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Asbestos

Scientific basis for setting a health-based occupational exposure limit

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ASBESTOS: SCIENTIFIC BASIS FOR SETTING A HEALTH-BASED OCCUPATIONAL EXPOSURE LIMIT

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National Research Centre for the Working Environment, 2019

FOREWORD

The Danish Working Environment Authority has 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 purpose of the present report is to suggest a health-based occupational exposure limit for asbestos.

The working group wishes to thank Chief Toxicologist Poul Bo Larsen, DHI, Denmark, for reviewing the report.

Copenhagen, June 2019

EXECUTIVE SUMMARY

Asbestos are silicate minerals containing elements such as Al, Ca, Mg and Fe. Asbestos encompass 6 different silicates, of which one, chrysotile has a serpentine (leaf like) structure and the other 5 have an amphibole structure (a chain-like crystalline structure). In Denmark, asbestos was previously used in products such as building materials and brake pads. Asbestos was banned in new products in 1987, but exposure still occurs due to its presence in materials installed prior to the ban.

In this report, a working group at the NFA has reviewed scientific data relevant to assessing the hazard of asbestos, i.e. human studies, toxicokinetics, animal studies, mechanisms of toxicity, previous hazard and risk assessments of asbestos, and the scientific basis for setting an occupational exposure limit (OEL). Finally the working group suggests a health-based OEL for asbestos. The focus of this report is occupational exposure by inhalation. The present working group evaluated the relevant literature on asbestos from both epidemiological studies and pulmonary exposure in animal studies. Cell culture studies were only used for the description and clarification of mechanisms and modes of action.

Concerning its absorption and distribution, asbestos has been fund in lungs and other organs of exposed workers. In addition, asbestos has been fund in foetal tissues of exposed mothers. In some workers all types of asbestos were found in the lungs, probably reflecting that the various types are cross-contaminated by each other. Following inhalation exposure of animals, asbestos was observed in a range of pulmonary structures and cell types as well as in the lymphatic and vascular compartments. In the lungs of rats, chrysotile has been described to break into smaller fibres, be partly bio-soluble and have a considerably lower persistence in comparison to amphibole asbestos types such as tremolite and crocidolite. The difference in elimination of the serpentine chrysotile and the amphibole asbestos types likely reflects that they break up in different ways inside the mammalian body.

The main asbestos induced diseases include cancer but also the non-cancer disease of asbestosis involving long term inflammation and scarring of the lungs. In spite of its importance, the current working group has assessed that asbestosis does not represent the critical effect endpoint for hazard assessment. This is based on the likelihood of a threshold mechanism of action in this disease – something that is in contrast to the mechanism of action of asbestos in carcinogenesis.

In the assessment of the presence of a carcinogenic threshold we assessed genotoxicity data. We found some evidence from animal experiments that asbestos has cytogenic effects – in terms of increased frequency of chromosome aberrations and sister chromatid exchanges. Thus, a genotoxic effect at the chromosome level is suggested. Furthermore, a number of studies have shown that asbestos fibres have mutagenic effects: amosite induced mutations in an *in vivo* mammalian mutagenicity assays, in one positive study. For crocidolite, there are three positive studies and one negative study. Overall, there is *in vivo* evidence for mutagenic effects of asbestos fibres. The current working group recommends to comply with the European Chemicals Agency (ECHA), who in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) R8

(ECHA, 2012) states the following: "*Unless a threshold mechanism of action is clearly demonstrated, it is generally considered prudent to assume that thresholds cannot be identified in relation to mutagenicity, genotoxicity, and genotoxic carcinogenicity, although a dose-response relationship may be shown under experimental conditions*". Based on this, 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.

There is evidence from studies on humans that asbestos causes cancer of the lung, pleural and peritoneal mesothelioma, gastrointestinal-tract cancers, cancer of the larynx, and cancer of the ovary. In animals, the inhalation of asbestos induced carcinogenicity at a mass concentration of 2 mg/m^3, and above. When presenting the data as fibre concentration, carcinogenicity has been reported already at 108 fibres/mL.

Risk assessments by *The Dutch Expert Committee on Occupational Safety* (DECOS, 2010) and by *The French Agency for Food, Environmental and Occupational Health & Safety* (Afsset, 2008), lead to practically identical risk estimates for excess human lung cancer risk mortality in relation to asbestos exposure. Taking both assessments together, a mean 8h-Time-weighted average (TWA) asbestos exposure over 40 working years of about 0.0001 fibres/mL would lead to an excess lung cancer mortality rate of 1×10^{-5}. Our calculations based on the K_L value for lung cancer set by DECOS based on a) DECOS' selected 4 studies based on their own quality criteria; and b) the DECOS' K_L value for their initially selected 18 studies - were in line with the number on lung cancer given by DECOS. Since smoking is not a risk factor for mesothelioma, the current working group recommends using the risk estimates by DECOS for asbestos-induced mesothelioma and their combined risk estimate for lung cancer and mesothelioma. In addition, the current working group recommends the use of DECOS' risk estimate for amphiboles to determine an OEL for all asbestos types. Risk estimates based on animal data did not indicate that animal studies would provide a lower risk estimate for lung cancer, also there is sufficient human data to base a hazard assessment upon. The current working group therefore recommends using human data in setting risk levels for a health-based OEL.

The current working group suggests that the following *exposure levels leading to excess cancer risk* are used:

Excess cancer incidence of lung cancer or mesothelioma	Risk levels (8h-TWA) based on a meta-analysis conducted by DECOS on Human studies of mesothelioma and lung cancer combined – calculated based on exposure to amphibole asbestos
1:1000	0.01 fibres/mL
1:10 000	0.001 fibres/mL
1:100 000	0.0001 fibres/mL

DANSK SAMMENFATNING

Asbest består af silikatmineraler, der indeholder grundstoffer såsom Al, Ca, Mg og Fe. Asbest består af 6 forskellige silikater, hvoraf én, chrysotil, har en serpentin-(bladlignende)-struktur, og de andre 5 har en amfibolstruktur (en kædelignende krystallinsk struktur). I Danmark blev asbest tidligere brugt i fx byggematerialer og bremseklodser. Asbest blev fra 1987 forbudt i nye produkter, men der er stadig eksponering fra produkter taget i brug før dette årstal.

I denne rapport vurderer en arbejdsgruppe ved Det Nationale Forskningscenter for Arbejdsmiljø (NFA) data, der er relevante for at vurdere faren ved udsættelse for asbest, dvs. humane studier, toksikokinetik, dyreforsøg, toksicitetsmekanismer, tidligere farevurderinger af asbest samt det videnskabelige grundlag for fastlæggelse af en grænseværdi. Endeligt opsummeres og foreslås en helbredsbaseret grænseværdi for asbest i arbejdsmiljøet. Fokus er i denne rapport på erhvervsmæssig eksponering ved indånding. Den nærværende arbejdsgruppe evaluerede den relevante litteratur om asbest fra både epidemiologiske undersøgelser og inhalationsforsøg med dyr. Celleforsøg er kun blevet evalueret, hvor de var nødvendige for at afklare og beskrive asbests virkningsmekanismer.

Absorption og fordeling af asbest er hos arbejdere påvist i lungerne samt andre organer. Asbest er blevet påvist i fostre fra eksponerede mødre. Samtlige asbest-typer er blevet påvist i lungerne hos nogle arbejdere. Dette afspejler sandsynligvis, at de forskellige typer optræder som forureninger af hinanden. I dyreforsøg er asbest efter indånding blevet målt i en række lungestrukturer og –celletyper, samt i lymfe- og kar-væv. I lungerne hos rotter er det blevet beskrevet at chrysotil knækker til mindre fibre; og at chrysotil er mindre bio-persistent i sammenligning med amfibol-asbesttyper som tremolite og crocidolit. Denne forskel skyldes sandsynligvis forskellig nedbrydningshastighed i kroppen.

De vigtigste asbest-inducerede sygdomme er kræft og asbestose. Asbestose er en sygdom med vedvarende inflammation og fibrose i lungerne. Den nuværende arbejdsgruppe har vurderet, at asbestose ikke repræsenterer det kritiske effekt-endepunkt til farevurdering. Dette er baseret på, at der sandsynligvis er en tærskelmekanisme for udvikling af denne sygdom.

I vores vurdering af om asbestinduceret kræft har en tærskelmekanisme har vi set på genotoksicitets-data. Der er data fra dyreforsøg, der peger på, at asbest udviser genotoksisk effekt på kromosomniveau: Asbest har virkninger i form af forhøjede kromosomaberrationer og såkaldte *sister chromatid exchanges*. Desuden har en række undersøgelser vist, at asbestfibre har mutagene effekter: Amosit-inducerede mutationer i et mutagenicitets-studie; for crocidolit var der effekt i tre studier, mens et studie var negativt. Samlet set peger data fra dyreforsøg på en mutagen virkning af asbestfibre. Den nuværende arbejdsgruppe anbefaler at følge ECHA's REACH-R8 retningslinje (ECHA, 2012), som anbefaler at: medmindre en tærskelværdi er klart påvist, anses det generelt for mest fornuftigt at antage, at en tærskel ikke kan identificeres i relation til mutagenicitet, genotoksicitet, og genotoksisk carcinogenicitet. På baggrund heraf anbefaler den nærværende arbejdsgruppe, at asbestfibre farevurderes ved brug af en såkaldt lineær udregningsmetode og altså baseret på en antagelse af, at asbest ikke har nogen tærskel i sin kræft-inducerende effekt.

Der er betydelig evidens for, at asbest kan inducere lungekræft, mesoteliom (lungehindekræft), mave-tarmkræft samt kræft i strubehoved og i æggestokken. I dyreforsøg inducerer asbest kræft ved inhalationen af massekoncentrationer på 2 mg/m^3 og derover; eller ved en koncentration på 108 fibre/mL og derover.

Farevurderinger fra *The Dutch Expert Committee on Occupational Safety* (DECOS, 2010) og fra *The French Agency for Food, Environmental and Occupational Health & Safety* (Afsset, 2008), giver næsten identiske vurderinger for overskydende kræftrisikoniveauer ved asbesteksponering. Hvis man tager begge vurderinger i betragtning, vil en gennemsnitlig *8-h-TWA* asbesteksponering over 40 arbejdsår på 0,0001 fibre/mL medføre en overskydende lungekræft- og mesoteliom-dødelighed på $1x10^{-5}$. Arbejdsgruppens egne beregninger baseret på K_L-værdien for lungekræft fastsat af DECOS baseret på enten: a) DECOS' værdi for 4 studier udvalgt vha. deres egne kvalitetskriterier; eller: b) DECOS' K_L-værdi for 18 brutto-udvalgte undersøgelser - var i overensstemmelse med DECOS' tal for lungekræft. Eftersom rygning ikke er en kendt risikofaktor for udvikling af mesoteliom anbefaler Arbejdsgruppen at bruge DECOS' risikoestimat for asbest-induceret mesoteliom; samt DECOS' kombinerede risikoestimat for mesoteliom og lungekræft. Samtidigt anbefaler Arbejdsgruppen at bruge DECOS' risikoestimat for amfibol asbest til at sætte en grænseværdi for alle asbesttyper. Vores farevurdering baseret på data fra dyreforsøg, viser at denne type forsøg ikke giver et lavere risikoestimat for lungekræft. Desuden er der tilstrækkelig humane data til at foretage en farevurdering. Den nærværende arbejdsgruppe anbefaler derfor at anvende humane data til at fastsætte fareniveauer for en sundhedsbaseret grænseværdi.

Den nuværende arbejdsgruppe anbefaler at følgende overskydende kræftrisikoniveauer anvendes:

Overskydende lungekræft- og mesoteliom-incidens	Risikoniveauer (8h-TWA) baseret på meta-analyser udført af DECOS på human mesoteliom samt lungekræft – baseret på eksponering til amfibol asbest
1:1000	0,01 fibre/mL
1:10 000	0,001 fibre/mL
1:100 000	0,0001 fibre/mL

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CONTENTS

Foreword *3*

Executive Summary *4*

Dansk sammenfatning *6*

Acknowledgements *8*

Contents *9*

Abbreviations *10*

Recommendation from the working group of the National Research Centre for the Working Environment *12*

Recommendation executive summary *13*

Derived Limit Values /Carcinogenic Risk Assessment **13**

Recommendation on occupational exposure limits for asbestos *14*

1. Chemical agent identification and physico-chemical properties **14**

2. EU harmonised classification and labelling **21**

3. Chemical agent and scope of legislation **21**

4. Existing occupational exposure limits **22**

5. Occurrence, use and occupational exposure **25**

5.1. Occurrence and use 25
5.2. Production and use information 25
5.3. Occupational exposure 25
5.4. Routes of exposure and uptake 26

6. Monitoring exposure **26**

6.1 Monitoring airborne asbestos in the workplace 26
6.2 Biomonitoring methods for asbestos in the workplace 27

7. Health effects **27**

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion) 27
7.2. Acute toxicity 34
7.3. Specific Target Organ Toxicity/Repeated Exposure 35
7.3.3. In vitro data 40
7.4. Irritancy and corrosivity 40
7.4.2. Animal data 40
7.5. Sensitisation 40
7.6. Genotoxicity 40
7.7. Carcinogenicity 44
7.7.1. Human data (covering the period up to 2012 - based on IARC 2012) 44
7.7.2. Human data after IARC 2012 48
7.8. Reproductive toxicity 82
7.9. Mode of action considerations 83
7.10. Lack of specific scientific information 84

8. Groups at extra risk **84**

References *85*

ABBREVIATIONS

8-oxo-dGua	8-Oxo-2'-deoxyguanosine
Afsset	Agence française de sécurité sanitaire de l'environnement et du travail / French Agency for Food, Environmental and Occupational Health & Safety
AAG	Anthophyllite, actinolite and glaucophane
ADME	Absorption, distribution, metabolism and excretion
ALARA	As low as reasonable achievable
ANSES	French Agency for Food, Environmental and Occupational Health
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	Broncho-alveolar lavage
BAuA	German Federal Institute for Occupational Safety and Health
BLV	Biological limit value
Bw	Body weight
CAS	Chemical Abstract Service
CI:	Confidence interval
Cm^3	Cubic centimetre; in the current document, Cm^3 and mL, although equal, are used interchangeably
DECOS	Dutch Expert Committee on Occupational Safety
DGUV/IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung
DHI	Dansk Hydraulisk Institut
DGS	Directorate General for Health
DGT	Directorate General for Work
DPPR	Directorate General for Pollution and Risk Prevention
ECHA	European Chemicals Agency
EEC	European Economic Community
IARC	International Agency for Research on Cancer
IER	Increased excess risk
IOM	Institute of Medicine
L/D	Length-to-diameter ratio
LDH	Lactat dehydrogenase
LNT model	Linear no-threshold model
LOAEC	Lowest observed adverse effect concentration
mRNA	Messenger RNA
NFA	National Research Centre for the Working Environment
NIEHS	National Institute of Environmental Health Sciences
NOAEC	No observed adverse effect concentration
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
OEL	Occupational exposure limit
PCM	Phase contrast microscopy
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RR	Relative risk

SAFs	Short asbestos fibres
SE	Standard error
SMR	Standardised mortality ratio
STEL	Short term exposure limit
TAFs	Thin asbestos fibres
TEM	Transmission electron microscopy
TWA	Time weighted average
WHO	World Health Organization
UK	United Kingdom
U.S.	United States of America

RECOMMENDATION FROM THE WORKING GROUP OF THE NATIONAL RESEARCH CENTRE FOR THE WORKING ENVIRONMENT

8-hour TWA: We recommend that the following *exposure levels leading to excess cancer risk* are used:

Excess cancer incidence of lung cancer or mesothelioma	Risk levels (8h-TWA) based on a meta-analysis conducted by DECOS on Human studies of mesothelioma and lung cancer combined – calculated based on exposure to amphibole asbestos
1:1000	0.01 fibres/mL
1:10 000	0.001 fibres/mL
1:100 000	0.0001 fibres/mL

The current working group calculated risk levels for lung cancer based on Danish incidence values and on K_L value for lung cancer set by DECOS. Notably, these were in line with DECOS' own risk levels on lung cancer.

