der Bij et al. 2013 studies (0.11–4710 f–y/cm^3. This large dataset is thus particularly informative to explore the shape of the exposure–response function in the low-dose range. An additional advantage was detailed adjustment for smoking.

The study is well-conducted, participation rate sufficient and the exposure assessment is considered robust enough for quantitative exposure-response analysis. The study is included in the meta-analysis. In order to avoid double counting, it will replace the study

of Gustavsson et al. (2002) that is included in the pooled data and was used as individual study in the previous meta-analyses.

Data from Olsson et al. (2017) Table 2.

CE (f–y/cm^3)	CE midpoint	Cases	Control	OR [a]	95% CI
Men					
0	0	6629	9608	1.00	ref
< 0.5	0.25	1206	1593	1.06	0.96-1.16
0.5- <1.2	0.85	1624	1713	1.26	1.15-1.37
1.2- < 2.8	2.00	1840	1724	1.25	1.15-1.36
≥ 2.8	4.67	2288	1772	1.38	1.27-1.50
Women					
0	0	2717	3898	1.00	ref
< 0.5	0.25	194	230	1.11	0.87-1.42
0.5- <1.2	0.85	104	104	0.95	0.69-1.31
1.2- < 2.8	2.00	110	106	1.22	0.90-1.68
≥ 2.8	4.67	74	70	1.23	0.84-1.78

[a] OR adjusted for study, age, smoking (pack-years, time-since-quitting smoking), and ever-employment in jobs with known increased lung cancer risk due to factors other than asbestos (Yes/No).

2. Mesothelioma

2.1 Updates of previously published cohorts

Balangero mine

In the recent cohort update from the Italian Balangero chrysotile mine and mill Pira et al. (2017) reported seven deaths from pleural cancer among 1056 men. Details of jobs held by cohort members were obtained from factory records and co-workers as already described in Pira et al. (2009) that was used in the earlier meta-analyses. Jobs were classified as mining, crushing, waste dumping, screening and fibre separation, bagging and storage and maintenance. For each worker, cumulative exposure was calculated by summing across all jobs the products of estimated exposure and duration of employment in that job. Fibre counts at the plant were first carried out in 1969. In order to categorise jobs by dust exposure levels before 1969, exposure circumstances occurring between 1946 and 1969 were simulated at the plant. Factory files were examined for information on daily production, equipment used, characteristics of the job and number of hours worked per day, and workers employed since 1935 helped to reconstruct the appropriate conditions. SMRs of pleural cancer compared to general population were calculated for 3 categories of cumulative exposure (< 100, 100 – 399 and > 400 f–y/cm^3). There was no significant trend in the mesothelioma analysis (p=0.76).

Ferrante et al. (2020) followed a slightly smaller number (972) of mine workers of the same Balangero chrysotile mine who had been employed at least 6 months. There were 10 incident cases of mesothelioma. The RRs were calculated for two highest tertile categories of cumulative exposure (27 – 345 and > 346 f–y/cm^3) in comparison to those with less than 27 f–y/cm^3. When using cumulative exposure as a continuous variable the estimated unit risk for 100 f–y/cm^3 for mesothelioma was RR = 1.019 (95% CI = 0.900-1.154)

It is noted that the studies of Pira et al. (2017) and Ferrante et al. (2020) used the same original exposure data set in their assessment of exposure. However, slightly different

assumptions were made. The previous meta-analysis by DECOS (2010) did not include the Balangero cohort as no mesothelioma risk estimates were published in the earlier follow-ups.

Both studies are of good quality. However, neither of them reports the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

North Carolina (NC) plants

In a further analysis of three of the plants of the NC asbestos textile cohort of 5397 workers Loomis et al. (2019) analysed pleural cancer and mesothelioma mortality by cumulative exposure to chrysotile asbestos. Cumulative exposure was generated from quantitative individual exposures to asbestos fibres estimated from 3420 air samples taken from the 1930s to the 1980s like in the lung cancer analysis of Loomis et al. (2009) used in earlier lung cancer meta-analyses. There were 8 cases of mesothelioma or pleural cancer and RRs were calculated per 100 f–y/cm^3 applying different lag times. In a model for cumulative exposure, lagged 10 years, the RR for pleural cancer mortality per 100 f–y/cm^3 was 1.15 (95% CI, 1.04-1.28). When modelled together with time since first exposure the RR was 1.05 (95% CI, 0.92-1.20) per 100 f–y/cm^3. Fitting the EPA/OSHA absolute risk model to data for the cohort gave a coefficient (K_M) of 0.088 × 10^{-8} (95% CI, 0.027 × 10^{-8} to 0.149 × 10^{-8}) per f–y/cm^3. The authors also conducted analyses in a subcohort that was still at risk in 1999 when ICD-10 diagnosis coding (including a specific code for mesothelioma) started to be used and when misclassification of diagnosis was presumed to be less common. In that subcohort the analyses were performed for mesothelioma instead of pleural cancer and the coefficient (K_M) for the EPA/OSHA risk model was 0.296 × 10^{-8} (95% CI, 0.0059 × 10^{-8} to 0.587 × 10^{-8}) per f–y/cm^3.

The NC cohorts were not included in the previous mesothelioma meta-analysis of DECOS (2010).

The study by Loomis et al. (2019) was included in the new mesothelioma meta-analysis and the subcohort still at risk when ICD-10 coding started, was used.

Wittenoom crocidolite mine

Berry et al (2012) extended by 8 years the mesothelioma follow-up of Berry et al. (2004) of the Australian crocidolite miner cohort of 6493 men and 415 women. Compared to the earlier follow-up the number of mesotheliomas increased from 235 to 316 in men and from 7 to 13 in women. Mesothelioma rates per 100 000 person-years were calculated for 3 categories of cumulative exposure (<10, 10 – 49, > 50 f–y/cm^3). The mesothelioma rate increased through the increasing exposure categories. For exposure > 50 f–y/cm^3 compared with < 10 f–y/cm^3, the increase was by a factor of four to five-fold depending on the adjustment method used.

The study is of good quality. However, it does not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

Libby vermiculite mine

Larson et al. (2010) extended the follow-up of the Libby MT vermiculite mining cohort that was exposed to what is called "Libby amphibole" consisting of tremolite and related fibrous amphiboles. Compared to the previous mortality study by Sullivan (2007), five more years of follow-up were added, also the female workers were included and multiple causes of death were considered. The cohort consisted of 1862 workers. There were 19

deaths from mesothelioma (the previous follow-up did not report results by cumulative exposure for mesothelioma). The previously generated NIOSH exposure estimates were used to calculate cumulative fibre exposure. RRs of mesothelioma were calculated in comparison to the lowest quartile (< 1.4 f–y/cm^3) for the following quartiles of cumulative fibre exposure: 1.4 – 8.5, 8.6 – 43 and > 44 f–y/cm^3. However, cumulative exposures were lagged 20 years. There was a significant trend in RR by cumulative exposure for mesothelioma (p=0.01).

The use of cumulative exposure lagged 20 is slightly at odds with the EPA model.

The study is of good quality. However, it does not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

It is further noted Elliott et al. (2012) followed 6136 workers of the NC and SC asbestos textile factories, Levin et al. (2016) extended the cancer follow-up of the 1130 amosite exposed Tyler TX asbestos factory workers, Larson et al. (2020) further extended the follow-up of the above-mentioned Libby MT vermiculite mining cohort and Finkelstein (2010) continued the mortality follow-up of 156 Ontario asbestos cement plant workers. However, these studies did not report mesothelioma risk estimates by exposure level and are therefore not considered further.

2.2 New cohort studies

French asbestos textile and friction material study

Clin et al. (2011a) followed 2024 workers of a French asbestos textile and friction material plant with exposure to crocidolite and chrysotile and observed 24 incident cases of mesothelioma in a follow-up until end of 2004. The vital status in 2004 could not be verified for 5.3% of the cohort. Cumulative exposure index (CEI) for asbestos at career end expressed in f–y/cm^3 were calculated according to the company's own employment exposure matrix. Hazard ratios (HR) of mesothelioma were calculated in comparison to those with CEI below 40 f–y/cm^3 for those with 40 – 140 and > 140 f–y/cm^3, using a 10-year lag. There was a borderline significant (p=0.10) trend of increasing HR for mesothelioma by cumulative exposure.

Job history and exposure assessment: Detailed information on the professional history and occupational exposure of each subject in the cohort was available in files held by the company occupational health department. Data on occupational exposure to asbestos included the following information: date of first employment, date of departure from the company, exposure sector (textile/friction), type of asbestos handled (chrysotile alone or mixed chrysotile/amphibole), duration of asbestos exposure. Dust concentration measurement data collected by the company was available since 1959 and double measurements done in 1974 were used to convert the earlier gravimetric results to fibre concentrations.

The study is of good quality. However, it does not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

Australian surveillance study

Kamiya et al. (2019) followed 1642 Australian men who were under health surveillance due to their past significant occupational asbestos exposure. Occupations such as carpenters, builders, boilermakers, electricians and dockyard workers were included. Cumulative exposure was estimated with a JEM. There were 40 cases of mesothelioma (209 per 100 000 person years). Hazard ratios were calculated for three categories of

cumulative exposure (medians 0.93, 2.23 and 12.8 f–y/cm^3) in comparison to the category with median cumulative exposure of 0.09 (range 0.002–0.67) f–y/cm^3.

Job history and exposure assessment: A panel of occupational hygienists, familiar with the Australian conditions, was used. Four time periods of interest were identified: 1943–1966 when the Wittenoom crocidolite mine was in operation; 1967–1986 when asbestos health hazards were recognized and occupational exposure limits were introduced; 1987–2003 when the use of raw crocidolite was prohibited and further limitations and controls were placed on other types of asbestos; and ≥2004 when all new asbestos use was prohibited. Mode exposure was defined as the most common exposure in a particular job, when exposed above background level. Peak exposure was defined as a short-term intense exposure (> 15 min). Collected monitoring data results were not statistically modelled but were used to assist the experts in the assignment of exposure intensity levels. The majority of the airborne asbestos measurements were expressed as fibres/cm^3. Some earlier estimates utilized airborne asbestos measurements in millions of particles per cubic foot, but these were few and were therefore only used to provide an indication of the presence of exposure. Intensity of exposure was assigned in five categories, based on the mid-point of five exposure ranges and expressed as a time-weighted average (TWA) for an 8-h working day. The estimated exposure levels were classified in the following categories: 0.0001 fibres/cm^3 as background; 0.05 fibres/cm^3 (0.01–0.1) as low; 0.5 fibres/cm^3 (0.1–1) as medium; 12 fibres/cm^3 (1–25) as high; and 37.5 fibres/cm^3 (25–50) as very high. Frequency of exposure reflected the experts' assessment of the occurrence of exposure in a particular job or industry within a working year (240 days, assuming 4 weeks of holidays): annually (1 day per year); biannually (2 days per year); monthly (11 days per year); weekly (48 days per year); or daily (240 days per year). Days represented a standard 8-h working shift. The expert panel assessment process started with the selection of an industry. All available literature for that industry was then reviewed. Exposures were discussed by occupation within the industry, taking into consideration factors influencing exposure over time, such as changes in work practices, legislation, the introduction of controls, and changes in the asbestos types which were used. Thus each industry–occupation– time period combination present in the AsbJEM was considered individually.

The annual average exposures were calculated for each industry–occupation combination by summing the peak, mode, and background exposures, divided by the number of working days in a year (240).

It is noted that the exposure estimation includes some semi-quantitative elements. Additionally, the study does not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

Italian asbestos cement pooled cohort study

Luberto et al. (2019) pooled 21 Italian asbestos cement manufacturing cohorts with 12 578 workers and calculated SMRs based on about 390 000 person-years of follow-up. In men there were 305 and 102 malignant neoplasms of pleura and peritoneum, respectively and in women 89 and 31 pleural and peritoneal malignant neoplasm, respectively. For cases lost for follow-up the last date of contact was used in calculation of person-years. The number of cases lost for follow-up is not reported but is not expected to be high. Exposure was mixed to amphiboles and chrysotile. For each plant and period, the experts estimated the proportion of workers exposed, the percentage of typical working time in tasks with asbestos exposure and the range of minimum and maximum concentration of asbestos airborne fibres (fibres/cm^3), separately for direct and indirect exposure. Tasks and jobs of individual workers were not known; therefore plant and period-specific data were used to compute for each plant and year an Average Exposure Index (AEI) to be applied to all members of a given cohort. From the AEI a

Cumulative Average Exposure Index (CEI) was computed for the occupational history of each worker summing the contribution of all periods of activity. SMRs for lung cancer were calculated for tertiles of CEI (< 54, 54 – 620, > 620 f–y/cm^3), no lag time was applied.

Job history and exposure assessment: Tasks and jobs of individual workers were not known; therefore plant and period-specific data were used to compute for each plant and year an Average Exposure Index (AEI) to be applied to all members of a given cohort. The cumulative average exposure index was calculated both crude and fibre-type-weighted. In the latter the weights were the malignant mesothelioma potency factors for chrysotile, amosite and crocidolite (respective 1:14:71) as estimated by Hodgson and Darnton (2010) resulting in the fibre-type-weighted CEI being expressed as "chrysotile equivalent" taking into account differences in the use of amphibole and chrysotile asbestos by plant and period. The same weighted CEI was also used for analyses of lung cancer and other studied cancers. The detailed results were presented only for the fibre-type-weighted CEI, while it was stated that "none of the other analyses showed relevant differences with the analyses presented for fibre-type-weighted CEI and all confirmed the exposure-response trends with increasing exposure."

The follow-up is methodologically well-conducted. However, only plant- and period-specific exposure estimates could be produced, assuming all workers at a given plant a given time had the same exposure. Furthermore, the calculation of chrysotile weighted cumulative exposure indices, combining all fibre types, does not allow to compare the results with other studies reporting non-weighted cumulative exposures either for chrysotile, amphibole or mixed exposure, nor for simply considering all asbestos non-weighted for fibre type.

It is noted additionally that the study would not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

Dutch general population study

Offermans et al. (2014) followed 58 888 male general population participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17 years (1986-2003). The number of cases lost for follow-up is not reported but is not expected to be high. Semi-quantitative cumulative exposure estimates were generated using both the Dutch (DOMJEM) and the Finnish job exposure matrixes (FINJEM). The cumulative exposure was expressed as non-dimensional "unit-years" in DOMJEM and as f–y/cm^3 in FINJEM. There were 132 cases of pleural mesothelioma. Hazard ratios were calculated in comparison to the unexposed for the three tertile categories of the exposed subjects (medians 0.20, 1.58 and 6.57 f–y/cm^3, according to FINJEM), no lag time was applied.

Job history and exposure assessment: Information on lifetime occupational history until 1986 was obtained from the questionnaire completed at study enrolment. Questions concerned the job title, name and type of the company, products made in the department, and period of employment. On the basis of these questions, occupations were coded according to the Standard Occupational Classification of 1984 of the Dutch Central Bureau of Statistics. Subjects could enter a maximum of five occupations, which was generally sufficient to cover the lifetime occupational history for the large majority of the cohort, because cohort subjects held on average 1.9 job codes during their working life up to 1986. For all subjects, the job code was assessed for each of the maximally five occupations held between starting work and 1986. Although FINJEM was constructed for Finland, exposure estimates were not adapted to Dutch occupational circumstances. The occupational information was used to semi-quantitatively estimate the cumulative exposure based on the FINJEM which gives mean group exposure (proportion of exposed and level of exposure) for carcinogenic agents by occupation for

four time periods (1945-59, 1960-74, 1975-84 and 1985-94). There was no individual-level information on exposure. The cumulative exposure was estimated as proportion x level x time summing the information for each of the maximum five occupation held by the individual. For those workers who started working before 1945, exposure was set to zero, because there was hardly any asbestos industry in the Netherlands in the period before 1945. Based on DOMJEM, only non-dimensional "unit-years" were calculated.

The follow-up is methodologically well-conducted. However, due to the nature of a follow-up study in the general population cohort, the exposure estimates are based on population level aggregate estimates of level of exposure. Such an approach involves also the introduction of an element of semi-quantitative probability of exposure (based on estimates of proportion of workers exposed in a given occupation/industry during a certain period of time). It is considered that such semi-quantitative estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

Swedish census cohorts study

Plato et al. (2018) studied 2757 male Swedish mesothelioma cases occurring in four Swedish census cohorts and 25 570 matched controls. Cumulative exposure to asbestos and 29 other carcinogenic substances was estimated with a job-exposure matrix applied to the job title history available from the census information. Hazard ratios were calculated in comparison to those unexposed for three estimated cumulative exposure categories (< 1.78, 1.79 – 15.2, > 15.2 f–y/cm^3).

Job history and exposure assessment. Occupational information was available from census data for 1960, 1970, 1980 and 1990. Employment period was not known but was assumed to start at age of 20 and end at 65 years of age. When estimating cumulative exposure, it was assumed that the occupation that cases and controls reported in the 1960 census also applied up to 45 years prior to that census (depending on the age of the individual in 1960).If occupational information changed at a subsequent census, the individual was assumed to have changed occupation in the middle of those two census years. Individuals who reported retirement in any census were recorded as such and considered retired only after the consensus date. The occupational information was used to (semi-quantitatively) estimate the cumulative exposure based on a JEM (NOCCA-JEM, Nordic Occupational Cancer study) which gives mean group exposure (proportion of exposed and level of exposure) for carcinogenic agents by occupation for four time periods (1945-59, 1960-74, 1975-84 and 1985-94). There was no individual-level information on exposure or maximum intensity. The cumulative exposure was estimated as *proportion of exposed x level of exposure x time of exposure* summing the information for each census occupation held by the individual.

The follow-up is methodologically well-conducted. However, due to the nature of a follow-up study in the general population cohort (nested case-control study therein), the exposure estimates are based on population level aggregate estimates of level of exposure. Such an approach involves also the introduction of an element of semi-quantitative probability of exposure (based on estimates of proportion of workers exposed in a given occupation/industry during a certain period of time). It is considered that such semi-quantitative estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

It is further noted that Courtice et al. (2016), Wang et al. (2014), Wang et al. (2013a), Wang et al. (2013b) Wang et al. (2012), Deng et al. 2012) and Lin et al. (2012) have published cancer follow-ups of Chinese asbestos mining and factory cohorts. Ferrante et al. (2017) pooled data from 43 Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding). However, these studies did not report mesothelioma or pleural cancer risk

estimates by exposure level and are therefore not considered further. Furthermore Magnani et al. (2020) reported risk estimates for the same Italian asbestos cohort pool as Ferrante et al. (2017) and using the same exposure assessment method as Luberto et al. (2019) above. This study was considered not suitable for a meta-analysis for the same reasons as the study by Luberto et al. (2019).

2.3 New case-control studies

Italian case control study

Ferrante et al. (2016) conducted a pleural mesothelioma case-control study in Casale Monferrato area in Italy. Altogether 200 cases of 223 eligible cases (89.7%) and 348 (63%) of 552 eligible controls accepted to be interviewed. The study included both occupationally and non-occupationally exposed individuals and the results by cumulative exposure were presented for all cases as well as separately for occupational, environmental and domestic/familial exposure (see online supplement for the separate analyses). The analyses for occupational exposure indicated a trend of an increasing OR by estimated cumulative exposure for categories <0.1, 0.1-1, 1.0-10 and > 10 f–y/cm^3. Adjustment was made for the effect of cumulative non-occupational exposure.

Job history and exposure assessment: A questionnaire was administered to each individual and included sections on demographic characteristics, lifelong occupational and residential histories, selected leisure time activities and characteristics of the home environment possibly relevant for asbestos exposure. A lifelong occupational history was elicited, including, for each job, the job title, industry, and dates of beginning and ending. A set of job specific modules (JSM) was used to facilitate a standardized collection of detailed exposure information, after the lifelong occupational history was completed. Thirty-three JSMs were available, including 58 industries or occupations, plus 3 general purpose JSMs, respectively for other blue-collar workers, other white collar workers and shopkeepers. Information was also collected for each dwelling as well as family members with focus to identify exposure from asbestos materials, nearby industrial sources and exposure via family members with occupational exposure.

As regards occupational exposure, at least one and potentially many exposure patterns were assigned to every job held by a study subject. The most appropriate reference value for fibre concentration in each exposure pattern was chosen from collections of fibre measurements organised by job, industry and calendar period available from the literature and the web. Fibre measurements were also available for asbestos industries active over the past four decades in Piedmont including the Balangero asbestos mine, asbestos cement production, asbestos-textile works, and production of brake and clutch linings. These were retrieved and then entered into a computerised database, which contributed to the EXPOSYN database (=database used by the SYENRGY pooled lung cancer study).

Probability of occupational exposure was classified as definite, probable, possible and unlikely. Frequency was assessed as the time spent under the exposure pattern under evaluation, relative to the duration of a standard 8 h work-shift. Intensity was rated according to an ordinal scale, arranged in eight increasing steps, one order of magnitude apart. Duration of exposure for a given period was computed as the difference between the year of start and year of end, or 6 months if both occurred in the same year. For every occupational exposure pattern, the exposure index was computed by multiplying frequency, intensity and duration. Probability of exposure was used to selectively include in analyses only exposure patterns fulfilling predefined criteria: only definite, definite and probable, or all exposures (definite, probable and possible). A similar procedure was applied to non-occupational exposure circumstances. Consideration was given to the fact that non-occupational exposures may last longer than a standard work shift, by allowing

for frequency indices larger than 100%: environmental and domestic exposures were typically assigned a standard 300% frequency index.

The analyses restricted to occupational exposure only were described only for all exposed, thus combining definite, probable and possible exposure. This introduces uncertainty to the estimates. It is considered that the exposure estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

It is noted additionally that the study would not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

French general population based case control study

Lacourt et al (2014) conducted a population-based case-control study including 437 incident pleural mesothelioma cases (identified from a national surveillance program) and 874 general population controls from 1998 to 2002 in France. Based on an expert assessment, a semi-quantitative cumulative exposure index (CEI, expressed in f–y/cm^3) was calculated by summing the products of probability, frequency, intensity and duration of exposure of each job held by a given subject. The study included also assessment of non-occupational exposure, however for those occupationally exposed, ORs were calculated in comparison to the unexposed for four occupational cumulative exposure categories (< 0.1, 0.1 – 1.0, 1 – 10, > 10 f–y/cm^3).

Job history and exposure assessment: A standardised interview with a questionnaire was performed for each subject. Only subjects alive at the time of the interview were included. Information about lifetime residential, educational and occupational history (including details on job tasks and do-it-yourself activities), etc. were collected. A more specific part of the questionnaire focused on specific lifetime situations that might have involved asbestos exposure. For occupational exposure, each job held for at least 6 months by a subject was translated into four semi-quantitative occupational asbestos exposure parameters, including the probability of exposure (possible = 0.5, definite = 1.0), frequency of exposure (sporadic = 0.025, intermittent = 0.25, frequent or continuous = 0.75), intensity of exposure (low = 0.1 f/cm^3, medium = 1 f/cm^3, high = 10 f/cm^3, very high = 100 f/cm^3), and the route of exposure (direct, indirect). The cumulative exposure index (CEI) was calculated by summing the products of probability, frequency, intensity and duration of exposure of each job held by a given subject. Since job occupational exposure parameters are semi-quantitative, the above-mentioned numerical values were assigned to each of them. It is not clear how potential changes in exposure intensity over decades were considered. Non-occupational exposure was assessed similarly using the same numerical values for each parameter, except that low intensity was split into very low and low.

The design of the study is appropriate, and it was well-conducted. The exposure assessment approach involves also the introduction of an element of semi-quantitative probability of exposure and uses a rather semi-quantitative estimation of frequency and intensity of exposure. It is considered that such semi-quantitative estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

It is noted additionally that the study would not report the data in a way that would enable estimating the K_M according to the EPA absolute mesothelioma risk model.

Chinese case control study

Jiang et al. (2018) conducted a study of predominantly female (83%) 46 mesothelioma cases and 230 controls in South Eastern China and found a statistically significantly

increased odds ratio for possible (OR=10; 95% CI 1.4 - 65) and definite (OR = 64; 95% CI 12 – 330) definite exposure to hand-spinning chrysotile. There was also indication of exposure-response by duration of exposure and semi-quantitatively estimated cumulative exposure index (CEI). It is noted that the study covered both domestic and occupational exposure.