RECOMMENDATION EXECUTIVE SUMMARY

Derived Limit Values /Carcinogenic Risk Assessment

The current working group recommends that the following *risk estimates for asbestos-induced cancer are used for health-based occupational exposure limits:*

Table 1. Our recommendation on: ***exposure levels leading to excess cancer risk***

Excess cancer incidence of lung cancer or mesothelioma	Risk levels (8h-TWA) based on a meta-analysis conducted by DECOS on Human studies of mesothelioma and lung cancer combined – calculated based on exposure to amphibole asbestos
1:1000	0.01 fibres/mL
1:10 000	0.001 fibres/mL
1:100 000	0.0001 fibres/mL

RECOMMENDATION ON OCCUPATIONAL EXPOSURE LIMITS FOR ASBESTOS

This recommendation is based on previous compilations performed by IARC (IARC, 2012), DECOS (DECOS, 2010), German Federal Institute for Occupational Safety and Health (BAuA) (BAuA, 2014), and Afsset (Afsset, 2009), as well as on evidence from the scientific literature based on a literature search conducted in 2019 by the National Research Centre for the Working Environment, Denmark.

1. Chemical agent identification and physico-chemical properties

Name: Asbestos
Synonyms: Asbestos in the current report, and for the purpose of European Union Directive 2009/148/EC on the protection of workers from the risks related to exposure to asbestos at work (EU, 2009), means the following fibrous silicates with listed Chemical Abstract Service (CAS) No :

(a) actinolite, CAS No 77536-66-4
(b) grunerite (amosite), CAS No 12172-73-5
(c) anthophyllite, CAS No 77536-67-5
(d) chrysotile, CAS No 12001-29-5
(e) crocidolite, CAS No 12001-28-4
(f) tremolite, CAS No 77536-68-6

Molecular formula: Asbestos are silicate minerals containing such elements as Al, Ca, Mg and Fe. The molecular formulas are presented in Table 3.

EC No.: 601-801-3[1].

CAS No.: Asbestos: 12172-73-5[2]; CAS numbers of each type are given in Table 2.

Molecular weight: The molecular weights depend on the length of the individual fibres. The molecular weights of the chemical formulas are listed in Table 2.

Description: Asbestos consists of 6 different silicates, of which one, chrysotile has a serpentine (leaf like) structure and the other 5 have an amphibole structure (a chain-like crystalline structure) (Table 2, Figure 1). When considering one of these asbestos types, impurities of one or more of the

[1] https://echa.europa.eu/substance-information/-/substanceinfo/100.121.453
[2] https://echa.europa.eu/substance-information/-/substanceinfo/100.121.453

other types have to be taken into account. Impurities e.g. in chrysotile include a long range of chemical elements as described by Platek et al., (1985).
In the EU countable asbestos fibres in relation to the OEL are defined as having a length >5 μm a diameter of less than 3 μm and a L/D (aspect) ratio of ≥3. In addition, there are asbestos fibres that are less than 5 μm in length.

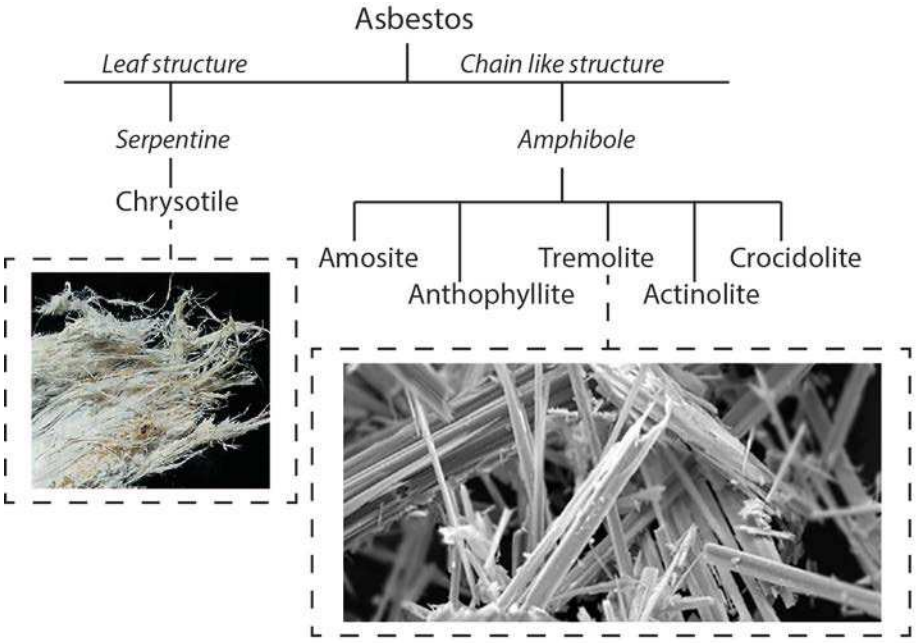


Figure 1. Overview of the asbestos types and their structures
Drawn based on[3]. The images stem from[4]. No scale-bars were available.

[3] http://www.nzdl.org/gsdlmod?e=d-00000-00---off-0hdl--00-0----0-10-0---0---0direct-10---4-------0-1l--11-en-50---20-about---00-0-1-00-0--4----0-0-11-10-0utfZz-8-00&cl=CL1.1&d=HASH011321ce4efc2579cf71e500.4&gt=2

[4] http://www.jewellery.org.ua/stones-katalog-engl/mineral-serpentin.htm;
https://www.nationalasbestos.co.uk/types-of-asbestos/

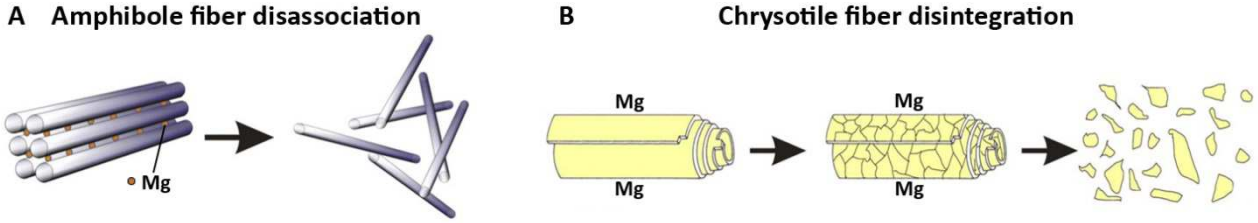


Figure 2. Proposed metabolism of amphiboles and serpentine asbestos in the mammalian body. (A) Structure and disassociation of amphibole fibre. The fibres are weakly connected by magnesium ions (orange spheres) and are highly resistant to neutral or acid dissolution. (B) Structure and disintegration of chrysotile fibre. The magnesium is dissolved at neutral pH and the silica matrix is broken up at acid pH. Modified from D.M. Bernstein, J.A. Hoskins. The health effects of chrysotile: current perspective based upon recent data, Regul.Toxicol Pharmacol. 45 (2006) 252-264.

Table 2., Origin, mineral group and use of each of the six asbestos types constituting the designation of "asbestos" in the European Union (EU); Supplemented with data on a seventh type (Libby amphibole)

Name	CAS number	Mineral group	Use
Chrysotile (white asbestos)	12001-29-5 Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (DGUV/IFA, 2018)	Serpentine (or curly in nature)	90 – 95% of all asbestos used for the manufacture of products in the United States has been reported to be chrysotile[5] A cement additive, a binding material in sealants, in many types of linoleum and floor tiles developed during the Twentieth Century, in congoleum products, i*n gasket materials for cars and for pumps, in asbestos roofing materials used in several forms after World War II and into the 1970s*[6]. Chrysotile made up 98% of the world asbestos production in 1988 (DGUV/IFA, 2018).
Amosite (brown asbestos) Amosite is a trade name for brown asbestos from South African mines. Amosite is an acronym for 'asbestos mines of South Africa'[7].	12172-73-5	Amphibole (straight, thin, needle-like fibres	Amosite has a high absorption ability, and was therefore commonly used in materials to reduce condensation or provide acoustic insulation against sound travel. Amosite's tensile strength and heat resistance also made it a common additive for structural steel[8].

[5] http://www.asbestosnews.com/asbestos/types/
[6] http://www.asbestosnews.com/asbestos/types/
[7] http://www.asbestosnews.com/asbestos/types/
[8] https://mesowatch.com/amosite-asbestos/#.XO5xMhYza70

Crocidolite (blue asbestos)	12001-28-4	Amphibole	Crocidolite has a greater tensile strength than chrysotile asbestos but is much less heat-resistant, fusing to black glass at relatively low temperatures [9].
Anthophyllite	77536-67-5	Amphibole	Anthophyllite asbestos has a more brittle fibre than other forms of the mineral and is formed by the breakdown of talc, thus resulting in it being a common contaminant in talc that is mined for commercial purposes [10].
Tremolite	77536-68-6	Amphibole	Was a common additive in talcum powder when the use of asbestos in commercial products was legal[11].
Actinolite	77536-66-4	Amphibole	Actinolite asbestos, the fifth member of the amphibole class, is commonly found in a number of rock forms, including iron ore. It has not been mined commercially but nevertheless may be found as a contaminant in asbestos products or in products derived from other mined minerals.
Libby amphibole	The CAS number is unknown	Amphibole	Libby Amphibole Asbestos is a transitional fibre. It is made of 3-5 chemically different fibres and the chemical composition may change from one end of the amphibole fibre to the other. Tremolite is the form of asbestos that contaminated the vermiculite mine in Libby Montana[12].

[9] https://www.britannica.com/science/crocidolite
[10] http://www.asbestosnews.com/asbestos/types/
[11] http://www.asbestosnews.com/asbestos/types/
[12] http://www.asbestosnews.com/asbestos/types/

Table 3. Chemical composition and data on physico-chemical properties of the 6 asbestos types

	Serpentine	Amphibole				
Type	**Chrysotile**	**Anthophyllite**	**Crocidolite**	**Actinolite**	**Tremolite**	**Amosite**
Chemical formula	$Mg_3(OH)_4Si_2O_5$	$(Mg,Fe^{2+})_7(OH)_2Si_8O_{22}$	$Na_2(Fe^{2+},Mg)_3Fe_2^{3+}(OH)_2Si_8O_{22}$	$(Ca,Na)_2(Fe,Mg,Al)_5(OH, F)_2(Si, Al)_8O_{22}$	$Ca_2(Mg,Fe)_5(OH,F)_2Si_8O_{22}$	$(Fe^{2+},Mg,Al)_7(OH)_2Si, Al)_8O_{22}$
Chemical composition in (%)						
SiO_2	35 - 44	52 - 64	49 - 57	Up to 63	50 - 63	45 - 56
MgO	36 - 44	25 - 35	3 - 15	18 - 33	18 - 33	4 - 7
Al_2O_3, Iron oxide	0 - 9	1 - 10	20 - 40	2 - 17	2 - 17	31 - 46
CaO, Na_2O	0 - 2	0 - 1	2 - 8	1 - 10	1 - 10	1 - 2
H_2O	12 - 15	1 - 5	2 - 4	1 - 4	1 - 4	1 - 3
Physical properties	fine light fibres	prismatic crystal and fibres	long, brittle fibres	prismatic crystal and fibres	prismatic crystal and fibres	prismatic crystal and fibres
Colour	white, grey, greenish	grey-white	blue	green	white, grey- white, greenish	ash grey
Texture	soft to rough, mostly silky	rough	soft to rough	rough	rough	rough
Flexibility	very high	low	good	low	low	good

Fibre diameter (nm)	18 - 30	60 - 90	50 - 90	0 - 90	60 - 90	60 - 90
Melting point (°C)	1500	1480	1180	1393	1320	1400
pH-Value	9.5 – 10.3	9.4	9.1	9.5	9.5	9.1
Electrical charge in aqueous suspension	+	-	-	-	-	-

The Source of this table is: "Umweltbundesamt (Publ.): Analysis of the Asbestos Industry, written by the Battelle-lnstitut Frankfurt e.V., Report 4/78, Berlin 1978"

2. EU harmonised classification and labelling

Information about the EU harmonised classification and labelling for asbestos (CAS number 12172-73-5; EC Number 601-801-3; Index 650-013-00-6) is provided by the EU (EU, 2008), as summarised in Table 4.