Job history and exposure assessment: The semi-quantitative cumulative exposure index (CEI) was based on assessment of two exposure experts using occupational history and self-reported exposure information collected in a structured interview. The CEI was calculated by the sum of the products of probability, frequency, intensity and duration of each job exposure. The probability was graded as not exposed =0, possible = 0.5, and definite = 1; frequency was graded as not exposed = 0, sporadic = 0.025 and continuous = 0.75; intensity was graded as not exposed = 0, low = 0.1 fibre/cm^3 and high = 1 fibre/cm^3. In is noted that only 5 mesothelioma cases were identified at diagnosis during 2009-2011 while 41 were included retrospectively from hospital records based on a diagnosis in 1998-2008. Consequently only 22% of the cases in comparison of 100% of controls were alive at investigation meaning that the questionnaire-based assessment of exposure of the mesothelioma cases relied more heavily on information from next of kin, compared to controls, and information may not be comparable.

It is noted that there is a possibility of information bias due to the large difference between cases and controls as regards use of information from next of kin. Furthermore, the exposure assessment approach involves also the introduction of an element of semi-quantitative probability of exposure and uses a rather semi-quantitative estimation of frequency and intensity of exposure. It is considered that such semi-quantitative estimates are not robust enough for quantitative exposure-response estimation and the study was not included.

Appendix 4. Modelling of asbestos-related lung cancer and mesothelioma risk and quantifying the exposure-risk relationship for excess cancer risk

1. Lung cancer

The lung cancer model initially described by EPA (1986) assumes that the relative risk (RR) of lung cancer at any given age is a linear function of cumulative asbestos exposure (CE) as measured by phase contrast microscopy (PCM), expressed as fibre–year/cm^3 (f–y/cm^3), not including any exposure in the most recent 10 years. This exposure variable is denoted by CE10. The 10-year lag embodies the assumption that exposures during the most recent 10 years do not affect current lung cancer risk (thus assuming a 10-year latency). The mathematical expression for this model is

$$RR = 1 + K_L \times CE10$$

where the linear slope, K_L, is the "lung cancer potency factor". To make allowance for the possibility that the background lung cancer risk in the exposed population differs from that of the comparison population, the model is expanded to the form

$$RR = \alpha \times (1 + K_L \times CE10)$$

With this form of the model the relative risk at zero exposure is α rather than 1. Both K_L and α are estimated by fitting the model to data.

More recently non-linear regression models have been applied to existing cancer epidemiology data (Eisen et al., 2004), which found application in meta-analyses for benzene (Vlaanderen et al., 2010), but also for asbestos (van der Bij et al. 2013). The flexibility of these models ensures that the exposure–response relationship can deviate from linearity and they combine all risk estimates. This has particular advantages for exploring the shape at low exposures and limits the need to extrapolate below the study-specific exposure range if observations are available at low exposure levels.

The above-mentioned studies have tested the non-linear models parallel to linear models and found that non-linear (natural spline) models predicted risk better. The natural splines used pre-specified knots at the 20th, 50th, and 80th percentiles of exposure estimates. Below the 20th percentile boundary knot, the association between lung cancer and exposure is linearly extrapolated to the zero exposure point. In these models the natural logarithm (LN) of the reported risk estimates was inversely weighted by their variance. I.e. studies with more precise risk estimate, due to the large size of the study, were assigned a higher weight. As risk estimates (ORs, RRs, HRs) for different exposure categories within a single study are correlated due to using the same reference group, the variance of the risks was adjusted by estimating the covariance between different risk estimates. For studies reporting SMRs, no covariance is estimated as it can be assumed that the independence assumption does hold for SMRs since the total population is used as the reference group instead of a subsample.

Also non-linear models assume that the RR is a function of cumulative exposure lagged 10 years (CE10). Assessing the shape of the function is particularly important in case of asbestos where current exposure circumstances and exposure limit values are often lower than the exposures in the historical cohort studies available or at the low end of the exposure distribution of these studies. Studies investigating (mixed asbestos) exposure levels closer to those of relevance for today's occupational exposures have become available only recently (e.g. Gustavsson et al 2002, Olsson et al 2017).

Studies included

Lung cancer studies included in the van der Bij et al. (2013) study were used as a starting point. More recent studies were identified with a literature search. These included (1) updates of the existing cohorts, (2) new cohort studies and (3) new case-control studies. The quality of the new studies was reviewed using the criteria used by van der Bij et al. (2013) further described in Lenters et al. (2011) and its supplementary material. The quality evaluation was in particular focussed on basic descriptive quality parameters; documentation of the study and completeness of job history information. Studies that (1) provided the data necessary for quantitative exposure-response estimation with the model used by van der Bij et al. (2013) and (2) qualified the set criteria were added to the data used by van der Bij. For updates or overlapping studies the most informative one was used. The details of the new lung cancer studies and rationale for including/excluding a given study are described in Appendix 3.

The lung cancer studies finally used, both old and newly added/replaced, are described in Table 11.

More precisely, in comparison to van der Bij et al. (2013) (and Lenters et al. (2011)), the lung cancer meta-analysis used a more recent follow-up study of Pira et al. (2017) instead of Pira et al. (2009) for the Italian Balangero chrysotile mine cohort and a more recent follow-up study of the Libby vermiculate miner cohort by Larson et al. (2010) was used instead of the study by Sullivan (2007). The analysis also included three cohorts for which the data were not yet available at the time of the previous meta-analyses. Notably, the French asbestos textile and friction material plant cohort of Clin et al. (2011a) with mixed exposure, the Chinese chrysotile mine cohort of Wang et al. (2013b) and the Chinese asbestos factory (textiles, rubber products and asbestos cement) cohort exposed to chrysotile (Courtice et al., 2016). The Swedish case-control study of Gustavsson et al. (2002) was replaced by the much larger pooled multi-centre case-control study of Olsson et al. (2017) which also includes the data from the Gustavsson study. It is noted that the earlier meta-analysis, based on largely the same studies, found the effect of publication bias to be minimal (Lenters et al. 2011, van der Bij et al. 2013).

Exposure-response relationship

From the 22 studies listed in Table 11 for lung cancer, 124 risk estimates (i.e., study points of the RR for lung cancer at a given exposure level) were available over a cumulative exposure range of 0.11–4710 f–y/cm^3. As Olsson et al. (2017) presented results separately for men and women, those risk estimates were both included.

Exposure-response relations for lung cancer were estimated using a (mixed effects) hierarchical model for the reported log-RR with intercept and/or slope(s) for each study included as (correlated) random effects and with a fixed residual covariance-matrix, as described by Sera et al. (2019) and implemented in the R software package mixmeta. The fixed residual covariance-matrix was estimated using methods described in Greenland and Longnecker (1992) and implemented in the R software package dosresmeta. Exposure-response model structures included a linear regression model structure, both with and without an intercept, and a (natural) regression spline model, also with and without intercept. The (natural) regression spline basis expansions were calculated using the R package splines, with a single interior knot at the median exposure value and boundary knots located at the 20% and 80% percentiles of the exposure distribution. The Akaike Information Criterion (AIC) was used to compare the predictive quality of different models.

The modelling results show that models with an intercept have a better lower AIC (Table 12, Figure 2). The spline models have a considerably lower AIC compared to linear models. The model with the smallest AIC value i.e. spline with intercept, was used for further risk calculations, adjusting the exposure response relation for the elevated risk at zero exposure (intercept). The fact that models with an intercept have a stronger fit may indicate that confounding or exposure misclassification may play a role. These may be due to for instance smoking differences between the asbestos exposed cohorts and external comparison populations or because misclassification of exposure changes the slope of the exposure response relation (attenuation). Both processes may play a role. However, smoking is not very likely a confounder in case of some specific studies for which smoking data were available and could be adjusted for.

Table 11. Cohort and case-control studies included in the lung cancer meta-analysis

Study		Reference	Study design	N	Risk estimate	Fibre type	Lowest-highest exposure category f–y/cm^3	Lagged CE
1	Quebec, Canada, mines and mills	Liddell et al. (1997)	Cohort	~ 11 000	SMR	Chrysotile	4.7-4710	CE to age 55
2	Italy, Balangero, mine and mill	Pira et al. (2017)	Cohort	1056	SMR	Chrysotile	50-667	CE
3	Connecticut, friction product plant	McDonald et al. (1984)	Cohort	3513	SMR	Chrysotile	15-400	CE
4	South Carolina, textile plant	Hein et al. (2007)	Cohort	3072	SMR	Chrysotile	0.75-200	CE10
5	North Carolina, textile plant	Loomis et al. (2009)	Cohort	5770	RR adj [a]	Chrysotile	5.7-408 [c]	CE10
6	Wittenoom, Australia, mine	Berry et al. (2004)	Cohort	6358	SMR	Amphibole, crocidolite	0.11-220	CE
7	Patterson, NJ, insulation manufacture	Seidman et al. (1986)	Cohort	820	SMR	Amphibole, amosite	3-417	CE
8	Tyler, TX, insulation manufacture	Levin et al. (1998)	Cohort	1121	SMR	Amphibole, amosite	11-375	CE
9	Libby, MT, mines and mills	Larson (2010)	Cohort	1862	RR	Amphibole, tremolite [b]	0.7-73	CE20
10	UK, friction products factory	Berry and Newhouse (1983)	Cohort	13460	SMR	Mixed	29.5-228 [c]	CE
11	Ontario, asbestos cement plant	Finkelstein (1984)	Cohort	740	SMR	Mixed	15-250	CE
12	New Orleans, LA, asbestos cement plants	Hughes et al. (1987)	Cohort	6931	SMR	Mixed	4.2-256	CE10
13	Sweden, asbestos cement plant	Albin et al. (1990)	Cohort (external reference)	2898	RR adj [a]	Mixed	3.1-88	CE
14	Belgium, asbestos cement plant	Lacquet et al. (1980)	Cohort	1973	SMR	Mixed	25-2000	CE
15	US factory retirees (Johns Manville)	Enterline et al. (1987)	Cohort	1074	SMR	Mixed	186-2928	CE
16	US and Canada, insulation workers	Selikoff and Seidman (1991)	Cohort	17800	SMR	Mixed	38-375	CE10
17	Pennsylvania, textile plant	McDonald et al. (1983)	Cohort	4024	SMR	Mixed	15-330	CE10
18	Rochdale, UK, textile plant	Peto et al. (1985)	Cohort	3211	SMR	Mixed	5.9-257	CE5
19	Calvados, France, textile and friction product plant	Clin et al. (2011a)	Cohort	2024	HR adj [a]	Mixed	90-500 [c]	CE10
20	China, textile, rubber product and cement plant	Courtice et al. (2016)	Cohort	577	HR adj [a]	Chrysotile	156-913 [c]	CE10
21	China, mine	Wang et al. (2013b)	Cohort	1539	SMR	Chrysotile	10-750	CE10
22	Europe and Canada pooled case-control study	Olsson et al. (2017)	Case-control	17705 cases, 21813 controls	OR adj [a]	Mixed	0.25-4.7	CE

[a] In the North Carolina textile plants study, results were adjusted for age, gender, race, calendar year, and birth cohort; In the Swedish cement plant study, results were adjusted for age and calendar year; In the Calvados plant study, results were adjusted for age and gender; In the Chinese textile, rubber product and cement plant study, results were adjusted for age and smoking (ever/never); In the Europe/Canada pooled case-control study, results were adjusted for study, age, smoking (pack-years, time-since-quitting smoking), and ever-employment in jobs with known increased lung cancer risk due to factors other than asbestos (Yes/No).