Table 4: Classification according to Regulation (EC) No 1272/2008 (EU, 2008) "List of harmonised classification and labelling of hazardous substances" (found in Table 3.1. in the regulation)

International Chemical Identification	CAS No	Classification	
		Hazard Class and Category Code(s)	Hazard statement Code(s)
Asbestos	12001-28-4 And individual types have the following CAS numbers: Actinolite, CAS No 77536-66-4 Grunerite (amosite), CAS No 12172-73-5 Anthophyllite, CAS No 77536-67-5 Chrysotile, CAS No 12001-29-5 Crocidolite, CAS No 12001-28-4 Tremolite, CAS No 77536-68-6	Carc. 1A STOT RE 1	H350 H372 **

Carcinogenic 1A: H 350: known to have carcinogenic potential for humans
STOT RE 1: H372 Causes damage to organs

3. Chemical agent and scope of legislation

Asbestos is according to the EU constituted by 6 different silicates as described above and in (EU, 2009); all of which are considered in the current document.

4. Existing occupational exposure limits

At EU level, an OEL of 0.1 fibres/cm^3 has been adopted for asbestos. However, some EU Member States as well as countries outside the EU have lower OELs as presented in in Table 5. There are to our knowledge no Biological Limit Values (BLVs) for asbestos available to date.

Table 5. Existing OELs for asbestos

	TWA (8 hrs)		**STEL (Short-term exposure limit) (15 min, in not stated otherwise)**		**Remarks**	**Reference**
Unit	Fibres/cm^3	µg/m^3	Fibres/cm^3	µg/m^3		
EU						
EU	0.1	Not provided directly in the legislation (EU, 2009). However, according to the EU Directive 87/217/EEC (EU, 1987): "*a conversion factor of two fibres/mL to 0.1 mg/m^3 of asbestos may be used*". Thus	Not reported in the Commission Directive 2009/148/EC (EU, 2009)	n/a	Citation: "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) (2) or any other method giving equivalent Results" from: (EU, 2009). (2) Determination of airborne fibre concentrations. A recommended method, by phase-contrast optical microscopy (membrane filter method), WHO, Geneva 1997	Commission Directive 2009/148/EC Article 8 (EU, 2009)

		the 0.1 fibres/cm^3 corresponds to 5 μg/m^3. Although we note that this depends on the length and mass of each fibre			(ISBN 92 4 154496 1). EU states that: "For the purpose of measuring asbestos in the air, as referred to in paragraph 1, 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" from (EU, 2009).	
Denmark	0.1	(see comment for EU above)	0.2	(see comment for EU for TWA above)		(DGUV/IFA, 2018)
Germany	TRGS 910 Substance-specific acceptance and tolerance concentrations Acceptance concentration Conc. (weight): 10000 F/m^3 [0.01 Fibres/cm^3] Acceptance concentration		0.8	(see comment for EU for TWA above)	Carcinogenic: Category 1 Substances which cause cancer and make a considerable contribution to the risk of cancer	(DGUV/IFA, 2018)

	associated with risk 4:10,000 Tolerance concentration Conc. (weight): 100,000 F/m^3 [0.1 Fibres/cm^3] Excursion factor: 8 also see TRGS 517, 519					
France	0.01	(see comment for EU above)				(DGUV/IFA, 2018)
United Kingdom (UK)	0.1	(see comment for EU above)	0.6 (10 minutes)	(see comment for EU for TWA above)		(DGUV/IFA, 2018)
The Netherlands	0.01	(see comment for EU above)				(DGUV/IFA, 2018)
Non-EU						
United States of America(U.S.)	0.1	(see comment for EU above)				(DGUV/IFA, 2018)
Switzerland	0.01	(see comment for EU above)				(DGUV/IFA, 2018)
Japan	0.15	(see comment for EU above)				(DGUV/IFA, 2018)
Japan JSOH	0.03 / 0.003	(see comment for EU above)			Only pertains to some of the fibre types.	(DGUV/IFA, 2018)

5. Occurrence, use and occupational exposure

5.1. Occurrence and use

Asbestos is released to the environment through natural and man-made sources. Natural sources include emissions from open mines. Man-made sources provide a much greater release volume than natural sources. The largest single source in Denmark is from building materials and materials e.g. locomotive parts, such as clutches, brake linings, and brake pads. These products were mounted before 1987 when the use of asbestos in new products was banned in Denmark. Concerning the ban on asbestos in Denmark in 1972, asbestos was prohibited in products for thermal-, noise- and moisture isolation. In 1980 a ban was set on the use of asbestos and asbestos-containing materials with the exception of asbestos-cement products such as roof tiling, frictional surfaces, gasket materials, *"lejeforinger"* and *"kommutatorer"*. In 1986 the ban was strengthened. After this date exceptions were only: "*asbestcementbølgeplader "B5" og "B9" og håndgods til tagdækning, bundne pakningsmaterialer, friktionsbelægninger, lejeforinger og kommutatorer"*. From 1993 to 2005 only few products such as "*bundne pakningsmaterialer, lejeforinger og enkelte friktionsbelægninger*" have been exempted from the ban (Arbejdstilsynet, 2016).

In 1991 five of the six asbestos types were banned for all use in the EU and the remaining type chrysotile was banned in 14 product categories. In 1999 Annex 1 of Directive 76/769/EEC (European Economic Community) was updated (EU_Commission, 1999) to extend the ban to chrysotile in asbestos cement products (mainly pipes and roofing), friction products (e.g. brake clutch linings for heavy vehicles) and seals and gaskets as well as various specialist uses. By January 1st 2005 this EU commission directive 1999/77/EEC (EU_Commission, 1999) was brought fully into force.

Airborne asbestos fibres are eliminated from the atmosphere through precipitation and dry deposition. Important sources of individual exposure to asbestos are inhalation of contaminated air at the workplace. Some environmental exposure cannot be excluded. Also contributions from ingestion and dermal/mucosal surface exposure cannot be excluded.

Notably the various asbestos types are often contaminated with each other, and it has e.g. been shown that even chrysotile samples from different mines that have similar size distribution show differences in biological effects (Muhle and Pott, 2000).

The background ambient air levels for the Parisian conurbation is estimated to be 0.0003 fibres/mL for fibres >5 μm and 0.002 for fibres <5 μm (Afsset, 2009).

5.2. Production and use information

Asbestos is mined from the earth several places around the world but in Denmark asbestos is not produced or used anymore. Yet, Asbestos, although banned in 1987 for new products, is still present in a range of materials installed before 1987.

5.3. Occupational exposure

Asbestos, although banned in 1987 for new products, is still present in some products in Denmark. The current exposure levels from these sources are unknown. Examples of asbestos fibres of different workplaces in Germany is given in Table 6.

Table 6 Examples of asbestos fibre concentrations in the air (fibres/cm3) of different workplaces in Germany. Taken from IARC (IARC, 2012)

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 works	FRG	15	15	8.6	0.2
	GDR	18	18	14.0	0.5

[a] Data for the GDR before 1967 are extrapolated
FRG, Federal Republic of Germany; GDR, German Democratic Republic

5.4. Routes of exposure and uptake

Occupational exposure to asbestos leading to uptake of fibres primarily occurs through inhalation. Skin exposure (and mucosal surface exposure e.g. ocular exposure) occurs but is not expected to result in systemic absorption through the skin due to the relatively large size of the asbestos fibres (Bos and Meinardi, 2000). Oral absorption may occur e.g. if food is contaminated at the work site, and possibly through the transport of fibres from the airways into the gastrointestinal tract. After the oral route asbestos may be located in the organs (Carter and Taylor, 1980). When taken up the asbestos fibres may distribute to various organs including the foetus of pregnant women (Haque et al., 1998).

6. Monitoring exposure

6.1 Monitoring airborne asbestos in the workplace

Asbestos can be monitored in the air of the workplace by applying the following fully or partially evaluated methods

In the EU Directive 2009/148EC (EU, 2009), the following is stated: "*Fibre counting shall be carried out wherever possible by PCM in accordance with the method recommended in 1997 by the WHO or any other method giving equivalent results. Determination of airborne fibre concentrations. A recommended method, by phase-contrast optical microscopy (membrane filter method), WHO, Geneva 1997 (ISBN 92 4 154496 1)*" (EU, 2009).

In the EU asbestos fibres are defined as having a length >5 µm a diameter of less than 3 µm and a length-to-diameter (L/D) ratio of ≥3. However, Afsset in France also investigated what they designated *thin asbestos fibres* (L≥ 5 µm, d<0.2 µm and L/D≥3) (Afsset, 2009). It was noted by Afsset that if thin fibres were also to be measured then novel distinct methods would have to be used.

6.2 Biomonitoring methods for asbestos in the workplace

Biomonitoring has to our knowledge not been applied for asbestos exposure.

7. Health effects

Asbestos fibres may cause various toxic effects. The carcinogenicity of individual asbestos types has been demonstrated in humans and in a series of animal studies using different exposure models (IARC, 2012). Genotoxic effects of asbestos were observed in numerous animal studies; they were also detected in human cells in vitro (Afsset, 2009; IARC, 2012).

This chapter is based on literature search performed and documented by the NFA library. The CAS numbers given by the EU: (a) actinolite, CAS No 77536-66-4; (b) grunerite (amosite), CAS No 12172-73-5; (c) anthophyllite, CAS No 77536-67-5; (d) chrysotile, CAS No 12001-29-5; (e) crocidolite, CAS No 12001-28-4; and (f) tremolite, CAS No 77536-68-6 were checked in ChemIDplus and then entered into the TOXLINE database combined with the search string: "inhalation exposure" OR "lung deposition" OR instillation. This search was supplemented with searches by N. Hadrup in the PubMed database using the word “asbestos” combined with relevant search terms on absorption, distribution, metabolism, excretion, and toxicity. In addition to using search engines, a number of relevant documents were identified by reviewing the reference list in other articles. The result of the combined effort was the ~150 articles and reports included as references in the current document.

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

Given that the likelihood of skin penetration of asbestos fibres is low (Davis et al., 1980a)(IARC, 2012), this chapter is focused on inhalation exposure, oral exposure, distribution to organs and exposure of the foetus.

7.1.1. Human data

In general IARC (IARC, 2012) stated based in a National Toxicology Program (NTP) (NTP, 2005) report that: “*the degree of penetration in the lungs is determined by the fibre diameter, with thin fibres having the greatest potential for deep lung deposition*”.

When investigating the human exposure it is difficult to pinpoint the exact pathway of exposure although inhalation is often a likely contribution as the individuals either worked at or lived near sites with high levels of asbestos. Also the potential of oral exposure occurs for the general population as asbestos can enter potable water supplies. As reported by IARC (IARC, 2012): in the U.S. the concentration of asbestos in the drinking water supplies is less than 1 fibres/mL. However in some locations the concentration can be extremely high (10 000 – 300 000 fibres per mL,(Agency for Toxic Substances and Disease Registry (ATSDR, 2001)).

Exposure to asbestos as determined in biomonitoring of tissues from adults

Findings in lungs

Asbestos has been demonstrated in lungs of humans. In shipyard and construction workers with mesothelioma all asbestos types, chrysotile, amosite, crocidolite, tremolite and what was designated AAG (consisting of anthophyllite, actinolite and glaucophane) were detected (Warnock, 1989).

In Quebec chrysotile miners and millers from *Asbestos Township*, fibre concentrations in lung were compared to those in a local reference population. The individuals included 38 patients with asbestosis without lung cancer, 25 with asbestosis and lung cancer, and 12 with mesothelioma: these individuals were necropsied. The local reference population was: "men who had died of either accidental death or acute myocardial infarction between 1990 and 1992. 23 were born before 1940 and 26 after 1940. Detected fibres were chrysotile, tremolite, crocidolite, talc, and anthophyllite fibres. The pulmonary concentrations of each fibre type did not show any differences between the three disease groups. Yet, there were some differences between the three disease groups in regard to observed fibre dimensions (Dufresne et al., 1996).

Another study compared the deposition in lung of a) pulmonary asbestos; and b) *non*-asbestos fibres- in 1) rural Korean residents, and 2) urban Korean residents with no known asbestos exposure. Chrysotile was the major fibre type in the lungs of both groups. The residents in the rural area had lower asbestos and non-asbestos fibre concentrations as compared to the urban residents (Lim et al., 2004). In a related study, the pulmonary asbestos and non-asbestos-fibres was determined in 36 normal Korean individuals and in 38 individuals with lung cancer. Again, chrysotile fibres were reported to be the major fibre type. No difference was found in the number of fibres between the two groups. In contrast, the non-asbestos fibre content was different between groups (Han et al., 2009)

Findings in organs other than lung

Auerbach *et al.* had the hypothesis that individuals with many asbestos bodies in their lungs would also have asbestos bodies in other organs. Thirty-seven individuals, of which nineteen cases had a diagnosis involving asbestos at death, were investigated. Of these, 18 had pleural plaques, 2 mesothelioma, and 5 lung cancer. Asbestos was found in lungs, but the number of other organs with one or more asbestos bodies ranged from 32 to 62% of examined organs. The organs examined were kidney, heart, liver, spleen, adrenals, pancreas, brain, prostate, thyroid (Auerbach et al., 1980).

In another study, three men were investigated. Two of them had pulmonary asbestosis and one had no known exposure to asbestos. Fibres were found in lung, pleura, bladder kidney and liver in the cases with known exposure (Pollice et al., 1997).

Carter investigated tissues of persons orally exposed to amphibole fibres called ferromagnesium silicate (Cummingtonite-Grunerite) from contaminated drinking water of Lake Superior. The number of fibres ranged between $2x10^6$ and $2x10^8$ fibres/L. In exposed persons, fibres were detected in lung, jejunum, liver. Both amphibole and chrysotile asbestos fibres were detected (Carter and Taylor, 1980).