[b] Exposure in the Libby cohort is for the so-called Libby amphibole that includes tremolite and closely related fibrous amphiboles (winchite and richterite

[c] The lowest exposure category (corresponding to 0.383 f–y/cm^3 in the North Carolina textile plant and 4.5 f–y/cm^3 in the British friction factory, 20 f–y/cm^3 in the Calvados plant and 44.5 f–y/cm^3 in the Chinese textile, rubber product and cement plant) was excluded as o risk estimate could be calculated because it was used as the reference category

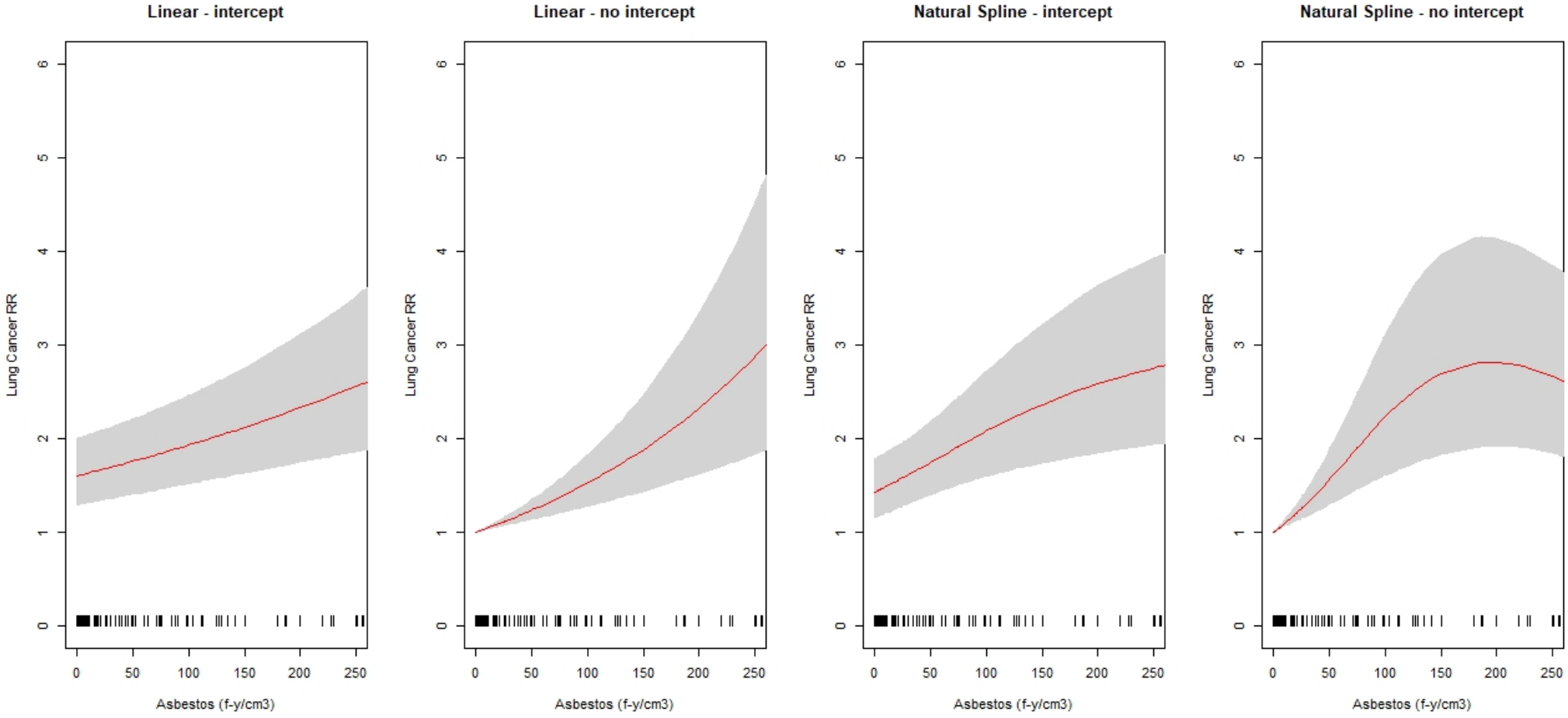
Table 12. AIC for each model and predicted lung cancer Relative Risk at different cumulative exposure levels

Models	AIC	RR (95% CI) by cumulative exposure (f–y/cm^3)			
		Intercept	0.4	4.0	40 *
1A. Linear model Adjusted for intercept	137.7	1.60 (1.28 – 2.00) 1.00 (1.00 - 1.00)	1.60 (1.28 – 2.01) 1.00 (1.00 – 1.00)	1.61 (1.29 – 2.02) 1.00 (1.00 – 1.01)	1.73 (1.37 – 2.17) 1.08 (1.04 – 1.12)
1B. Linear model, no intercept	871.6	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.00)	1.02 (1.01 – 1.02)	1.18 (1.10 – 1.27)
2A. Natural spline Adjusted for intercept	114.7	1.43 (1.14 – 1.79) 1.00 (1.00 - 1.00)	1.43 (1.14 – 1.79) 1.00 (1.00 – 1.00)	1.45 (1.16 – 1.81) 1.02 (1.01 – 1.03)	1.68 (1.34 – 2.01) 1.18 (1.07 – 1.29)
2B. Natural spline, no intercept	508.4	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.01)	1.04 (1.02 – 1.05)	1.43 (1.23 – 1.67)

AIC = Akaike information criterion

* The cumulative exposure category 40 f-y/cm^3 corresponds to an air concentration above the current OEL when assuming 40 year career and is included only in order to illustrate the model differences

Figure 2. Meta-exposure-response relationships for cumulative asbestos fibre exposure and lung cancer based on data from 22 (cohort and case-control) studies based on modelling logRR on exposure using linear and spline models with and without intercepts. The fit of the different models is, using the Akaike Information Criterion from left to right 137.7, 871.6, 114.7, 508.4.



The shaded area indicates 95% confidence intervals of the RRs and the vertical lines at bottom of the graphs indicate individual cumulative exposure data points available. The graphs include only cumulative exposures below 260 f-y/cm^3 which corresponds to 6.5 f/cm^3 assuming 40-year career. Graphs with full data range are presented in Appendix 6.

2. **Mesothelioma**

The absolute risk model adopted for mesothelioma in the EPA (1986) update is a particular adaptation of the multistage model for carcinogenesis, which predicts that incidence is independent of age at first exposure and increases as a power of time since first exposure. The model adopted in the EPA 1986 update was based on evidence of the time course of the mortality rate in several cohorts. Berman and Crump (2008a,b) 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. This model can be derived by assuming that the mortality rate at time t after the beginning of exposure, $I_M(t)$, is the sum of the contributions from exposure at each increment of time in the past. As with the lung cancer model the mesothelioma model assumes a 10-year lag before exposure has any effect upon risk. However, while the lung cancer model estimates relative risk, the mesothelioma model estimates absolute risk. With the additional assumption that the background rate of mesothelioma is zero, and if exposure (fibre concentration) is at a constant intensity, E, for a fixed duration, D, beginning at t = 0, this model can be written in the form presented in the EPA 1986 update for the time periods when (1) there is less than 10 years from start of exposure, (2) there is at least 10 years from start of exposure and exposure still continues, (3) there is at least 10 years from start of exposure and exposure no longer continues

$$I_M(t,D,E) = \begin{cases} 0 & t < 10 \\ K_M \times E \times (t - 10)^3 & 10 \leq t < 10 + D \\ K_M \times E \times [(t - 10)^3 - (t - 10 - D)^3] & 10 + D \leq t \end{cases}$$

This model predicts that the mesothelioma mortality rate varies linearly with an asbestos potency factor (K_M), exposure intensity E (for fixed duration, D, and time since first exposure, t). The model also predicts that mesothelioma mortality rates increase indefinitely, even after exposure ends, and approximately as the square of time since exposure began lagged 10 years for times that are large in comparison to the duration of exposure. When sufficient study data are available, K_M can be estimated. In an extensive review, Berman ad Crump (2008a,b) undertook a considerable effort to estimate potency factors for existing cohorts for which sufficient data was available to estimate K_M. For several of the cohorts they contacted research groups and obtained original data which enabled estimating K_M. They showed that K_M was considerably larger for cohorts exposed to crocidolite and amosite in comparison to chrysotile and cohorts exposed to mixed asbestos.

In the EPA model no distinction was made between pleural and peritoneal mesothelioma. That practice is followed here as well. Both cancers are relatively rare, and the diagnostic coding has been problematic until recently (see section 7.7.1). Consequently, since some studies do not distinguish between the two types, requiring such a distinction would leave fewer studies for analysis. This approach does not imply that risk from the two types of mesothelioma are equal or even that their individual mortality rates have the same exact mathematical form; other studies have suggested that they do not (See section 7.7.1). Rather, the approach suggests only that the combined rate can be approximated by the above equation. In any case pleural mesothelioma is much more common than peritoneal.

Studies included

Mesothelioma studies for which K_M values have been estimated and were included in DECOS (2010) were used as a starting point. More recent studies were identified with a literature search. These included (1) updates of the existing cohorts, (2) new cohort studies and (3) new case-control studies. The quality of the new studies was reviewed using the criteria used by van der Bij et al. (2013) further described in Lenters et al. (2011) and its supplementary material. Studies that (1) provided the data necessary for quantitative exposure-risk estimation by the EPA model and (2) qualified the set criteria were added to the data used DECOS (2010) for mesothelioma. For updates or overlapping studies the most informative one was used. The details of the new mesothelioma studies and rationale for including/excluding a given study are described in Appendix 3.

The studies finally used, both old and newly added/replaced, for mesothelioma are described in Table 13.

Although there were many high-quality studies published since DECOS (2010) analysis, only one published the results in a way that enabled estimation of K_M according to the EPA 1986 absolute mesothelioma risk model. The study by Loomis et al. (2019) reported mesothelioma risks (including the K_M value) in the NC asbestos textile cohort exposed to chrysotile. No data from that cohort had been available in the mesothelioma meta-analysis of DECOS (2010). All K_M values, apart from the one published by Loomis et al. (2019) were taken from Berman & Crump (2008a, b) applying the same study exclusion criteria as DECOS (2010), i.e. only the latest follow-up if several available and exclusion of one study that was based on one mesothelioma case only. It is noted that of the four more recent studies that were considered of sufficient quality but did not report the results in away allowing use of EPA model, one was an update and the previous follow-up data were used. The three others represented exposure circumstances similar to the studies that were included (asbestos mines and asbestos textile/friction material plants) and covered an exposed population that was 9% of the exposed population of studies that could be included. Therefore, it is unlikely that these omitted studies would have importantly influenced the results.

Estimating the meta K_M

The meta K_M-value was calculated weighted based on the standard errors of K_M and using the software package STATA. Because of existing heterogeneity between studies, weighting was based on random effects model. The estimated meta K_M values are presented in Table 14. The meta K_M value combining all studies, regardless of asbestos fibre type ($x10^8$ in $(f–y/cm^3)^{-1}$) was 0.337, i.e. very similar to the value of 0.34 calculated by DECOS (2010). This K_M value is almost three times lower than the K_M value for cohorts with mixed asbestos exposure. Despite this difference, the overall K_M is considered a justified estimate of mixed asbestos exposure as it occurs at present in the work environment, as extensively discussed in the section on uncertainties.

Table 13. Cohort studies included in the mesothelioma meta-analysis

Study		Reference	Study design	N of workers	Fibre type	K_M x 10^8 in (f–y/cm^3)$^{-1}$	Standard error
1	Quebec, Canada, mine a Asbestos	Liddell et al. (1997)	Cohort	2127	Chrysotile	0.012	0.0043
2	Quebec, Canada, mine at Thetford	Liddell et al. (1997)	Cohort	2664	Chrysotile	0.021	0.0045
3	Quebec, Canada, factory workers at Asbestos	Liddell et al. (1997)	Cohort	416	Mixed	0.095	0.0417
4	Connecticut, friction product plant	McDonald et al. (1984)	Cohort	3513	Chrysotile	0	0.0357
5	South Carolina, textile plant	Hein et al. (2007)	Cohort	3072	Chrysotile	0.15	0.0842
6	North Carolina, textile plant	Loomis et al. (2019)	Cohort	5379	Chrysotile	0.296	0.148
7	Wittenoom, Australia, mine	Berry et al. (2004)	Cohort	6358	Amphibole, crocidolite	12	0.893
8	Patterson, NJ, insulation manufacture	Seidman et al. (1986)	Cohort	820	Amphibole, amosite	3.9	0.923
9	Ontario, asbestos cement plant	Finkelstein (1984)	Cohort	740	Mixed	18	3.27
10	New Orleans, LA, asbestos cement plants	Hughes et al. (1987)	Cohort	6931	Mixed	0.3	0.174
11	US and Canada, insulation workers	Selikoff and Seidman (1991)	Cohort	17800	Mixed	1.3	0.0595
12	Pennsylvania, textile plant	McDonald et al. (1983)	Cohort	4024	Mixed	1.4	0.238
13	Rochdale, UK, textile plant	Peto et al. (1985)	Cohort	3211	Mixed	1.3	0.405

[a] In the North Carolina textile plant, results were adjusted for age and gender.