Foetal exposure to asbestos

The tissues and placentas of autopsied stillborn infants were investigated for the presence of asbestos fibres. Asbestos fibres were detected in 50% of digests of foetal tissue and 23% of the digests of the placenta of 82 stillborn infants. There were various types present, 88% were chrysotile, 10% were tremolite, and 2% were actinolite and anthophyllite. The organs that were most frequently positive for fibres were: Lungs (50%), muscle (37%), placenta (23%), and liver (23%). Nevertheless, the mean fibre counts were highest in the liver (58 736 fibres/g[13]), placenta (52 894 fibres/g), lungs (39 341 fibres/g), and in skeletal muscle (31 733 fibres/g). Concerning placentas from live-born foetuses asbestos fibres were detected in 15% of these, but only in small numbers. In placentas of the stillborn the fibre counts was 52 894 fibres/g whereas in live-born foetuses it was only 19 fibres/g. The fibre presence in the stillborn foetuses was associated with the history of previous abortions and with placental diseases (Haque et al., 1998). In a study by the same group in 1996 similar results were obtained studying 40 stillborn infants and placental digests of 45 live-born infants (Haque et al., 1996), and similar data were reported by the same group in 1992 (Haque et al., 1992). Data in animals corroborated these findings - as described below (Haque et al., 2001; Haque and Vrazel, 1998).

Summary

Asbestos has in workers been demonstrated in lungs but also in a range of other organs. In addition, asbestos has been demonstrated in foetal tissues. In some workers all types of asbestos can be found in the lungs - probably reflecting that the different types are impurities of each other.

7.1.2. Animal data

Inhalation exposure

Absorption and distribution

A range of animal inhalation studies were reviewed. There were data on absorption and deposition for chrysotile, amosite and crocidolite. The data are presented graphically in Figure 3.

[13] It was not specified if this was per wet or dry weight

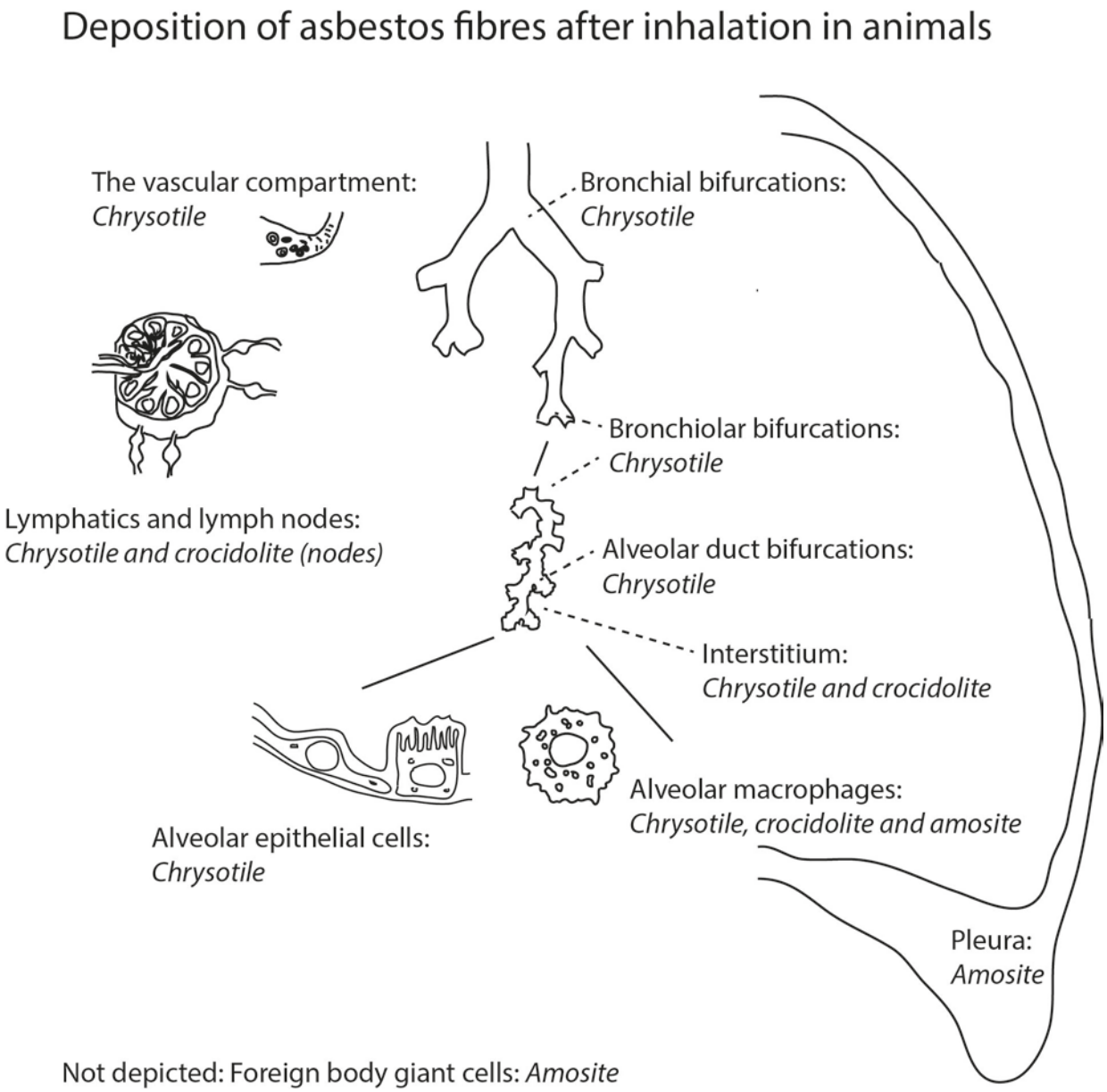


Figure 3. The distribution of asbestos in animals following inhalation (illustration by N. Hadrup)

Chrysotile

The accumulation of chrysotile after inhalation was observed in: the (alveolar) macrophages, alveolar epithelial cells, pulmonary interstitium, lymphatics and in lymph nodes as well as in the vascular compartment. The airway location was described to be in the bifurcations of the bronchi, bronchioles and alveolar ducts. But fibres were also described to be located in the airspace and also in so-called microcalcifications (Barry et al., 1983; Bernstein et al., 2004; BéruBé et al., 1996; Boorman et al., 1984; Brody et al., 1981; Brody and Hill, 1982; Crapo et al., 1980; Davis et al., 1986a, 1980b; Hesterberg et al., 1998; Oghiso et al., 1984; Pinkerton et al., 1984; Platek et al., 1985; Roggli

and Brody, 1984). Concerning the location in bifurcations of alveolar ducts, Brody et al described this to be the site where the majority of fibres were located, and that the farther a bifurcation was from its terminal bronchiole the fewer fibres were observed (Brody et al., 1981).

After inhalation exposure to amosite fibres, these were located in macrophages and multi-nucleate foreign body giant cells (Davis et al., 1991); and observed in the interstitial space and also found to be penetrating the visceral pleural wall and were observed on the parietal pleurae (Bernstein et al., 2011).

After inhalation exposure to crocidolite, fibres were observed in alveolar macrophages, the diaphragm, mediastinal lymph nodes, pulmonary interstitium (Bernstein et al., 2015; Oghiso et al., 1984; Roggli et al., 1987). In one study crocidolite but not chrysotile deposition was found in lungs (BéruBé et al., 1996). In Beagle dogs, inhalation of crocidolite resulted in a lung deposition of 17% and a total body deposition of 63%. Excretion of radioactivity showed that the percent of initial body burden fell from ~80% to a little more than 20% over the course of 3 days (Griffis et al., 1983). This may reflect rapid clearance of the upper airways,

Metabolism and elimination

Chrysotile

In rats inhaling chrysotile, macrophages and epithelial cells were cleared of fibres during a recovery period. In contrast, there was no clearance of fibres in the lung interstitium (Pinkerton et al., 1984). In another study, in rats inhaling chrysotile, the elimination rate of short chrysotile fibres was higher than observed for long fibres (Davis and Jones, 1988).

(Bernstein et al., 2006 exposed male rats to chrysotile by nose-only inhalation for 5 days/week, 6 h/day for 13 weeks. The fibre concentration was 1.3 mg/m^3 (having 76 fibres/cm^3 of fibres > 20 μm, or 3413 total fibres/cm^3 or 536 WHO fibres/cm^3), and 3.6 mg/m^3 (having 207 fibres/cm3 for fibres > 20 μm or 8941 total fibres/cm^3 or 1429 WHO fibres/cm^3)The exposure period was followed by a recovery periods of 0, 50 or 92 days. The content of long chrysotile fibres >20 μm in the lung were found to decrease considerably during the recovery period, and it was inferred that the longer fibres broke apart into particle and shorter fibres. Fibres were observed to become thicker during the recovery period at the medium dose (Bernstein et al., 2006).

Rats were exposed to chrysotile fibres at 4.3 mg/m^3. The duration was 6h/day for 5 days. After the exposure there were recovery periods of 1, 2, 7, 14 days, 1, 3, 6 and 12 months. The clearance half-time of the fibres longer than 20 μm was 1.3 days. No fibres longer than 20 μm were observed 3 months after exposure (Bernstein et al., 2004).

Rats inhaled chrysotile at a mass concentration of 15 mg/m^3 for 1 h. Animals were euthanised following recovery periods of 0, 24, 192, 336, and 744 h (1 month). There was a progressive decrease in fibre diameter ranging from 0.17 at 0 h to 0.1 μm at 744 h. (Roggli and Brody, 1984).

Rats were exposed to Calidria chrysotile or tremolite by inhalation. Mass concentrations were for chrysotile 200 fibres having a length of at least > 20 μm/cm^3 (1.7 mg/m^3); and for tremolite 100 fibres having a length of at least > 20 μm/cm^3 (11.5 mg/m^3). It was stated that the exposure technique was optimised to maximise the number of long respirable fibres. The exposure time was 6 h/day for 5 days. Animals were killed at 0, 1, 2, 7 days, 2 weeks, 1 month, 3 months, 6 and 12 months after exposure. After a recovery period of 12 months 99.2% of remaining chrysotile in the

lungs was shorter than 5 μm. In contrast, tremolite exposure showed persistence with what was described as essentially an infinite half-time (Bernstein et al., 2005).
Rats inhaled a) brake-dust of brake-drums made from chrysotile, b) a mixture of chrysotile and the brake-dust, or c) crocidolite. Exposure time was 6h/day for 5 days. The concentrations were a) 189 fibres ≥ 20 μm/cm^3, b) 3.6 fibres ≥ 20 μm/cm^3, c) 93 fibres ≥ 20 μm/cm^3 (the total number of fibres were 6953, 389, and 2013/cm^3 in the three groups, and the mass concentrations 3.5, 1.5, and 6.3 mg/m^3). Chrysotile fibres were observed to be somewhat bio-soluble in that short (<8 μm) fibres decreased rapidly for as long as 30 days after exposure, and continued to decrease for as 180 days of exposure. Longer fibres decreased to around 50% during the first 30 days, but then there was almost no further clearance during the period ranging from 30 to 180 days. In comparison, crocidolite fibres persisted for the life-time of the rats (Bernstein et al., 2015). Rats inhaled chrysotile asbestos at 10 mg/m^3 for 3-5 hour periods over 3 consecutive days (~12 h). Recovery periods were in the range of 1 to 180 days. Deposition was investigated, whereas short fibres were rapidly cleared, a large number of the longest fibres, defined as longer than 8 μm, were observed in the lungs for up to 6 months (Coin et al., 1996).

Amosite
Rats were exposed by nose-only inhalation to Libby amphibole and amosite 6h/day 5 days/week for a total of 10 days (mass concentration: Libby amphibole: 0.5, 3.5, or 25.0 mg/m^3 and amosite asbestos: 3.5 mg/m^3). Or alternatively exposure to Libby amphibole: 1.0, 3.3, or 10.0 mg/m^3 or amosite at 3.3 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. Endpoint evaluation was done at 1 day, 1, 3, and 18 months post exposure. Lung fibre burdens investigated at 13 weeks of exposure declined over the 18 month post exposure period. Libby amphibole fibres had a mean length of 3.7 μm, with 1% being longer than 20 μm (Gavett et al., 2016).
Rats were exposed by inhalation to amosite at 6.4 mg/m^3 6 h/day for 5 days. The length the number of fibres longer than 20 μm decreased only slightly over a 1 year recovery period, from 2.8 million fibres per lung at the end of exposure to 1.4 million at 1 year of recovery (Bernstein et al., 2011). Rats inhaled 1000 amosite fibres (longer than 5 μm)/mL, 7 h/day, 5 days/week for 12 months. Assessment of elemental composition of fibres recovered from the lungs showed that these contained 61% Fe, 32% Si, 1.2 % Mg and 1.3 % Ca at the end of recovery (essentially the same composition as untreated fibres). After an additional 12 months of recovery, 44% of the fibres were still present for amosite (Cullen et al., 2000).

Crocidolite
Rats were exposed by inhalation to chrysotile or crocidolite asbestos. The mass concentration was 8 mg/m^3 and the time period was for 5 or 20 days. The latter period was followed by a 20 day post-exposure period. Inhalation of crocidolite resulted in a higher fibre lung retention as compared to the inhalation of chrysotile fibres (BéruBé et al., 1996). Rats inhaled crocidolite at mass concentrations of 3.5 mg/m^3 or 4.5 mg/m^3. The duration was 1 h and recovery periods were 0 h, 2 days, 8 days, 4 weeks, 2 months, or 3 months. A progressive increase in mean fibre length with the time post exposure was observed. No changes were observed in the diameter of crocidolite fibres in the lung. Thus the longitudinal splitting described previously for serpentine fibres was not observed for crocidolite (Roggli et al., 1987). Rats were exposed by nose-only inhalation to crocidolite. The mass concentration of crocidolite was 10 mg/m^3 . The exposure period was 6 h/day

for 5 days. Lung fibre burden was evaluated by use of electron microscopy during a subsequent 1-year period. Only 17% of long crocidolite fibres longer than 20 μm were eliminated. The mean diameter of the crocidolite fibres remained unchanged, whereas the mean length had increased. The latter was likely due to the elimination of shorter fibres. No morphological or chemical changes were observed in crocidolite fibres (Hesterberg et al., 1996).
The number of crocidolite fibres in rats of lungs exposed to 8 mg/m^3 crocidolite 6 h/day, 5 days a week for a total of 20 days, did not decrease substantially over an additional 20-day recovery period (BéruBé et al., 1996).

Tremolite
Rats were exposed to tremolite by inhalation of 11.5 mg/m^3 (100 fibres having a length of at least > 20 μm/cm^3). The exposure duration was 6 h/day for 5 days. It was stated that the exposure technique was optimised to maximise the number of long respirable fibres. Recovery periods were 0, 1, 2, 7 days, 2 weeks, 1 month, 3 months, 6 and 12 months after exposure. Tremolite exposure showed persistence with what was described as essentially an infinite half-time (Bernstein et al., 2005).

Oral exposure

A baboon was administered cumulative doses of 800 mg each of chrysotile and crocidolite asbestos by gavage. Penetration of the gastrointestinal tract and migration to the stomach, heart, spleen, pancreas, and blood was observed (Kaczenski and Hallenbeck, 1984). In one baboon administered chrysotile by gavage, fibres were observed in the urine (Hallenbeck and Patel-Mandlik, 1979).
Rats were administered asbestos via the drinking water at 1.5 or 3 g/L. After 6 and 9 months of chrysotile exposure, mesothelial proliferation and asbestos bodies were observed in the lungs and pleura. At 9 months, asbestos was observed in the spleen with dose-dependency. Mesothelial proliferation was observed in the high dose group at 12 months. The authors of that study concluded that the ingested asbestos traveled from the gastrointestinal system to the lungs, and that this likely occurs via a "*lympho-hematological*" route and that this lead to mesothelial proliferation and ultimately carcinogenicity (Hasanoglu et al., 2008). Cunningham *et al.* found that rats ingesting chrysotile - 1% in the diet for 6 weeks - had elevated levels of fibres in all investigated tissues. The highest levels were observed in the omentum, followed by: brain, lung liver, blood, and kidney (Cunningham et al., 1977).

A gavage study gave data concerning the trans-placental transfer of asbestos in pregnant mice. Pregnant mice were administered two doses each of 50 μg chrysotile. After mating, the mice received two additional doses. The lungs and liver of pups were found to contain 780 chrysotile fibres/g lung and 214 /g liver. Weight gain and mortality was not different from that of pups in a control group (Haque et al., 2001).

Summary

Following inhalation exposure of animals, asbestos was observed in a range of pulmonary structures and cell types (Figure 3) as well as in the lymphatic and vascular compartment. In the lungs of rats, chrysotile has been described to break into smaller fibres, be somewhat bio-soluble and have a considerably lower persistence in comparison to tremolite and crocidolite fibres. Amosite was also reported to have a low clearance. The difference in elimination of the serpentine

chrysotile and the amphibole asbestos types likely reflects that they break up in different ways inside the mammalian body – as illustrated in Figure 2.

Following oral exposure, asbestos was found in a range of organs in baboons and rats including distribution to the rat lung. Trans-placental transfer of asbestos has been demonstrated in rats.

7.1.3. In vitro data

The data on the inhalation exposure of animals to different asbestos types are sufficient to provide a picture on the absorption, distribution, metabolism and excretion (ADME) properties of asbestos. Therefore, the application of in vitro models is not needed.

7.1.4. Toxicokinetic modelling

The data on the inhalation exposure of animals to different asbestos types are sufficient to provide a picture on the ADME properties of asbestos. Therefore, the application of toxicokinetic modelling is not deemed relevant.

7.1.5. Biological monitoring

There is no evidence in the literature that biological monitoring e.g. through urine or blood metabolites is routinely applied; the serum level of mesothelin-related proteins has been proposed as a biological marker of the development of mesothelioma (Robinson et al., 2003).

7.2. Acute toxicity

7.2.1. Human data

In 2009 Afsset reported that no evidence of acute toxicity of asbestos was found (Afsset, 2009). We also found no relevant data in our literature search.

7.2.2. Animal data

We found some relevant data concerning inhalation exposure of short acute duration. These are however mostly focussed on the investigation of cell proliferation, e.g.: (Barry et al., 1983; Chang et al., 1988). In the current document we, in the light of the high number of inhalation studies with asbestos, only shortly describe the most relevant intratracheal instillation studies in the remainder of this section. The reason for this is that inhalation studies are in general of higher priority in hazard assessment than intratracheal instillation studies.

Rats were administered amosite at 0.65 mg/rat, or Libby amphibole at 0.65 or 6.5 mg/rat. Recovery periods were 1 day or 3 months. Amosite at 0.65 mg resulted in higher levels pulmonary injury, inflammation, and fibrotic events as compared to the equal dose of Libby amphibole. Amosite, 0.65 mg/rat, and Libby amphibole, 6.5 mg/rat, resulted in increased cellular permeability and injury, inflammatory enzymes, and iron binding proteins in both bronchoalveolar-lavage (BAL) fluid and lung tissue and lower Messenger-RNA (mRNA) levels of some growth factors. Pathological findings were: thickening of interstitial areas surrounding the alveolar ducts and terminal bronchioles (Padilla-Carlin et al., 2011). Rats were administered Libby amphibole or amosite by intratracheal instillation of 0.15, 0.5, 1.5, or 5 mg/rat. These doses were administered

either as single or multiple doses over 13 weeks. Recovery periods lasted up to 20 months. Libby amphibole resulted in more pronounced neutrophilic inflammation and cellular toxicity as compared to amosite; whereas histopathological changes were similar for the two groups. Mesothelioma and lung carcinomas were observed only in single animals (not statistically significantly) both after exposure to low and high doses of these two asbestos types (Cyphert et al., 2015). Rats were administered amosite by intratracheal instillation at doses ranging between 0.05 and 1.0 mg/rat. Recovery periods were 1, 3, and 7 days. Amosite exposure resulted in increased total protein in BAL fluid at the highest dose for all time points and on day 1 at all doses. These effects were normalised at 7 days of recovery (Ishihara et al., 1999). A study in mice using aspiration exposure to 100 μg crocidolite suggested that a change in the redox status of the lung was associated with acute asbestos induced lung injury (Leonard et al., 2002).

Summary: In summary, some acute effects such as increased proliferation of cells in the airways, increased cytotoxicity of airway cells and acute lung injury have been reported.

7.2.3. In vitro data

Relevant data on genotoxicity are presented in the section of genotoxicity.

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

In addition to cancer, inhalation of asbestos types has also been linked to other pulmonary and pleural conditions. The most important adverse effect besides of cancer is asbestosis, but other conditions described by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) are pleurisy and diffuse pleural fibrosis (Afsset, 2009).

Asbestosis

Asbestosis is a disease specifically occurring after the exposure to asbestos, hence the name. The following section is based on a review article by (Lazarus and Philip, 2011), and an original article by (Roggli et al., 2016). Inhaled asbestos fibres can lead to pulmonary fibrosis, which has a latency of 20-30 years and is often mild, but can progress to diffuse pulmonary fibrosis. Pulmonary fibrosis often begins at the subpleural level at the respiratory bronchioles. As fibrosis progresses, it involves the alveolar ducts, alveolar septa, and terminal bronchioles. Rarely, in advanced cases, so-called honeycombing with cysts and fibrotic walls may occur; and areas of desquamative interstitial pneumonia may also be present. Asbestos fibres are at this stage only detectable with iron stain. The presence of asbestos bodies in the alveoli or interstitium, with pulmonary fibrosis on histology, supports a diagnosis of asbestosis. Frequently, diffuse visceral pleural fibrosis is associated with pulmonary fibrosis. Another change that might be evident is parietal pleural plaques that may or may not be calcified (Lazarus and Philip, 2011; Roggli et al., 2016).

Concerning the amount of asbestos needed to incite asbestosis, Omland *et al.* published a review article in which they wrote that there is an unofficial lower limit for the recognition of asbestosis and that this is at 25 fibre years (1 fibre year = number of years exposed at 1 fibre/cm^3) and that this is similar to the cumulated exposure estimate that increases the risk of lung cancer by a factor 2 (Omland et al., 2018). Concerning studies in which dose response relations were considered,

Huang (Huang, 1990) found an expected asbestosis prevalence of 3% at a cumulated exposure of 43 fibre years and of 1% at 22 fibre years. Hein reported a hazard ration of about 2 at an exposure of 50 fibre years (Hein et al., 2007), and Berrry *et al.* (Berry et al., 1979) concluded that a 1% prevalence was associated with 55 fibre years in cumulated exposure. Stayner *et al.* found no threshold value for asbestos exposure and asbestosis (Stayner et al., 1997). Finkelstein *et al.* described sigmoid dose response curve (with an X-axis unit of "fibres/mL x years^2") in which the 1% prevalence for asbestosis was related to 10 fibre years (Finkelstein, 1982).

Discussion on whether asbestosis could be the critical effect used for hazard assessment

The question is whether these asbestos exposure–response relations warrant that asbestosis constitutes the critical effect for setting a health based OEL. If we for example consider the 10 fibre-years giving a prevalence of 1%, as reported by Finkelstein, then a $1x10^{-5}$ risk would correspond to 0.00025 fibres/cm^3 (10 fibres/cm^3 / 40 years = 0.25 fibres/cm^3 for a risk of $1x10^{-2}$). The $1x10^{-5}$ risk levels calculated by DECOS (DECOS, 2010), and discussed below, are 0.0005 fibres/cm^3 for chrysotile and 0.0001 fibres/cm^3 for amphibole types. Thus the risk of asbestosis could be suggested to be in the range of lung cancer/mesothelioma - used by DECOS - if a linear extrapolation is used. There is some indication of a threshold for asbestosis as described above, but there are also references that describe that a threshold could not be determined (Stayner et al., 1997). At the same time the current working group is of the opinion that the carcinogenic effect of asbestos should be considered not to have a threshold mechanism and therefore linear extrapolation is warranted for this effect. Nevertheless, we cannot totally exclude that asbestosis occurs at exposure levels similar to those inducing carcinogenicity. On the other hand there is not much evidence to support that asbestosis occurs at lower exposures than those inducing carcinogenicity. Thus in the current document we use carcinogenicity as the critical effect but note that asbestosis has been described at similar levels of exposure.

Summary

Asbestosis is a disease of pulmonary fibrosis occurring after exposure to asbestos. We do not assess asbestosis to represent the critical effect. This is based on the likelihood of a threshold mechanism of action – as compared to an absence of threshold in asbestos-induced cancer.

7.3.2. Animal data

7.3.2.1. Inhalation

Inhalation data have been extensively reviewed by the current working group. In summary most inhalation studies have been conducted at a mass concentration of asbestos fibres of about 10 mg/m^3, with some exceptions in the range of 1 to 10 mg/m^3. When considering *non*-cancer endpoints, e.g. fibrosis, pathological lesions or lung function endpoints - these provide lowest observed adverse effect concentrations (LOAECs) and no observed adverse effect concentrations (NOAECs) in the range of 1 to 10 mg/m^3 and these dose descriptors are summarised in Figure 4. Also, the findings in the chronic and subchronic investigations are summarised in the following text sections. To limit the extent of this document the findings of subacute and shorter duration studies are only presented in the graphs in Figure 4. As inhalation data are considered the most relevant data for hazard assessment, no data following intratracheal instillation were included.

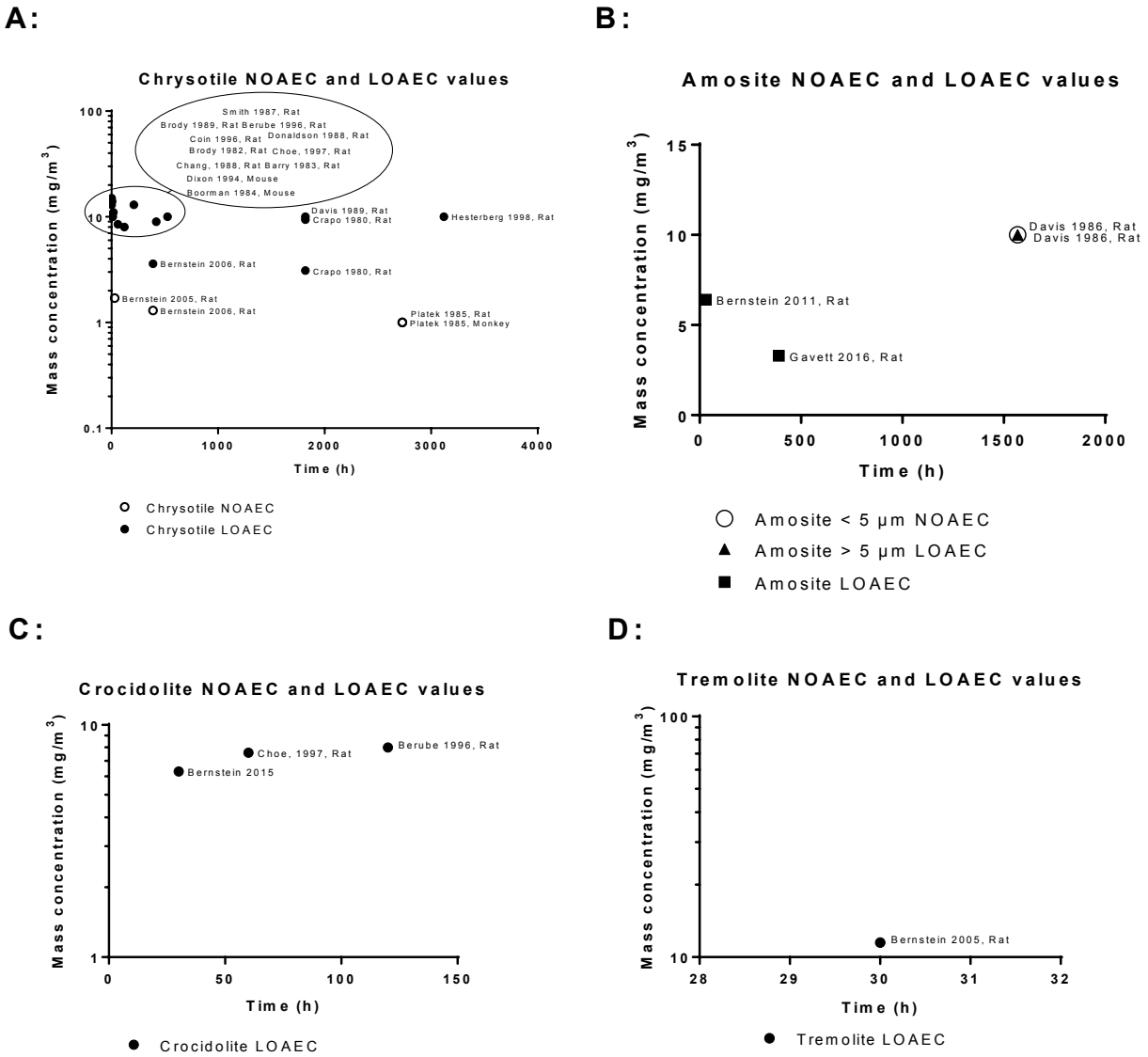


Figure 4. Overview of *non*-cancer endpoint resulting in NOAEC and LOAEC values in animal subchronic and chronic inhalation studies. **A: Chrysotile, B: Amosite, C: Crocidolite, and D: Tremolite.**