Table 14. Summary of all mesothelioma studies considered, with a subgroup analysis by asbestos type, showing the pooled asbestos potency factors K_M value (x10^8 in (f–y/cm^3)$^{-1}$) and the confidence interval

Inclusion	Number of studies	Pooled K_M value (×10^8) and 95% confidence interval	Heterogeneity I^2 (%)
All studies	13	0.337 (0.246-0.429)	98.4
Only chrysotile	5	0.017 (0.004-0.031)	52.3
Only amhiboles	2	7.953 (0.015-15.891)	97.5
Mixed exposure (amphiboles (≤20%) and chrysotile)	6	1.076 (0.330-1.821)	98.5
Mixed exposure or amphiboles only	8	2.461 (1.638-3.284)	98.5

3. **Calculation of excess risk levels**

The meta exposure response spline for lung cancer and meta-K_M value for mesothelioma were used to calculate the combined risk for lung cancer and mesothelioma mortality after a working life of exposure at several exposure levels for 8 hours per day and 5 days per week over a 40 years working life period (starting at 20 years). For lung cancer this was done using the so called life table analysis to adjust for the fact that at higher age mortality from other causes reduces the population at risk compared to the original population initially exposed, which influences excess risk estimates when not adjusted for (so called unconditional excess risk). The input for the life-table analysis (lung cancer and total mortality) were mortality rates, per January 2021, averaged across all EU countries for the years 2011-2016 from the Eurostat database. For this purpose, the average male and female mortality rates were calculated by age. The excess risk was calculated until 89 years of age. The analyses focused on exposure levels at and below the current EU OEL. The resulting excess risk of lung cancer and mesothelioma (combined) by level of exposure is described in Table 15. Lung cancer and mesothelioma each contributed roughly 50% of the excess over the entire exposure range presented in Table 15. There is evidence that the cancer potency differs between asbestos types, amphiboles being more potent that chrysotile. Under current exposure conditions, the exposure can be assumed mixed to all types of asbestos. The rationale for this assumption is that while handling of asbestos products during removal or maintenance work on a given day may concern only one fibre type, e.g. amphiboles, in the long run the exposure is expected to reflect the share of past use of different types of asbestos. Thus, either using excess risk calculations integrating all asbestos types combined or those coming from populations with mixed exposure to various asbestos types seem most relevant. Chrysotile accounts for the largest share of asbestos produced and used globally. However, the exact share of the past use in the EU is not known, neither is the share of chrysotile in those available cohorts with mixed exposure. Consequently, it was considered justified to use the excess risk calculations based on risk estimates combining all asbestos types. It is noted that the lowest cumulative exposure category available in the lung cancer studies included was 0.11 f–y/cm^3, which assuming a 40-year career, corresponds to an asbestos fibre concentration of about 0.003 f/cm^3.

Table 15. Cancer exposure-risk relationship (lung cancer and mesothelioma combined) after working life exposure to given 8-hour air concentration for five working days a week as measured by PCM

Air concentration of mixed asbestos as measured by PCM		Excess life-time cancer risk (cases per 100 000 exposed)
Fibres/cm^3	Fibres/m^3	
0.001	1000	1.2
0.002	2000	2.5
0.005	5000	6.2
0.01	10000	12
0.02	20000	25
0.05	50000	62
0.1	100000	125

Uncertainties related to the ERR and risk calculations

A few issues are expected to contribute most to the uncertainties in the risk estimates presented. The first is statistical uncertainty associated with heterogeneity between studies in the meta-analysis and small sample sizes. A second uncertainty relates to to accuracy of exposure assessment in the studies used and the third to the fibre counting methods. Fourth, other cancers that are associated to asbestos exposure, but which are not included in the risk assessment because quantitative exposure response relations are not available which hampers inclusion in calculations. A fifth uncertainty relates to the estimation of the K_M value for mixed asbestos exposure and, but more secondary, the exposure response relation for asbestos exposure and lung cancer. The sixth category of uncertainties relates to some assumptions and choices in the risk calculations.

Statistical precision in the exposure response or potency estimates

Exposure response relations have been estimated on the basis of 22 studies on lung cancer and 13 studies on mesothelioma. Uncertainties arise because of limited statistical precision in the risk estimates due to limited quality of the exposure estimates, differences in design, conduct and analysis of the studies, leading to heterogeneity between studies. Some studies have a small sample size contributing to random estimation error. All these factors together lead to uncertainty in the meta-exposure-response relation and risk calculations. In all risk calculations, point estimates for the exposure response slope (lung cancer) or potency factors (KM in case of mesothelioma) have been used. The confidence intervals around these point estimates indicate that for both lung cancer and mesothelioma, variation around these point estimates can be up to a factor 1.5-2 (see table 12 and 14 for lung cancer and mesothelioma, respectively). When considering specific types of asbestos, statistical uncertainties increase considerably, because inferences about potency differences are based on a very limited number of studies (for mesothelioma and amphiboles, only two studies are available and five study are available with chrysotile exposure only). Choices made in modelling of exposure-response relations, used to calculate lifetime risks may contribute to larger differences in risk estimates. A spline model described the exposure response relation for lung cancer best. Use of a more conventional linear model led to a shallower exposure response relation at low exposure levels, and this would have led to 35% lower lifetime risk estimates for lung cancer and mesothelioma combined. Further sensitivity analyses indicated that the spline gave a robust description of the available data for lung cancer and exposure. Changes in the spline modelling approach (knot placement) changed the exposure response slope at exposure levels to a limited extent (10% maximally).

Exposure assessment methodology

In all quantitative exposure response studies, asbestos exposure of individual workers has been estimated by combining data from measurement surveys on the level of job titles, with worker job title information and job tenure (duration of exposure), see Appendix 3 for details. Poor quality of exposure estimates may lead to exposure misclassification and underestimation of exposure–response relationships in epidemiological studies. The magnitude of underestimation is study specific. Overall, the exposure response slope is steeper in studies on asbestos with higher quality exposure assessment as has been shown for lung cancer. Limiting exposure response modelling for lung cancer to studies with higher quality results in a exposure response slope that is 1.5-2 times higher compared to using all studies (See Appendix 6).

Fibre analysis

In all the used epidemiological studies with quantitative exposure data fibre concentrations have been measured using PCM or converted to PCM from earlier

methods (see Appendix 3 for details). With PCM, exposure to long but thin fibres is underestimated leading to an overall underestimation of exposure (see Chapter 6). As a result, the risk from asbestos exposure in these studies is associated with exposure levels that have been underestimated leading to a higher risk per unit of exposure. This only becomes an issue of concern when, for instance in the context of compliance testing, exposure is assessed using other, more modern, techniques to assess fibre concentrations which do measure thinner fibres as well (See Appendix 5 for details).

Other cancer sites than lung cancer and mesothelioma considered

The ERR described in this Appendix is based on cancer excess from lung cancer and mesothelioma combined. For these cancers robust quantitative dose-response data exist by (cumulative) exposure to asbestos. In addition to these cancers, asbestos has more recently been identified as an established causative agent for cancer of the larynx and cancer of the ovaries. The increases in risk for these other cancer sites have more often been observed in heavily exposed populations and the risk from exposures occurring currently is expected to be relatively small (see section 7.7.1).

In order to estimate the extent of potential underestimation of the overall excess cancer risk when focusing only on lung cancer and mesothelioma, attributable excess cases for each of the above cancers in asbestos exposed cohorts were compared to the excess of lung cancer and mesothelioma in the same cohort. For each of the two cancers types the excess of that cancer and excess of lung cancer and mesothelioma were summed over the most relevant cohorts and the percentage of the excess from the cancer of interest of the excess of combined lung cancer and mesothelioma excess was calculated. The attributable excess cases where counted with the formula:

N of attributable excess cases = N of exposed cases x (SMR - 1)/SMR,

when relevant, other risk estimates than SMR (e.g. SIR, RR, HR) were used.

It is to be noted that case-control studies were not suitable for this comparative analysis as they only estimate the risk for one specific cancer type at a time.

In study selection, preference was given to cohorts with exposure levels closer to the current situation instead of historical heavily exposed cohorts. However, only for cancer of the larynx a large (European) study assessing asbestos related risk in a general (male) population cohort was identified where majority of exposure had occurred in construction and similar settings, instead of asbestos product manufacturing, insulation work or other heavy exposure occupations. For cancer of the ovaries suitable cohorts were identified from the meta-analysis of Camargo et al. (2011) as well as from among more recent cohorts or updates that had been reviewed in the context of the assessment described in Appendix 3, provided that they reported the parameters necessary for the formula above for the cancer of the ovaries and lung cancer and mesothelioma. For each cohort identified only the latest update that provided the necessary information was used if several were available.

For cancer of the larynx the study by Offermans et al. (2014) was used. It followed 58 888 male participants aged 55-69 years of the Netherlands Cohort Study with a mean follow-up time of 17.3 years. Exposure estimates were generated using both the Dutch and the Finnish job exposure matrixes (JEM). For cancer of the larynx there was a statistically non-significantly increased hazard ratio for ever exposure both based on Dutch (HR 1.2; 95% CI 0.9-1.7) and Finnish JEM (HR 1.4; 95% CI 1.0- 2.0). It is noted that this general population cohort represents nearly exclusively effects of downstream work exposures (e.g. construction occupations) which are closer to current exposure circumstances than are those of the heavily exposed asbestos product manufacturing

etc. cohorts. Furthermore, the risk estimates were adjusted for the effect of relevant potential confounders (smoking and occupational exposure to silica and polycyclic aromatic hydrocarbons for lung cancer and smoking and alcohol consumption for cancer of the larynx). Calculating the attributable cases using the HR for ever asbestos exposure estimated using the Dutch JEM exposure data indicated that asbestos exposure contributed to 119 lung cancer excess cases, 41 pleural mesothelioma excess cases and 9 laryngeal cancer excess cases, i.e. 5.6% of excess laryngeal cancer cases over excess from lung cancer and mesothelioma combined. Using the Finnish JEM based risk estimates resulted in 5.0% of excess cases from laryngeal cancer over the excess from lung cancer and mesothelioma. Risk estimates for peritoneal mesothelioma were not analysed in the study due to the small number of cases overall (N=10), but it is very likely that most of these cases would also have been due asbestos and would have slightly decreased the share of laryngeal cancer compared to lung cancer and mesothelioma combined. It is also noted that this study analysed incidence and not mortality overcoming the problem of laryngeal cancer being less often fatal and thus not captured in mortality studies as comprehensively as lung cancer and mesothelioma.

For cancer of the ovaries there were 10 cohorts that provided the necessary parameters. In order to investigate a potential dependence of the effect on intensity of exposure, the studies were further divided according to whether the lung cancer risk was above 2 or increased but below 2. Only one study population without high exposure. i.e. a lung cancer risk below 2 was identified (Ferrante et al 2017). It consisted from a pooled population from 43 Italian asbestos cohorts (asbestos cement, rolling stock, shipbuilding) with 2362 female cohort members and showed SMRs of 1.38, 1.43, 28.4 and 6.75 for ovarian, lung, pleural and peritoneal cancers, respectively. Based on the observed numbers of cancers and these risk estimates, the estimated excess cases were 11.8 for ovarian cancers and 182.6 for lung cancer and mesothelioma combined. Ovarian cancer excess was thus 6.5% of the excess estimated for lung cancer and mesothelioma combined. Nine cohorts representing cohorts of patients compensated for asbestosis or other heavily exposed populations (SMRs between 2.1 and 6.8) were identified providing the necessary information (Acheson et al. (1982), Ferrante et al. (2007), Germani et al. (1999) 2 cohorts, Magnani et al. (2008), Pira et al. (2007), Reid et al. (2008), Szeszenia-Dabrowska et al. (2002), Wilczyńska et al. (2005)). In these more heavily exposed cohorts, the estimated excess cases were 34.7 for ovarian cancer and 255.1 for lung cancer and mesothelioma combined. Ovarian cancer excess was thus 13.6 % of the excess estimated for lung cancer and mesothelioma combined when exposure was very heavy. So, there is some evidence that the share of ovarian cancer excess of all female asbestos cancer excess is higher in highly exposed than more moderately exposed populations. It is to be noted that none of the studies adjusted the risk estimated for potential confounders other than age.

As mentioned, the estimates presented above are coming from historical cohorts with relatively high exposure, while the ERR presented is derived for cumulative exposures orders of magnitude lower. The lung cancer risk is non-linear with exposures at low levels being higher than the risk estimated with linear extrapolation from high exposures. Thus, it is likely that at low exposure lung cancer risk dominates the overall excess even more than in the estimates above. Apart from cancer of the larynx, the risk estimates were also not adjusted for the potential confounding effect of factors other than age. Overall, it is estimated that at the low cumulative exposure for which the ERR is derived the potential underestimation of the overall excess risk when focusing the calculations to lung cancer and mesothelioma only, is of the order of 10% or less. This is in line with estimates generated in the Global burden of disease project of WHO (GBD, 2020): in EU countries in 2019 deaths from cancer of the ovaries and larynx due to occupational asbestos exposure represented 3.2% and 1.6%, respectively, of deaths from lung cancer and mesothelioma (combined) due to occupational asbestos exposure (detailed results available in https://vizhub.healthdata.org/gbd-compare/). Thus it is

concluded that the uncertainty arising from lack of quantitative dose-response data for these two cancers and focusing on lung cancer and mesothelioma instead, is considered small in comparison with other uncertainties related to low risk extrapolation either from historical human data with exposure higher than today or from standard animal assays based on relatively small dose groups with even higher exposure.