Chrysotile Subchronic studies

Rats were exposed by inhalation to chrysotile at a mass concentration of 9 mg/m^3. Exposure to chrysotile for 3 months (420 h) resulted in increased numbers and volume of type II cells in the epithelium. Also an increase in number and cell volume was observed in the interstitial cell population. These latter increases were almost accounted for by changes in interstitial macrophages. Microcalcifications were observed in interstitial macrophages (LOAEC: 9 mg/m^3) (Barry et al., 1983). Rats were exposed to chrysotile by inhalation. The mass concentration was 10.7 mg/m^3. The duration was 6h/day, 5 days/week for 91 days. The animals were killed at 2 to 16

months after cessation of exposure. Exposure to chrysotile was associated with thickened alveolar duct bifurcations associated with aggregates of macrophages. Exposure to chrysotile resulted in microcalcifications and slight pulmonary fibrosis (no NOAEC is set by the current working group as no statistics was applied to the effects) (Oghiso et al., 1984).

Rats were exposed to chrysotile by nose-only inhalation for 5 days/week, 6 h/day for 13 weeks (390 h). The fibre concentration was 76 fibres (having a length of more than 20 μm)/cm^3 (equal to 3413 total fibres/cm^3 or 536 WHO fibres/cm^3) (1.3 mg/m^3) or 207 (having a length of more than 20 μm)/cm^3 (equal to 8941 total fibres/cm^3 or 1429 WHO fibres/cm^3) (3.6 mg/m^3). The exposure period was followed by a recovery periods of 0, 50 or 92 days. Inhalation of chrysotile resulted in increased lung weights at both mass concentrations, however this difference was normalised at 92 days of recovery. Concerning the number of neutrophils, lactatdehydrogenase (LDH) and total protein in BAL, these were increased at the end of the exposure to high dose. And for LDH and total protein also at both dose level at 92 days of recovery. Slight fibrosis in was reported in the lung at the highest dose, but not at the lowest (no statistics applied) ($NOAEC_{neutrophils/fibrosis}$: 1.3 mg/m^3) (Bernstein et al., 2006).

Chrysotile chronic studies

Monkeys and rats inhaled short chrysotile fibres at 1 mg/m^3, 7 hr/day, 5 days/week for 18 months (2730 h). In monkeys, lung biopsies were recovered 10 months after end of exposure. No fibrosis was observed (NOAEC monkey 1 mg/m^3). In rats exposure to the fibres did not result in fibrosis. Also no other lesions were detected by gross and histopathologic examination (NOAEC rat 1 mg/m^3) (Platek et al., 1985). Rats were exposed by inhalation to chrysotile fibres (National Institute of Environmental Health Sciences (NIEHS) short-range and NIEHS intermediate-range fibres). The mass concentration was for short fibres 3.1 mg/m^3 (192 x 10^8 fibres/m^3) and for intermediate fibres 9.4 mg/m^3 (13 x 10^8 fibres/m^3). The duration was 1 h, 7 h, 5 days, 3 months and 12 months (7 h /day, 5 days/week) (up to 1820 h). Increases in the volume of the alveolar epithelium, the interstitium and in alveolar macrophages were observed at 3 months of exposure to either type of chrysotile fibre. More pronounced lung pathology in the alveolar epithelium and the interstitium was observed after 12 months of exposure to intermediate-range chrysotile fibres. Decreases in total lung capacity and in vital capacity were observed at 12 months of exposure by both particle lengths, although more pronounced after exposure to the intermediate-range fibres (LOAEC short 3.1 mg/m^3, LOAEC intermediate 9.4 mg/m^3) (Crapo et al., 1980).

Amosite subchronic studies

Rats were exposed by nose-only inhalation to amosite (or Libby amphibole) 6h/day 5 days/week for a total of 10 days (mass concentration: Libby amphibole: 0.5, 3.5, or 25.0 mg/m^3 and amosite asbestos: 3.5 mg/m^3). Or alternatively exposure to Libby amphibole: 1.0, 3.3, or 10.0 mg/m^3 or amosite at 3.3 mg/m^3 for 6 h/day, 5 days/week for 13 weeks. Investigations were done at 1 day, 1, 3, and 18 months post exposure. Lung fibre burdens investigated at 13 weeks of exposure declined over the 18 month post exposure period. Libby amphibole fibres had a mean length of 3.7 μm with 1% being longer than 20 μm. Increased lung inflammation, fibrosis, bronchiolar epithelial cell proliferation and hyperplasia, as well as increased inflammatory cytokine gene expression were observed with 25.0 mg/m^3 Libby amphibole exposure for 10 days. Markers of acute lung injury and inflammation were increased by 3.5 mg/m^3 Libby amphibole as compared to amosite exposure.

BAL markers of inflammation as well as lung associated cytokines were increased by both fibres with exposure periods ranging from 1 day to 3 months. Concerning pathological changes, alveolar inflammation was observed at all doses with both asbestos types, while interstitial fibrosis was only found at 25 mg/m^3 Libby amphibole. Alveolar epithelial hyperplasia and bronchiolar/alveolar adenoma or carcinoma were observed to show *positive trends* in Libby amphibole exposed animals (Amosite $LOAEC_{neutrophils}$: 3.3 mg/m^3) (Gavett et al., 2016).

Crocidolite subchronic studies
Rats were exposed to crocidolite (amphibole) or chrysotile (serpentine) by inhalation. The mass concentration was for crocidolite 11.2 mg/m^3 and for chrysotile 10.7 mg/m^3. The duration was 6h/day, 5 days/week for 91 days (estimated to be 390 h). The animals were killed at 2 to 16 months after cessation of exposure. Both materials were after inhalation associated with thickened alveolar duct bifurcations associated with aggregates of macrophages. Exposure to crocidolite was also associated with subpleural collections of alveolar macrophages and lymphocytes. Exposure to chrysotile resulted in microcalcifications. Slight pulmonary fibrosis was observed following exposure to either of the materials (no NOAEC set because no statistics was applied to the effects) (Oghiso et al., 1984).

Crocidolite chronic studies
Rats were exposed to crocidolite asbestos. The mass concentration was 10 mg/m^3 6 h/day for 5 days/week and the period of exposure was in the range of 1 day to 12 months (up to 1560 h). Exposure to crocidolite was associated with an increase in type II cells in the lung at day 1 and the number of interstitial and alveolar macrophages were increased after 3 months. Forty-nine percent of the alveolar macrophages contained particles after 1 day and 92 percent contained particles after 12 months. Also the number of particles in each cell was increased with increased time period. The interstitium of airway bifurcations were the initial sites where cell damage and collagen deposition was observed. The finding of weak fibrosis was by the current working group considered too weak to set a NOAEC/LOAEC (Johnson, 1987).

Summary
In the majority of the assessed studies, the tested aerosol concentrations were in the range of 1 to 10 mg/m^3, with most studies testing at the highest level. The NOAEC and LOAEC values are all located at these levels, although - for chrysotile - there seems to be a level at 1 mg/m^3 where there is generally no toxicological effect of the asbestos exposure. Concerning the nature of the effects, these were of pathological findings including for example fibrosis and hyperplasia; but also of inflammatory effects were observed - including altered bronchoalveolar lavage cellularity.

7.3.2.2. Oral exposure
We only identified one relevant study: Rats were administered chrysotile or a mixture of chrysotile/crocidolite (75%/25%) in a palm oil vehicle. The duration was 24 months and the doses were 10, 60 and 360 mg/day. Both normal diet and a palm oil control groups were included. A recovery period of 6 months was included. No toxic effects (including no carcinogenic) were observed (Truhaut and Chouroulinkov, 1989).

7.3.2.3. Dermal exposure

We identified 26 references. Of these, there was one relevant study on the carcinogenicity of asbestos on the skin of mice (Roe et al., 1966). This study is described in the section of carcinogenicity.

7.3.3. In vitro data

No relevant data upon repeated exposures were identified.

7.4. Irritancy and corrosivity

7.4.1. Human data

Asbestos fibres seem not to have irritating or corrosive effects on the skin. No relevant data were identified on asbestos and corrosion or on asbestos and irritation.

7.4.2. Animal data

7.4.2.1. Skin

No relevant data were identified.

7.4.3. In vitro data

No relevant data were identified.

7.5. Sensitisation

The potential is low as demonstrated by a lack of literature on the subject.

7.5.1. Human data

No specific data on sensitisation were identified.

7.5.2. Animal data

No specific data on sensitisation were identified.

7.5.3. In vitro data

No specific data on sensitisation were identified.

7.6. Genotoxicity

A key question when making suggestions for health-based OELs is: whether or not a compound's genotoxic effect occurs by a mechanism of action that involves a threshold? In the end of each section in 7.6 we include a paragraph that summarises the evidence for and against a threshold effect.

When determining levels of exposure that are safe to humans it is important to know whether the carcinogenic mechanism of action involves a threshold effect. In the case of absence of thresholds as is for example the case for mutagenic substances that form DNA-adducts) (such as vinyl chloride), a linear extrapolation (the Linear no-threshold model (LNT)) model is applied to calculate levels that are relatively safe for humans (Bolt et al., 2004). In contrast if a threshold is present as has been suggested for 2,3,7,8-Tetrachlorodibenzo-p-dioxin, then a no-observed-

adverse-effect level (NOAEL) can be adjusted with assessment factors to set an OEL (Bolt et al., 2004).

In the current document the current working group have reviewed the evidence for and against a threshold effect of asbestos-induced carcinogenicity. And discuss the placement into the concept of non-threshold effect with numerical risk assessment or of a threshold as defined by (ECHA, 2016) (The concept is presented in Figure 5). To do this, we retrieved the literature on asbestos and mutagenicity/genotoxicity and assessed whether the observed effects could be classified as mutagenic (DNA reactive) or genotoxic - according to the categorisation presented in Figure 5. The evidence was then collectively evaluated to determine whether asbestos fibres should be hazard assessed using a linear non-threshold approach or if they can be placed into the practical/apparent or the perfect/statistical categories to justify the use of assessment factors for threshold effects in the hazard evaluation of asbestos.

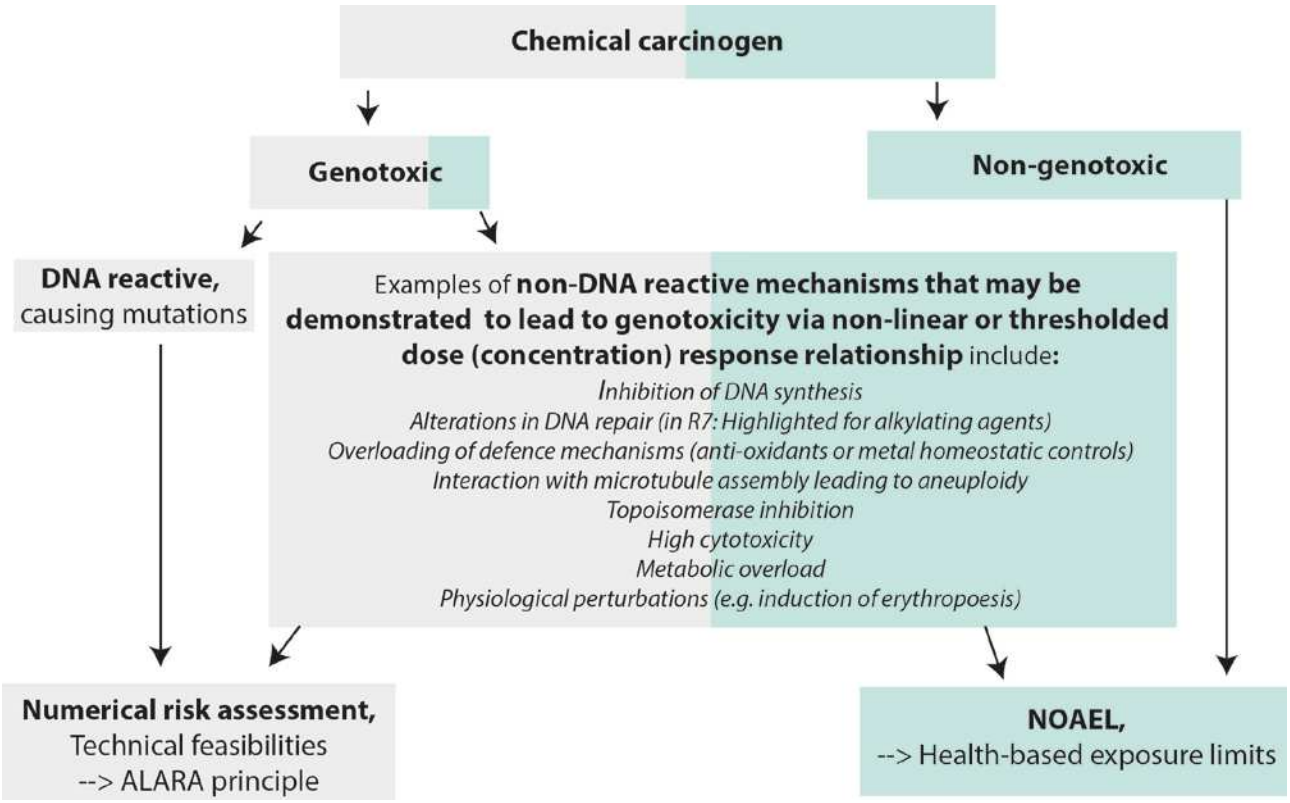


Figure 5. The concept of a non-threshold or threshold mechanisms as described in the REACH R.7a guidance. The numerical risk assessment designation used by ECHA corresponds to a non-threshold assessment, whereas the NOAEL designation corresponds to the presence of a threshold as low as reasonable achievable (ALARA). The diagram is made by Niels Hadrup based on text in (ECHA, 2016).

7.6.1. Human data

There was no relevant data

7.6.2. Animal data

Gene mutations in mammals (transgenic assays)

Amosite Big blue rats (containing a *lacZ* reporter gene) were exposed to amosite by intratracheal instillation of with either single doses of 1 or 2 mg or with 4 doses per week of each of 2 mg/rat. Recovery periods were 4 and 16 weeks, After 16 weeks of recovery, the mutation frequency was increased in lung at both the single dose of 2 mg and at the four times 2 mg dosage. There was no effect after the shorter 4 week of recovery period. In wild type rats, amosite in the same dosage regimen induced DNA strand breaks in macrophages and type II cells as measured in the comet assay. Micronuclei were increased in alveolar macrophages at 16 weeks but not after the shorter 4 week recovery period, there were no effects on this endpoint in lung epithelial cells (Topinka et al., 2004).

Crocidolite Mice transgenic for the *lacI* reporter gene were exposed to crocidolite by nose-only inhalation to 5.75 mg/m^3 for 6 hr/day for 5 days. The experiment was terminated 1, 4, and 12 weeks after the beginning of exposure (Recover periods ~0, 3 and 11 weeks). After 4 weeks, the mutant frequency was increased by crocidolite. However this effect was not seen at 1 or 12 weeks. *The mutation spectrum of control lung DNA and exposed lung DNA was similar,* and the authors of that study suggested *the possible involvement of a DNA repair decrease in crocidolite-treated animals* (Rihn et al., 2000). The current working group notes that if the mutation frequency is only increased by 15%, then only 15/115=13% of the mutations can be expected to be caused by asbestos exposure, and thus, the mutation spectrum will appear similar to the background spectrum. Crocidolite was administered to mice by pharyngeal aspiration and one year later K-ras mutations were evaluated. Crocidolite at 120 μg, in contrast to single-walled carbon nanotubes and carbon fibres, did not increase the incidence of K-ras oncogene mutations in the lung. None of the 3 fibre types increased the lung tumour incidence (Shvedova et al., 2014).

Rats were dosed with crocidolite by intraperitoneal injection of 2 mg. DNA fingerprint analysis of induced tumours showed a mutation frequency of 14.8%; in comparison benzo[*a*]pyrene and nickel powder induced frequencies of 18.2 and 40.9%, respectively. A negative control of NaCl injection was included in the study. In this control group only a few peritoneal tumours were detected and these tumours exhibited no mutations in the fingerprint assay (Kociok et al., 1999). *LacI* transgenic rats were exposed to crocidolite by intraperitoneal injection. The mutation frequency was investigated in omenta – representing a relevant target tissue for mesothelioma carcinogenesis. The doses were 2 and 5 mg, and the recovery periods were 4, 12 or 24 weeks. Crocidolite at 5 mg increased the mutation frequency at 12 and 24 weeks of recovery. There was a difference in mutation types between crocidolite-induced mutations and spontaneous mutations. Based on this the authors suggested that the molecular mechanism of crocidolite differed from the generation of spontaneous mutations. The most frequent crocidolite induced mutation (29%) was G to T transversions. In addition in rats given 1 or 2 mg of crocidolite the levels of 8-Oxo-2'-deoxyguanosine in were increased in omenta (Unfried et al., 2002).

Mammalian cytogenic assays

Chrysotile was investigated in rhesus monkeys, mice. Oral dosage of 100 or 500 mg/kg bw did not increase the level of chromosome aberrations in the monkeys. Oral or intraperitoneal dosing of 0.4 or 400 mg/kg bw of chrysotile was not associated with the induction of micronuclei formation in

bone marrow cells in mice (Lavappa et al., 1975). Mice were intraperitoneally injected with 50 mg/kg /bw) of chrysotile and peritoneal cells were investigated and chromosome aberrations were found to be increased (Durnev et al., 1993).

Crocidolite fibres were given to rats by gavage at 50 mg/kg bw in the presence or absence of various concentrations of benzo[*a*]pyrene (0.25 to 2.5 μg/mL). Ames test was performed on concentrated urine or serum samples of the treated animals: No effects were observed in this assay. Formation of micronuclei and sister chromatid exchanges was studied in the bone marrow of the rats, There was no effect of crocidolite alone, but effect on micronuclei in combination with benzo[*a*]pyrene at 1 μg/mL and at in sister chromatid exchange in combination with all levels of benzo[*a*]pyrene (Varga et al., 1996b).

Anthophyllite was orally administered to rats at 50 mg/kg (bw) in the presence or absence of absorption of benzo[a]pyrene as an organic pollutant (0.25 to 2.5 μg/mL). In bone marrow samples taken 24 h later, The combined exposure increased the sister chromatid exchange frequencies (benzo[*a*]pyrene at 0.5, 1 and 2.5 μg/mL), something that was not seen for the fibre alone (Varga et al., 1996a).

7.6.3. In vitro

We note that as asbestos are fibres, the value of in vitro investigations is questionable. This is because fibres penetrate the tissues and cells inside the mammalian body - by a physical process; and this mode of bio-distribution is not readily mimicked in vitro. Therefore we have not included in vitro data on this endpoint in our assessment.

7.6.4. Conclusion on whether asbestos should be evaluated by non-threshold mechanisms

There is some *in vivo* evidence that asbestos have cytogenic effects in the form of increased frequency of chromosome aberrations and sister chromatid exchanges. Thus, a genotoxic effect at the chromosome level is suggested. Furthermore, a number of studies have shown that asbestos fibres have effects in mutagenic assays. Amosite induced mutations in an *in vivo* mammalian mutagenicity assays, in one positive study. For crocidolite there are three positive studies and one negative study. Overall, there is *in vivo* evidence for mutagenic effects of asbestos fibres.

The current working group recommends to comply with ECHA in REACH R8 (ECHA, 2012) states the following: "*Unless a threshold mechanism of action is clearly demonstrated, it is generally considered prudent to assume that thresholds cannot be identified in relation to mutagenicity, genotoxicity, and genotoxic carcinogenicity, although a dose-response relationship may be shown under experimental conditions*". The decision tree is shown in fig 6. Based on this 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.

Notably our assessment is in line with both the EU (EU, 2009) and Afsset (Afsset, 2009) who considers asbestos not to have a lower threshold. In the EU council directive 2009/148/EC it is stated that: "*Although current scientific knowledge is not such that a level can be established below which risks to health cease to exist, a reduction in exposure to asbestos will nonetheless reduce the risk of developing asbestos related disease*"; and: "*Even though it has not yet been possible to identify the exposure threshold below which asbestos does not involve a cancer risk, occupational exposure of workers to asbestos should be reduced to a minimum*".

7.7. Carcinogenicity

7.7.1. Human data (covering the period up to 2012 - based on IARC 2012)

All asbestos types are classified by IARC as having a carcinogenic potential for humans. There is a classification of Category 1A in the European Union and Group 1 by the International Agency for Research on Cancer (IARC, 2012). And asbestos was previously evaluated in 1987 and also classified as Group 1 then (IARC, 1987). This section is based on (IARC, 2012).

There is a large body of epidemiological data pointing towards that asbestos induces carcinogenicity (IARC, 2012). The main cancer forms associated with the exposure to asbestos are lung cancer and mesothelioma. The latter primarily occurs in the pleura of the lungs, but it also occurs in the peritoneum of the abdomen and in the pericardium of the heart. Notably there is a latency period of 20-40 years in the development of these conditions. Lung cancer (broncho-pulmonary cancer) is the first cause of mortality in asbestos exposed humans. The risk factor of asbestos induced lung cancer is increased by simultaneous exposure to tobacco smoke. This synergetic effect of tobacco smoke is not observed for mesothelioma. Concerning mesothelioma, asbestos is the only proven risk factor although other risk factors have also been suggested including infection with certain viruses and the exposure to ionising radiation. There is evidence from epidemiological studies that exposure to the serpentine asbestos, chrysotile, is less potent in the development of these cancers, in particular for mesothelioma, as compared to the amphibole asbestos types. There is however a debate on whether this is the case lung cancer.

Based on IARC (IARC, 2012) the following cancers are described in the current section:

- Cancer of the lung
- Pleural and peritoneal mesothelioma
- Gastrointestinal tract cancers
- Cancer of the larynx
- Cancer of the ovary

These cancers form subdivisions of the next sections containing cohort- and case-control studies

The IARC evaluation from 2012 (IARC, 2012) gives an informative description of the data pointing towards the different cancer forms. The following sections on cohort studies and case-control studies are written based on this IARC 2012 evaluation.

Lung cancer

In IARC (IARC, 2012) it is described that the first reported signs of cancer of the lung induced by asbestos in worker were reported already in 1935 (Gloyne, 1935; Lynch and Smith, 1935); and the first cohort study to demonstrate excess cancer of the lungs among asbestos workers was a study in textile workers published in 1955 (Doll, 1993). After that numerous cohort and case-control studies were published demonstrating an association between cancer of the lungs and exposure to asbestos (IARC, 2012).

IARC notes that still in 2012 (publication year of the IARC report), there were still substantial controversies on how the risk might vary by exposure to different fibre types and sizes, and

whether there is a risk at low levels of exposure (i.e. environmental exposure). And that a particular controversy was whether chrysotile asbestos is less potent for the induction of cancer of the lungs as compared to the amphibole asbestos types. This is what has been described as the "amphibole hypothesis". One of the reasons for this is a lower biopersistence of chrysotile as compared to the amphiboles. But it is noted by IARC that a lower biopersistence of chrysotile does not necessarily imply that it would be less potent for cancer of the lungs. IARC notes that a meta-analysis by (Lash et al., 1997) based on findings in 15 cohort studies with quantitative information on the relation between asbestos exposure and the risk of cancer of the lungs, did not find evidence that differences in fibre type explained the heterogeneity of the data (IARC, 2012; Lash et al., 1997).

Another meta-analysis was conducted by (Hodgson and Darnton, 2000) and was based on 17 cohort studies. Substantial heterogeneity in the data was also found in this study. This heterogeneity was largely attributable to differences in the findings from the studies of chrysotile miners and millers in Quebec (McDonald et al., 1983) and asbestos textile workers in South Carolina (Dement and Brown, 1994; Hein et al., 2007). No definite explanation for these differences was found, although the co-exposure to mineral oils in the South Carolina textile plant was proposed as an explanation. Increased fibre length in the textile industries was also suggested as an explanation, as compared to exposure to shorter fibres of the miners and millers in Quebec. Ratios between lung cancer risk for chrysotile and the amphiboles are in the range of 1:2 to 1:50 depending on which studies that are excluded.

A meta-analysis was published by Berman and Crump in 2008 (Berman and Crump, 2008a), and lung cancer risk potency factors derived in their analyses were specific for both fibre types (chrysotile *vs.* amphiboles) and fibre size (length and width). For this fibres there was evidence that chrysotile fibres were less potent than amphiboles. Exclusion of the South Carolina cohort from the analysis resulted in in a highly significant result that the potency was greater for amphiboles than for chrysotiles; exclusion of the Quebec study resulted in that there was no evidence of differences in-between the fibre types. Considering fibre size, there was only weak evidence in Berman and Crump that long fibres (>10 μm) were more potent than short fibres (5 μm<length<10 μm) in models using all widths (p=0.07). It is noted by IARC that there was a lack of size specific data.

Stayner *et al.* (Stayner et al., 2008) analysed the South Carolina asbestos textile cohort using size information established from reanalysis of archived air samples by (Dement et al., 2008). Long fibres (>10 μm) and thin ones (<0.25 μm) were found to be the strongest predictors of lung cancer in that study. Loomis et al (Loomis et al., 2010) did a retrospective cohort study in workers from 4 plants in North Carolina that had never been studies before. The workers in these plants were primarily exposed to asbestos that was imported from Quebec. IARC notes that a small amount of amosite was used in an operation at one of the plants. Overall and standardised mortality ratio (SMR) of cancer of the lung was 1.96 (95% confidence interval (CI): 1.73 to 2.20) noted by IARC to be similar to that reported in the South Carolina study (Hein et al., 2007), although the slope for the dose-response curve was considerably lower than that reported for the South Carolina cohort study.

Concerning environmental exposures, IARC reports that there is evidence for an association between cancer of the lungs and environmental exposures in New Caledonia to field dust containing tremolite and the use of a so-called whitewash ("po") containing tremolite (Luce et al., 2000). Also a positive association with heavy residential exposure to asbestos was reported in a

lung cancer case-control study from the crocidolite and amosite mining area of the Northern Province of South Africa (Mzileni et al., 1999). Concerning negative data, there was no increase in lung cancer of women in the Quebec mining regions as compared to women from other areas of Canada (Camus et al., 1998).

IARC also discusses that there is emerging evidence that non-commercial amphibole fibres that are asbestiform have a carcinogenic potential. These are not technically "asbestos". Amphibole fibres that contaminated vermiculite mined in Libby Montana USA. These were originally characterised as from the tremolite-actinolite series, but have later been described by the US Geological Society as approximately 84% Winchite, 11% Richterite, and 6% tremolite. For these fibres there was an increased SMR for all cancers as well as lung cancer (Sullivan, 2007).