Uncertainties arising from the potency estimate for mixed asbestos exposure

The estimate used for the meta K_M value in this risk assessment combined K_M values from all studies, regardless of asbestos fibre type ($x10^8$ in $(f–y/cm^3)^{-1}$). The point estimate for this K_M was 0.337, i.e. very similar to the value of 0.34 calculated by DECOS (2010), but almost three times lower than the K_M value for cohorts with mixed asbestos exposure. This difference led to the question whether use of this overall K_M is considered a justified approach. Therefore, an alternative approach was explored to estimate a K_M for mixed exposure on the basis of global asbestos usage data and K_M values for chrysotile and amphiboles respectively.

Therefore, alternatively, a meta K_M was also estimated by using global production data for chrysotile and amphiboles (estimated between 94% and 96% of all asbestos produced respectively), and calculating a meta K_M value by taking the production weighted average of the K_M values of chrysotile (0.017 ($x10^8$ in $(f–y/cm^3)^{-1}$)) and amphiboles (7.95 ($x10^8$ in $(f–y/cm^3)^{-1}$)).

Chrysotile accounts for more than 90% of asbestos historically produced and used globally (NIOSH 2011). In the context of the European Asbestos Forum (Lemen et al., 2016) estimated more precisely that (globally) it has constituted over 95% of all asbestos marketed over the past century. This share most likely increased over the time of the 20th century when information on the hazards of amphiboles started to accumulate since the 1980-ies. However, IWL (1992) estimated that in 1976 chrysotile accounted for 94% of world asbestos production, crocidolite for less than 4% and amosite for less than 2% and the other amphiboles for negligible amounts. This estimate coincides with the time of the peak use of asbestos (see Chapter 5). In France chrysotile accounted for more than 95% of asbestos imports, while in the UK the share was slightly lower and about 85% (Ilg et al., 1998). A comprehensive picture of EU import statistics over the whole asbestos use era could, however, not be compiled. The information coming from import statistics would also be omitting the effect of some EU countries (e.g. Italy, Cyprus) having had important domestic chrysotile mines, while amosite and crocidolite were not mined in Europe (Virta 2006). Thus, the exact share of the past use of chrysotile of all asbestos use in the EU is not known, while in e.g. US it was estimated to be 98% of the imported asbestos (Virta 2006). Asbestos cement products accounted for the highest share of asbestos product manufacturing globally and e.g. in Germany and chrysotile was the main asbestos type in that production (see chapter 5). In summary, information available about the world production and for some individual countries suggests that amphibole use varied between a few percent maximally from 2% to 15% in more extreme cases, with an average around 4-6%.

If the average amphibole use between 4-6% is used for calculating a weighted K_M, this leads to K_M values between 0.33 and 0.49 ($x10^8$ in $(f–y/cm^3)^{-1}$). These values are close to the overall meta-K_M value based on all cohort studies, considerably lower than the K_M value for cohorts with mixed exposure and maximally 48% higher than the meta-K_M based on all available cohort studies. Consequently, it was considered justified to use the excess risk calculations based on risk estimates combining all asbestos exposed cohorts, regardless of the fibre type. Thus, weighting the amphibole and chrysotile potency factors for mesothelioma with the use percentages indicated that the use of all cohorts, regardless of main asbestos fibre type was considered a justified approach with limited uncertainties.

Also, the share of chrysotile in those available cohorts with mixed exposure is not exactly known. This overall K_M value of 0.337 is smaller than the average K_M value of cohorts with mixed exposure (up to 20% of amphiboles) to asbestos (K_M value 1.076, confidence interval (0.330-1.821); based on 6 studies) ($x10^8$ in $(f–y/cm^3)^{-1}$). The definition of mixed exposure allowed up to 20% of amphibole exposure. This is a high and very conservative value in relation to the likely contribution of amphiboles in the long-term exposure during asbestos removal work given the share of amphiboles of the past use of asbestos.

Consequently, it was considered justified to use the excess risk calculations based on risk estimates combining all asbestos exposed cohorts, regardless of the fibre type. The exposure risk relationship is calculated assuming a 40-year career with 5 days per week and 8 hours a day. Given the above past use information it is very unlikely that the long-term cumulative exposure of any worker would result exclusively or predominantly from amphibole exposure, but rather to reflect the share of different asbestos fibre types of the overall past asbestos use in manufacturing those asbestos containing materials that nowadays are removed, handled during maintenance activities or are releasing asbestos fibres due to their deteriorated structure.

Potency issues between the different asbestos types are less relevant for lung cancer. Spline analyses presented by van der Bij et al., (2013) did not show that statistically significant differences exist in potency between different asbestos types. Earlier meta-analyses did show that differences in potency existed between chrysotile and amphiboles. However, these potency differences became smaller when quality criteria were used to select studies that were allowed into the meta-analysis (DECOS 2010). Potency differences seem in particular apparent when linear models are used to describe exposure response relations. DECOS (2010) used for lung cancer (estimation of K_L) only studies passing a number of quality criteria while all suitable lung cancer studies were used by ECHA (and earlier by EPA, on which the other national assessments were based). It is to be noted that the quality criteria used by DECOS deal mostly with quality of exposure information in the historical cohorts. This is important in the application of a linear model where the data points representing very high exposure levels have a strong influence on risk estimates for much lower exposures. These data points were mostly coming from the cohorts that did not fulfil all quality criteria applied. ECHA used a spline function allowing a non-linear relationship where studies with high exposure level estimates have less influence on the risks estimated for lower exposures. Thus, the quality aspects used by DECOS are less relevant. Sensitivity analyses focused on lung cancer and the choice made to combine all fibre types and all studies as well as parameter choices made are described in Appendix 6 and indicate limited uncertainty arising from these choices. Overall the combined risk of mesothelioma and lung cancer would be almost 13 times higher in case of amphibole exposure only (16 cases per 100 000 exposed at 0.001 fibres/m^3). In this analysis, mesothelioma dominates excess risk figures. This gives an impression of risk differences for different exposure scenarios. However, as explained before lifetime exposure to amphiboles only is not a realistic exposure scenario in the present work environment in the European Union

ECHA notes additionally that setting different exposure limits for different asbestos fibres would have two major drawbacks: (1) electron microscopy would be the only method that could to be used as the fibre type would need to be identified and (2) a complex approach would be needed to combine the worker's exposure level so that the risk arising from different fibres would not exceed the level of overall excess risk set as target.

Choices made in calculating the ERR

Apart from focusing only on lung cancer and mesothelioma and averaging all asbestos fibre cohorts in risk calculations, the results are also affected by parameter and other choices for which there is no explicit guidance or legal provision.

ECHA used the life-table method to calculate the ERR. Two methods have been used in risk assessment (Goldbohm et al., 2006): the life table method and the cumulative risk method. Both the life table method and the cumulative risk method represent the probability of a disease (or death attributed to a disease) during lifetime or up to a certain age (e.g., 75 years). However, the cumulative risk is a measure conditional upon survival, whereas the life table risk is an unconditional and therefore more accurate estimate of lifetime risk. In contrast to the conditional cumulative risk, the life table risk takes into account that a cohort is dying out from other causes of death than the disease under study. The life table method thus provides a more accurate and realistic estimate, accounting for the effect of competing risks which becomes more and more important the higher the cut-off age for risk calculations. In an example calculating the excess lung cancer risk from occupational exposure to Cr(VI) until a relatively old age, 89 years of age, the cumulative risk method overestimated the excess risk by a factor of about 2 (Goldbohm et al., 2006).

However, also parameterization choices for the chosen method (e.g. the cut off age, choice of background rates, e.g. both genders or only men, or smokers, non-smokers or general population, time period of reference rates which have developed e.g. for lung cancer due to past changes in smoking habits) influence the results (Goldbohm et al. (2006), Seidler et al. (2013)). There are no commonly agreed parameters to be used and the choice of method and parameters applied are also not always clearly reported. The ERR derived by ECHA resulted in risks about 2 to 3-fold lower than national ERRs reported in section 9.1.1. However, due to lack of detailed information on the method and parameters applied nationally it is not possible to assess the contribution of each choice in the observed differences.

ECHA calculated the risk until 89 years of age which is the cut-off age used recently by RAC when deriving an ERR from human data (e.g. Chromium VI compounds, Inorganic As-containing substances). In a sensitivity analysis calculating the current asbestos ERR until 120 years of age, the asbestos related excess risks were about 1.1 times higher than when applying the cut-off of 89 years, illustrating that the fraction of population living beyond 90 years has only a minor influence. The above-mentioned previous RAC ERRs based on human data expressed the risk of mortality from cancer as was done for asbestos in the present report. The influence of this choice is relatively small as mesothelioma is a fatal disease and also the survival from lung cancer continues to be poor.

ECHA used reference rates averaged for males and females. The historical occupational exposure affected occupations with a predominantly male population. However, under the current circumstances the compliance with OEL is no longer an issue limited to occupations with a predominantly male workforce, e.g. construction. Also e.g. maintenance and service sectors, cleaners and waste handlers are affected and lowering the OEL considerably might expand the population concerned even further and involve many occupational groups exposed from asbestos materials in buildings. Asbestos is a non-threshold carcinogen and the future OEL is decided only later in the process and not yet known and thus the gender distribution of potentially affected occupational groups cannot be estimated. It was considered justified to apply the average rates for males and females. Such an average was also used by DECOS (2010) in their life table analysis. Sensitivity analyses described in Appendix 6 also indicate that the effect of this

is limited in the overall ERR as it influences only the lung cancer estimations, not mesothelioma.

Appendix 5. Comparison of exposure measurements in historical epidemiological data and current monitoring methods

Before the 1970s, airborne asbestos levels were usually measured with the midget impinger method by trapping total airborne dust particles and counting via light microscope (Gibbs, 1994). These measurements refer to the total particle concentration in the air, including also the non-fibrous particles. In very early measurements also gravimetric methods were used to simply calculate total dust as mg/m^3.

Membrane filter-based methods replaced the midget impinger method; fibres, generally defined as structures more than 5 µm in length with a length to width ratio (aspect ratio) ≥ 3:1, were identified and counted via phase-contrast microscopy (PCM). There were originally slightly different standards for the PCM method, while current standard is the one of WHO (1997). The PCM method is able to detect fibres thicker than approximately 0.25 µm. The PCM measurements refer to total fibre concentration (within the above fibre definition and the resolution limit) without differentiating between asbestos and non-asbestos fibres. However, in asbestos and asbestos product industry in the past it was a reasonable assumption that the majority of fibres counted were asbestos.

As reported in section 7.7.1, only most recently have electron microscopy measurement been used to analyse historical dust samples of the old cohorts. As described in Chapter 6, with transmission electron microscopy (TEM) or scanning electron microscopy (SEM), it is possible to 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. Electron microscopes are also equipped with analysers allowing the identification of the type of different asbestos or non-asbestos fibres based on their elemental composition by using energy dispersive x-ray spectroscopy (TEM-EDS) or provide information on the fibre's crystal structure by electron diffraction (TEM-ED).

When assessing the exposures in cohorts with long-term exposure under varying production processes, conversion factors are needed between historical measurements done with different methods. It is obvious that conversion between particle counts (midget impinge method) and fibre counts (PCM) is process specific. In some cohorts internal conversion factors were established based on pairwise measurements with the two methods in various departments of the facility in question, while in other cohorts a single conversion factor was applied for the entire facility or only external conversion factors from studies other than the study itself were used. Consideration of such exposure assessment quality aspects have only recently been used in meta-analyses in order to compare risk slope factors from studies of different quality and considering the slope factors from highest quality studies the most reliable (see section 7.7.1 and DECOS assessment in section 9.1.1). However, there is not yet a commonly agreed quality assessment protocol or grading system for all these aspects as illustrated by the scientific debate after the Lenters et al. (2011) lung cancer meta-analysis (see section 7.7.1).

As described in section 5.2., it is known that fibre size distribution varied according to the industry, e.g. fibre length is longer in more refined asbestos products compared to asbestos mining. It is obvious that for PCM/TEM comparison the dimensional characteristics of the fibres influence the conversion factor between those techniques. Verma and Clark (1995) 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. They also found that the proportion of long thin fibres (length > 8 µm, width < 1.5 µm) increased as the asbestos operation moved from primary sector (mining) to end use sector (manufacturing). Cherrie et al. (1989) compared asbestos fibre and general fibre counts by SEM, TEM and PCM in (1) laboratory-prepared samples

of different fibre types, (2) chrysotile asbestos textile factory samples and (3) non-occupational and environmental samples. TEM produced total fibre number assessments which were greater than those found with SEM which, in turn, produced fibre counts greater than those obtained with the PCM. For fibres longer than 5 µm the two EM methods provided similar results. The PCM fibre counts in samples from the non-occupational situations were shown to be poor predictors of airborne asbestos fibre concentrations determined by EM. This was mainly due to the presence of high and variable proportions of non-asbestos fibres in these samples. Cherrie et al. (1989) concluded PCM to EM conversion factors (for fibres longer than 5 µm) of 4.0 for chrysotile and 1.7 for amphibole asbestos. In the context of the revised French limit value and the related methodological and fibre definition discussion concerning short and thin asbestos fibres (see Ch 9.1.1), TEM and PCM methods were recently compared in 265 samples from 29 current worksites where different types of asbestos containing materials were removed with different methods in different environments (Eypert-Blaison et al. (2018b) and Eypert-Blaison et al. (2018a)). When restricting the counting to WHO fibres, the arithmetic mean TEM/PCM ratio was 4.6 when combining all asbestos fibre types, but it ranged from 0.1 to 19 depending on the type of asbestos material removed. The rare settings where the TEM/PCM concentration ratio was less than one are due to PCM counts also including non-asbestos WHO fibres. In addition to the type of material, also type of asbestos fibre (the difference was smaller for amphiboles) and method of removal (highest ratio in hydroblasting) influenced the ratio.

The above comparisons are mostly based on fibres thicker than about 0.25 µm and longer than 5 µm. Obviously, if thinner and shorter fibres are also considered, the difference between the two methods gets more pronounced. TEM counts were performed in 84 historical dust samples in South Carolina (Dement et al., 2008) and in 77 samples in North Carolina (Dement et al., 2009) chrysotile asbestos textile plants. Most fibres were shorter than 5 µm and thus not detected by PCM. The ratio of fibres longer than 5 µm varied considerably by plant and operation and was from 6.9% to 20.8% in the South Carolina plants and from 2.9% to 10.0% in the North Carolina plants. In the context of the above-mentioned French studies (Eypert-Blaison et al. (2018b) and Eypert-Blaison et al. (2018a)), when including all fibre widths (i.e. also thin asbestos fibres) the arithmetic mean of TEM/PCM ratio was 15 and range by type of material 0.2 to 95. The TEM-PCM comparisons were not made including also short fibres, but in TEM counts short fibres accounted for the largest faction of all fibres (64-95% depending on removal technique) while thin fibres accounted for 1-29% and WHO fibres for 2-14%.

Regulatory bodies have taken pragmatic approaches to overcome the above methodological uncertainties. RIVM (1987) and WHO (1987) used a pragmatic factor of 2 between TEM and PCM in their assessments of environmental exposure. EPA (1986) 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. It is noteworthy that fibre dimension distribution and the share of non-asbestos fibres may differ between the environmental and occupational setting. The results described above for France illustrate the variability between PCM and TEM in the occupational setting currently faced in EU but are based on a relatively limited number of samples, i.e. on the average 9 (=265/29) samples per worksite. It is also noted that most of the studies having assessed the TEM/PCM ratio were restricted to fibre dimensions detectable by PCM and there is much less data on TEM/PCM ratio when including also the thin fibres in the TEM counts.

Approaches used in OEL setting context are further described in section 9.1.1. In brief, DECOS (2010) used the same factor of 2 when deriving an exposure-risk relationship for occupational setting to be monitored by TEM but based on epidemiological data expressed as PCM measurements. AGS (2008) did not consider it necessary to introduce a correction factor to take account of different methods of fibre detection (optical or

electron microscope) while setting standards to be monitored by SEM but based on EPA (1986) exposure-risk relationship relying on optical microscopy. Afsset (2009) acknowledged the higher sensitivity of TEM but based its recommendation on PCM while calling for development of a TEM method (see section 6 for references to new French methods). Danish NFA (2019) did not consider a modification factor in its recommendation to adapt the DECOS (2010) approach to the national setting.

Appendix 6. Additional sensitivity analyses concerning exposure response modelling for lung cancer presented in Appendix 4

A number of issues were explored in sensitivity analyses of the exposure response relation for lung cancer and/or risk calculations.

1.Change in mid-point exposure level estimates of the Olsson study.

Exposure levels in the Olsson et al. (2017) large multicentre case-control study have been estimated on the basis of Geometric Mean fibre concentrations for each job title. This underestimates the derived cumulative exposures when these are not based on arithmetic means. Peters et al. (2016) suggest that the arithmetic mean could be a factor 1.47 higher than the geometric mean exposure. In an alternative analysis, exposure midpoints were adjusted for this factor and the meta-exposure response association of Appendix 4 was re-analysed as well as risk calculations. The meta-exposure response did not show any major differences after this adjustment (Table 16). Thus, also risk calculations within the range presented were similar compared to earlier calculations (not shown).

2.Changes in knot placement of the spline model.

For the original model boundary knots were place at the 20- and 80-percentile of the exposure distribution with values of exposure >0 and an interior knot at the 50-percentile. Sensitivity analyses were performed to investigate the effect of varying knot placements. These analyses were only undertaken for the spline models with (adjustment for) intercept (Table 17). Results do not seem very sensitive for location of boundary knots and/or the number of interior knots. In most cases, changes in the point estimates are within 10% range of the original model. For the last model in Table 17, the differences are somewhat larger, but this model has a considerably higher AIC value.

3. The effect of fibre type and study quality.

The effect of fibre type and lung cancer mortality risk has been extensively explored in the literature. The meta-analyses by Hodgson and Darnton (2010), Berman and Crump (2008a,b), DECOS (described extensively in Lenters et al. 2011)) and van de Bij et al. (2013), illustrate this clearly. In general, potency differences for the different asbestos types are considerably smaller in case of lung cancer in comparison to mesothelioma. Earlier estimates are in a range of a factor 10-50 for the potency difference between amphiboles and chrysotile (Hodgson and Darnton). In their analysis the association between exposure to asbestos and lung cancer was calculated across the different studies, with each study contributing one aggregate exposure-lung cancer risk coordinate, ignoring within study exposure-response relations. The association between asbestos exposure and lung cancer risk was best described by a relationship between a linear and square relationship. Berman and Crump showed a nine times higher increased risk for long amphiboles compared to long chrysotile fibres of all widths, and had even higher estimates for specific diameters: a ratio of 16:1 for long amosite versus long chrysotile for fibres with widths <4 µm. Their analysis was based on using linear exposure response relations for each individual cohort (calculating per study a lung cancer potency factor K_L and subsequently performing a meta-analysis using these cohort specific K_L factors. Lenters et al. (2011), used a similar approach and observed a difference in risk ratio of a factor 8 when all 19 studies were included. Van der Bij et al. (2013), observed a non-significant three- to fourfold difference in potency between chrysotile and amphibole fibres in a more recent meta-regression analysis using a non-linear (spline) modelling approach to improve estimation of the exposure response curve in the low exposure range observed higher overall risks for all fibre types together in this range. The differences between the van der Bij results and earlier results is likely due to the fact that the spline at low exposure levels is less affected by observations at high

levels. The latter are more likely affected by measurement error. This may explain the smaller differences between asbestos types in spline analyses compared to results from linear models. All estimates of fibre type specific potency for chrysotile are highly sensitive to two influential studies (the Quebec miners study and the Carolina textile industry study, see section 7.7.1). DECOS discusses these studies explicitly and classifies the Quebec miners' study as a study with several major quality issues, while the Carolina study is considered a higher quality study. Removal of these studies diminished the effect of fibre type considerably. Evaluation of potency differences is complicated by study quality. Lenters et al. investigated in their meta-analysis the role of quality of the asbestos exposure assessment to potentially explain heterogeneity in linear exposure-response slope estimates. Study quality was expressed in different ways; completeness of documentation, completeness and quality of job history data for each study, coverage of the study follow-up period by measurements, use of internal (cohort specific) conversion factors or external conversion factors (from other studies or the literature). They showed that the exposure-response slope estimates become steeper when the analysis is stratified by study quality.

As regards the analyses described in Appendix 4, the effects of both fibre potency and study quality were evaluated in the updated study base of 22 studies on cumulative asbestos exposure and lung cancer mortality as described below. Fibre potency differences were explored in a stratified analysis, stratified by amphibole, mixed and chrysotile asbestos. As regards quality, studies were classified as studies with a low quality when documentation was not adequate and when indications existed that the job title information was of poor quality. The newly included studies were graded for study quality as described by Lenters et al. (2011).

Results from the analysis with fibre type (Table 18) for splines are comparable with the results by van der Bij et al. (2013) The model with three fibre types has a relatively high AIC, which is explained by the high number of variables in the model. In both spline analyses (van der Bij et al. (2013), and the one in Table 18) with models with intercepts, relatively large intercepts are being observed. Van der Bij et al., reasoned that high intercepts point to differences in risk between exposed and non-exposed populations independent of exposure. Besides differences in risk factors between the exposed and unexposed population, systematic and random measurement errors can lead to an intercept greater than one. This fits with results from earlier analyses by Lenters et al., that showed that in particular studies with lower quality have the largest intercepts in comparison with studies of higher study quality. It was therefore, considered reasonable to assume that the observed intercept above RR = 1 is at least partly due to exposure measurement error/exposure misclassification. When the spline was also adjusted for intercept, potency differences between asbestos types were smaller in this analysis compared to the van der Bij analyses. This is likely the result of updating the study base with new and updated studies in particular with populations with mixed asbestos and chrysotile exposure.

Also in the updated database with 22 studies described in Appendixes 3 and 4, an effect of study quality was observed. Studies with poor quality had higher intercepts (in spline models with an intercept). After adjustment for intercept, a considerable effect of study quality on the exposure response slope could be observed. It is of interest that that AIC of the model with study quality was in close range to the original model.

In the context of this evaluation it is important to note that because of the approach taken, derivation of an exposure risk relation for mixed asbestos, the issue of different fibre types is not a central issue to this evaluation. Because potential potency differences between different fibre types for lung cancer seems relatively small, the meta-estimate of the exposure response relation for lung cancer, taking all studies together, is expected to yield an acceptable meta-estimate for mixed asbestos. Differences in relative risk

between the meta-exposure response estimate and the estimate for mixed asbestos types only were below 10%, using the spline model adjusted for intercept.

Choices in the risk assessment process irrespective of the exposure response chosen (mortality rates and lifetime risk period).

The input for the life-table analysis (lung cancer and total mortality) were mortality rates, per January 2021, averaged across all EU countries for the years 2011-2016 from the Eurostat database. For this purpose, the average male and female mortality rates were calculated by age. The excess risk was calculated until 89 years of age. A sensitivity analysis was undertaken by using male rates only. The rationale is that male rates are higher and this will potentially lead to higher excess risks at the end of the lifetime risk period (age 89). Use of male rates only, led to a 30% higher lifetime risk in comparison to the figures calculated using mortality rates of both genders (Table 19). It is to be noted that the choice of background rates affects only the lung cancer excess calculations as for mesothelioma an absolute risk model was used.

Calculation of lifetime risk at age >100 in comparison to 89 years of age as applied in Appendix 4 led to an approximately 10% higher excess lifetime risk. It should be noted that the effect of considering a longer period for reading out the lifetime risk, has limited effect on the excess risk because the lung cancer rate become smaller at very high age and the influence of total mortality (other causes of death) becomes dominant and limits the influence of the disease of interest. In particular, this category of choices, arising from the lifetime excess calculations, may contribute to the explanation of differences with other risk assessments in which other rates and other lifetime risk periods may have been used.

Table 16. Asbestos exposure and lung cancer mortality meta-exposure response models including 22 studies for the original model and with exposure adjustment for the Olsson et al. (2017) study. Presented are the AIC for each model and predicted lung cancer Relative Risk at different cumulative exposure levels.

Original models	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept	**0.4**	**4.0**	**40 ***
1A. Linear model Adjusted for intercept	137.7	1.60 (1.28 – 2.00) 1.00 (1.00 - 1.00)	1.60 (1.28 – 2.01) 1.00 (1.00 – 1.00)	1.61 (1.29 – 2.02) 1.00 (1.00 – 1.01)	1.73 (1.37 – 2.17) 1.08 (1.04 – 1.12)
1B. Linear model, no intercept	871.6	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.00)	1.02 (1.01 – 1.02)	1.18 (1.10 – 1.27)
2A. Natural spline Adjusted for intercept	114.7	1.43 (1.14 – 1.79) 1.00 (1.00 - 1.00)	1.43 (1.14 – 1.79) 1.00 (1.00 – 1.00)	1.45 (1.16 – 1.81) 1.02 (1.01 – 1.03)	1.68 (1.34 – 2.01) 1.18 (1.07 – 1.29)
2B. Natural spline, no intercept	508.4	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.01)	1.04 (1.02 – 1.05)	1.43 (1.23 – 1.67)
Models with Olsson et al. (2017) exposure estimates adjusted (1.47 x midpoint)	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept	**0.4**	**4.0**	**40 ***
1A. Linear model Adjusted for intercept	137.7	1.60 (1.28 – 2.00) 1.00 (1.00 - 1.00)	1.60 (1.28 – 2.01) 1.00 (1.00 – 1.00)	1.61 (1.29 – 2.02) 1.00 (1.00 – 1.01)	1.73 (1.37 – 2.17) 1.08 (1.04 – 1.12)
1B. Linear model, no intercept	871.4	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.00)	1.02 (1.01 – 1.02)	1.18 (1.10 – 1.27)
2A. Natural spline Adjusted for intercept	114.7	1.43 (1.14 – 1.79) 1.00 (1.00 - 1.00)	1.43 (1.14 – 1.79) 1.00 (1.00 – 1.00)	1.45 (1.16 – 1.81) 1.02 (1.01 – 1.03)	1.68 (1.34 – 2.01) 1.18 (1.07 – 1.29)
2B. Natural spline, no intercept	508.2	1.00 (1.00 - 1.00)	1.00 (1.00 – 1.01)	1.04 (1.02 – 1.05)	1.44 (1.23 – 1.68)

AIC = Akaike information criterion

* The cumulative exposure category 40 f-y/cm^3 corresponds to an air concentration above the current OEL when assuming 40 year career and is included only in order to illustrate the model differences

Table 17. Asbestos exposure and lung cancer mortality meta-exposure response models including 22 studies with different knot[a] placements. Presented are the AIC for each model and predicted lung cancer Relative Risk at different cumulative exposure levels. Only spline models with intercept were analysed.

Original model	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept	**0.4**	**4.0**	**40 ***
Natural spline Adjusted for intercept Knots [0.2,0.8]/[0.5]	114.7	1.43 (1.14 – 1.79) 1.00 (1.00 – 1.00)	1.43 (1.14 – 1.79) 1.00 (1.00 – 1.00)	1.45 (1.16 – 1.81) 1.02 (1.01 – 1.03)	1.68 (1.34 – 2.01) 1.18 (1.07 – 1.29)
Alternative knot placements	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept	**0.4**	**4.0**	**40 ***
Natural spline Adjusted for intercept Knots [0.0*,1.0*]/[0.5*]	113.9	1.41 (1.13 – 1.77) 1.00 (1.00 – 1.00)	1.41 (1.13 – 1.77) 1.00 (1.00 – 1.00)	1.44 (1.15 – 1.80) 1.02 (1.01 – 1.03)	1.69 (1.35 – 2.11) 1.20 (1.08 – 1.32)
Natural spline Adjusted for intercept Knots [0.0,1.0]/[0.5]	114.5	1.42 (1.17 – 1.78) 1.00 (1.00 – 1.00)	1.43 (1.17 – 1.79) 1.00 (1.00 – 1.00)	1.45 (1.16 – 1.81) 1.02 (1.01 – 1.03)	1.68 (1.35 – 2.10) 1.18 (1.08 – 1.29)
Natural spline Adjusted for intercept Knots [0,1]/[0.3,0.7]	121.2	1.40 (1.13 – 1.74) 1.00 (1.00 – 1.00)	1.40 (1.13 – 1.74) 1.00 (1.00 – 1.00)	1.43 (1.15 – 1.77) 1.02 (1.00 – 1.04)	1.71 (1.35 – 2.15) 1.22 (1.05 – 1.41)
Natural spline Adjusted for intercept Knots [0,1]/[0.2,0.4,0.6]	131.2	1.38 (1.09 – 1.74) 1.00 (1.00 – 1.00)	1.38 (1.09 - 1.74) 1.00 (1.00 – 1.01)	1.41 (1.13 – 1.76) 1.02 (0.98 – 1.07)	1.70 (1.34 – 2.14) 1.23 (1.02 – 1.49)

[a] Knot placements are described as [Quantiles used for boundary knots]/[Quantiles used for knots], where a * describes that quantiles were calculated including also not exposed categories.

* The cumulative exposure category 40 f-y/cm^3 corresponds to an air concentration above the current OEL when assuming 40 year career and is included only in order to illustrate the model differences

Table 18. Asbestos exposure and lung cancer mortality meta-exposure response models including 22 studies stratified by asbestos type (mixed, amphibole and chrysotile) and study quality (limited, good). Presented are the AIC for each model and predicted lung cancer Relative Risk at different cumulative exposure levels. Only spline models with intercept were analysed.

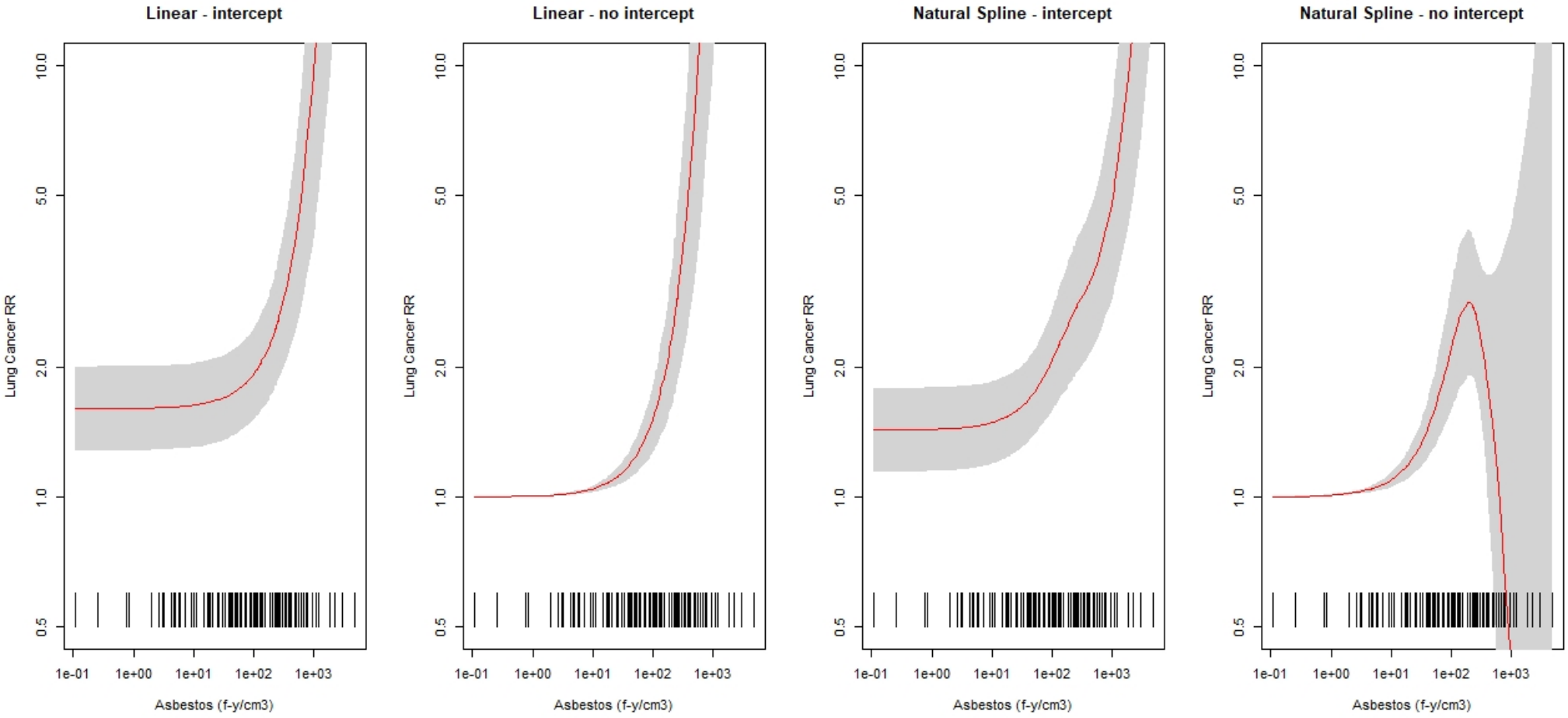
Fibre type	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept	**0.4**	**4.0**	**40 ***
	124.5				
Mixed	Spline Adjusted for intercept	1.17 (0.89 – 1.54) 1.00 (1.00 – 1.00)	1.17 (0.89 – 1.54) 1.00 (1.00 – 1.00)	1.19 (0.91 – 1.56) 1.02 (1.00 – 1.03)	1.37 (1.01 – 1.85) 1.17 (1.00 – 1.36)
Amphibole	Spline Adjusted for intercept	2.63 (1.99 – 3.46) 1.00 (1.00 – 1.00)	2.63 (1.99 – 3.47) 1.00 (1.00 – 1.00)	2.67 (2.02 – 3.54) 1.02 (1.01 – 1.03)	3.12 (2.21 – 4.40) 1.19 (1.05 – 1.34)
Chrysotile	Spline Adjusted for intercept	1.35 (1.13 – 1.60) 1.00 (1.00 – 1.00)	1.35 (1.13 – 1.61) 1.00 (1.00 – 1.00)	1.37 (1.15 – 1.62) 1.01 (1.00 – 1.03)	1.56 (1.23 – 1.97) 1.16 (0.97 – 1.38)
Study quality	**AIC**		**RR (95% CI) by cumulative exposure (f–y/cm^3)**		
		Intercept –	**0.4**	**4.0**	**40 ***
	115.9				
Limited	Spline Adjusted for intercept	1.68 (1.32 – 2.14) 1.00 (1.00 – 1.00)	1.68 (1.32 – 2.15) 1.00 (1.00 – 1.00)	1.69 (1.32 – 2.17) 1.01 (1.00 – 1.02)	1.83 (1.37 – 2.44) 1.09 (1.00 – 1.19)
Good	Spline Adjusted for intercept	1.20 (0.83 – 1.72) 1.00 (1.00 – 1.00)	1.20 (0.84 – 1.72) 1.00 (1.00 – 1.00)	1.23 (0.86 – 1.75) 1.03 (1.01 – 1.04)	1.58 (1.17 – 2.14) 1.32 (1.13 – 1.55)

* The cumulative exposure category 40 f-y/cm^3 corresponds to an air concentration above the current OEL when assuming 40 year career and is included only in order to illustrate the model differences

Table 19. Cancer exposure-risk relationship (lung cancer and mesothelioma combined) after working life exposure to given 8-hour air concentration for five working days a week for 40 years as measured by PCM. Comparison of overall risk when reference rates of both genders vs males only.

Air concentration of asbestos (fibres/cm^3) as measured by PCM	Excess life-time cancer risk (cases per 100 000 exposed)	
	Using both genders	Males only
0.001	1.2	1.6
0.002	2.5	3.2
0.005	6.2	8.1
0.01	12	16
0.02	25	32
0.05	62	81
0.1	125	163

Figure 3. Meta-exposure-response relationships for cumulative asbestos fibre exposure and lung cancer based on data from 22 (cohort and case-control) studies based on modelling logRR on exposure using linear and spline models with and without intercepts. Full range *



The shaded area indicates 95% confidence intervals of the RRs and the vertical lines at bottom of the graphs indicate individual cumulative exposure data points available.

* Unlike Figure 2 in Appendix 4, the graph shows the relationship over the entire cumulative exposure range for which data points were available in the combined studies (i.e. from 0.11–4710 f–y/cm3, corresponding to 0.0028 to 118 f/cm3 assuming a 40-year career). The confidence intervals are large for the spline model without intercept at high exposures. The spline is being pulled down because of a few low RRs at high exposure because data is sparce at those high levels.