Mesothelioma

According to IARC the first reports on asbestos exposure and mesothelioma was by (WAGNER et al., 1960). Here an outbreak of mesothelioma occurred in a crocidolite mining region of South Africa 23 out of 33 of the cases had worked in the mines but the remaining 10 had no history of occupational exposure to crocidolite. A large number of subsequent studied have reported excess mesothelioma in both cohort and case-control studies (IARC, 2012).

Concerning fibre types, all types have been described to cause mesothelioma, but there is evidence that chrysotile is less potent than the amphibole types. This was found in cohort studies of chrysotile exposed miners and millers in Quebec (Liddell et al., 1997) and in the South Carolina textile workers who were predominantly exposed to chrysotile asbestos from Quebec (Hein et al., 2007). IARC notes that the fact that chrysotile from Quebec is contaminated with a small amount (<1%) of the amphibole tremolite, however, should be taken into account when interpreting these data. It was found that there was an association between mesothelioma and asbestos in an area that had higher tremolite concentrations in the asbestos, and that this association was not found in a region where the amount of tremolite was lower (McDonald et al., 1997). However this difference could also be explained in differences in the sizes of the workforce at the two sites (Bégin et al., 1992), and in a separate analysis of the workers at mines and mills in this area that was no difference in exposure-relationship for asbestos and mesothelioma in the two mining areas (McDonald and McDonald, 1995). In case-control study for mesothelioma in South Africa there was a an association with exposures to crocidolite and amosite, whereas no cases were found to have been exclusively exposed to chrysotile (Rees et al., 1999). One explanation for this could be that there is only little contamination of chrysotile with tremolite – in South Africa (Rees et al., 1992), or that chrysotile mining began later and production levels were lower in South Africa, and that in Zimbabwe cases of mesothelioma was reported from chrysotile asbestos not contaminated with tremolite (Cullen and Baloyi, 1991). Excess mortality from mesothelioma was reported in miners and millers from a chrysotile mine in Balangero, Italy that was reported to not be contaminated with amphibole (Piolatto et al., 1990).

Hodgson and Darnton studied mesothelioma deaths and estimated a ratio of the potency for mesothelioma to be 1:100:500 for chrysotile, amosite and crocidolite, respectively (Hodgson and Darnton, 2000). A meta-analysis was conducted by (Berman and Crump, 2008b, 2008a) a hypothesis that chrysotile and amphibole types were equipotent was strongly rejected. And they could not reject a hypothesis that the relative potency of chrysotile was zero, and found that the best estimates for the relative potency of chrysotile ranged from zero to about 1/200th that of

amphibole asbestos. However, IARC notes that there is a high degree of uncertainty concerning the accuracy of these relative potency estimates from Berman and Crump.

IARC reported two studies not included in the previously described meta-analyses. The first was in a cohort in North Carolina (Loomis et al., 2010). The workers were predominantly exposed to chrysotile imported from Quebec. They had a SMR for mesothelioma of 10.9 (95% CIl: 3.0 to 28.0); and for pleural cancer the SMR was 12.4 (95 CI: 3.4 to 31.8). In addition, Stayner *et al.* estimated that the percentage of deaths per unit of fibre exposed was 0.0058% per fibre-year/mL (Stayner et al., 1996). Whereas, Hodgson and Darnton described previously estimated 0.0010% per fibre-years/mL for cohorts exposed to chrysotile. In an additional study concerning Balangero in Italy, an area in which the mined chrysotile is reported to be free of tremolite and other amphiboles, six cases of mesothelioma were identified among blue-collar miners. Additional cases of mesothelioma were identified among white-collar miners (3 cases), workers in the mine hired by subcontractors (5 cases) and from non-occupational exposures or exposures to re-used tailings (10 cases) (Piolatto et al., 1990).

Concerning fibre sizes, There is only weak evidence for an effect of fibre size on mesothelioma in humans (Lippmann, 1990).

Concerning environmental exposures, Excess mesothelioma has been reported in: villages in Turkey exposed to erionite that was used to whitewash their homes (Baris et al., 1987), in people living near crocidolite mining regions in South Africa and Western Australia (Wagner and Pooley, 1986), among people residing in areas of tremolite contamination in Cyprus (McConnochie et al., 1987) and New Caledonia (Luce et al., 2000) and after non-occupational exposures in Europe (Magnani et al., 2000), Italy (Magnani et al., 2001) and California (Pan et al., 2005). Also, mesothelioma has been reported to occur among household members of families of asbestos workers (Anderson et al., 1976; Ferrante et al., 2007).

Concerning non-commercial fibres, like for lung cancer there are positive findings for amphibole fibres that contaminated vermiculite mine in Libby Montana, U.S. The SMR for mesothelioma was 14.1 (95% CI: 1.8 to 54.4) and the SMR for pleural cancer was 23.3 (95% CI: 6.3 to 59.5) (McDonald et al., 2004). Also the exposure to fluoro-edenite a fibre similar in morphology and composition to the tremolite actinolite series has been reported to be associated to mesotheliomas (IARC, 2012).

Other cancer sites

IARC notes that the literature on the association of asbestos and other forms of cancer is sparse in comparison to that for lung cancer and mesothelioma. IARC describes cohort studies and case-control studies investigating the associations between exposure to asbestos and the following cancers (IARC, 2012):

a) Cancer of the pharynx
b) Cancer of the larynx
c) Cancer of the oesophagus
d) Cancer of the stomach
e) Cancer of the colorectum
f) Cancer of the ovary

Concerning a) to e), IARC bases its text on a report published by the Institute of Medicine IOM (IOM, 2006). Concerning f) cancer of the ovary, IARC has gathered the data themselves. After a section on each of these cancers IARC has a "Synthesis chapter". In the current document we base the text on this particular "Synthesis chapter".

IARC wrote that a causal association between exposure to asbestos and cancer of the larynx was clearly established but that with the current data there is insufficient information to discern whether any differences exist among fibre types. The IARC working groups noted that a causal association between exposure to asbestos and cancer of the ovary was clearly established. The IARC working group noted a positive association between exposure to asbestos and cancer of the pharynx. The IARC working group noted a positive association between the exposure to asbestos and cancer of the stomach. The IARC working group noted a positive association between the exposure to asbestos and cancer of the colorectum (IARC, 2012).

Summary

There is evidence from studies on humans that asbestos causes cancer of the lung, pleural and peritoneal mesothelioma, gastrointestinal-tract cancers, cancer of the larynx, and cancer of the ovary. Concerning risk levels as function of exposure we discuss this in section 7.7.4. – the section of carcinogenic risk assessment.

7.7.2. Human data after IARC 2012

The IARC monograph was published in 2012 (IARC, 2012), the Afsset report was published in 2009 (Afsset, 2009) and the DECOS report in 2010. Therefore we reviewed the literature published during the period of 2008 to 2019. This review includes epidemiological studies of asbestos exposure and the induction of lung cancer/mesothelioma. In reviewing the identified articles we focussed on studies that provide dose-response estimates. These are presented in detail (the next section), whereas other studies are only shortly mentioned.

Studies in which exposure levels were addressed

A study by Van der Bij *et al.* was identified (van der Bij et al., 2013). This study is presented in section 7.7.4. the section: "Carcinogenic risk assessment".

Deng *et al.* and Courtice *et al.* in two separate articles evaluated the same cohort of Chinese workers that had been exposed to chrysotile at a textile factory (Courtice et al., 2016; Deng et al., 2012). Deng *et al.* in 2012 had 586 workers in the cohort. The workers were followed from 1972 to 2006. Air sample measurements from the workshops were used to convert dust concentrations to fibre concentrations. The estimated asbestos fibre concentration in the study factory was 13.8 fibres/mL. Individual cumulative asbestos exposure was estimated as the product of fibre concentrations and duration of employment in each job and expressed as fibre-years/mL. The vital status of cohort members was followed annually. Poisson regression analysis was applied to fit log-linear, log-quadratic, power, additive relative risk (RR) and categorical models to estimate exposure response relationships between cumulative fibre exposure and mortality from lung cancer and asbestosis. Out of 226 deaths over the 35-year follow-up, 51 were from lung cancer and 37 from asbestosis. A significant exposure-response relation with either lung cancer or asbestosis was observed. A power model with lagged 10 years was found to be the best model of those

evaluated for both lung cancer and asbestosis (Deng et al., 2012). The current working group notes that comparison between the risk obtained in this article and those of the reports by DECOS and Afsset described later in this report is difficult. Difficulties to comparison to the results on life-time cancer risk in the DECOS and Afsset reports stems from 1) difficulty to estimate the life time risk from "per 100 person-years"; and 2) no reporting in the Deng article of lung cancer risk in a comparable control population.

The cohort was reinvestigated in 2016 by Courtice *et al.*, however, in this study no lung cancer risk base level was given. Only the hazard ratio was reported and found to be increased for both lung cancer and asbestosis (Courtice et al., 2016).

Larson *et al.* conducted an exposure-response study to obtain estimates of the hazard of asbestos-related mortality association with cumulative asbestos exposure. The study cohort was the so-called vermiculite worker cohort reconstructed by the Agency for Toxic Substances and Disease Registry (ATSDR). The number of workers was 1862; the workers were exposed to Libby amphibole. Historical air sampling data were used to estimate the 8-hour TWA fibre exposure for all areas of the vermiculite operation for various time periods in the company's history. The proportion of each day spent at each location was calculated for each job title, and an 8-hour TWA exposure was estimated for each job at a given time. Cumulative fibre exposures for each job that a worker held was estimated by weighting the 8-hour TWA exposure for a given job held by the worker by length of time spent at that job. Finally, lifetime cumulative fibre exposures for each worker was obtained by summing the cumulative fibre exposures for each job that worker held. The SMR of mesothelioma was 94.8 (95% CI: 57.0–148.0); of Malignant neoplasms of the bronchus or lung: 1.6 (95% CI: 1.3–2.0) and of asbestosis: 142.8 (95% CI: 111.1–180.8). The estimated RR was given for certain categories of exposure levels (below 1.4; 1.4 to 8.6; 8.6 to 44; and above 44 fibres/mL-year) demonstrating dose-responsiveness for mesothelioma, asbestosis and lung cancer (data not included here), but no dose response curve was established (Larson et al., 2010). Due to the use of exposure categories a calculation into extra cancer risk, for comparison to the DECOS and Afsset reports (described later in this report), is not readily done.

Wang *et al.* studied the relation between mortality from lung cancer and other selected causes to asbestos exposure levels. A cohort of 1,539 male workers from a chrysotile mine in China was followed for 26 years. Data on vital status, occupation and smoking were collected from the mine records and individual contacts. Causes and dates of death were further verified from the local death registry. Individual cumulative fibre exposures (fibre-years/mL) were estimated based on converted dust measurements and working years at specific workshops. SMRs for lung cancer, gastrointestinal cancer, all cancers and non-malignant respiratory diseases stratified by employment years, estimated cumulative fibre exposure, and smoking were calculated. Poisson models were fitted to determine exposure-response relation between estimated fibre exposures and cause-specific mortality, adjusting for age and smoking. In conclusion there were clear exposure-response relationships in this cohort, which imply a causal link between chrysotile asbestos exposure and lung cancer and non-malignant respiratory diseases, and possibly to gastrointestinal cancer, at least for smokers (Wang et al., 2013).

Data on asbestos environmental concentrations in Thetford Mines, a mining city in Quebec, Canada, provided an opportunity to undertake a prospective cancer risk assessment in the general population exposed to these concentrations. Using an updated Berman and Crump dose-response model for asbestos exposure, Bourgault *et al.* selected population-specific potency factors for lung

cancer and mesothelioma(K_L and K_M values[14]), and these were multiplied by a factor of 4.2 to account for the difference in exposure duration between workers (40 h/week) and the general population (168 h/week). These factors were evaluated on the basis of population-specific cancer data attributed to the studied area's past environmental levels of asbestos. Also employed were more recent population-specific mortality data along with the validated potency factors to generate corresponding inhalation unit risks. These unit risks were then combined with recent environmental measurements (range in outdoor air: 0.0015 to 0.056 fibres/mL; range in indoor air: 0.00055 to 0.01) made in the mining town to calculate estimated lifetime risk of asbestos-induced lung cancer and mesothelioma. Depending on the chosen potency factors, the lifetime mortality risks varied between 0.7 and 2.6 per 100,000 for lung cancer and between 0.7 and 2.3 per 100,000 for mesothelioma. In conclusion, the estimated lifetime cancer risk for both cancers combined – for the general population - was close to Health Canada's threshold for "negligible" lifetime cancer risks (i.e. 1:100 000) (Bourgault et al., 2014).

Other studies

A number of studies support that asbestos exposure is associated with lung cancer (Boffetta et al., 2019; Cole et al., 2013; Elliott et al., 2012; Ferrante et al., 2017; Hamra et al., 2017, 2014; Järvholm and Aström, 2014; Ngamwong et al., 2015; Offermans et al., 2014a; Villeneuve et al., 2012; Wu et al., 2015). And a number of studies support the association with mesothelioma (Boffetta et al., 2019; Ferrante et al., 2017, 2016; Lacourt et al., 2014; Langhoff et al., 2014; Markowitz et al., 2013; Oddone et al., 2017; Offermans et al., 2014a; Pira et al., 2017; Plato et al., 2016; Reid et al., 2014; Van den Borre and Deboosere, 2014). And the association between asbestos exposure and mortality (Repp et al., 2015); and the association of asbestos exposure with gastrointestinal cancer (Fortunato and Rushton, 2015; Li et al., 2016; Offermans et al., 2014b; Peng et al., 2015; Wu et al., 2015); laryngal cancer (Offermans et al., 2014a); and ovary cancer (Ferrante et al., 2017)

Summary

The literature from the period after the 2012 IARC evaluation provides further evidence from epidemiological studies that asbestos causes cancer of the lung, pleural and peritoneal mesothelioma, gastrointestinal-tract cancers, cancer of the larynx, and cancer of the ovary. The Van Den Bij 2013 study provides a number of extra lung cancer cases after asbestos exposure that is comparable to the risk levels obtained by DECOS and presented below in section 7.7.4. – the section of carcinogenic risk assessment.

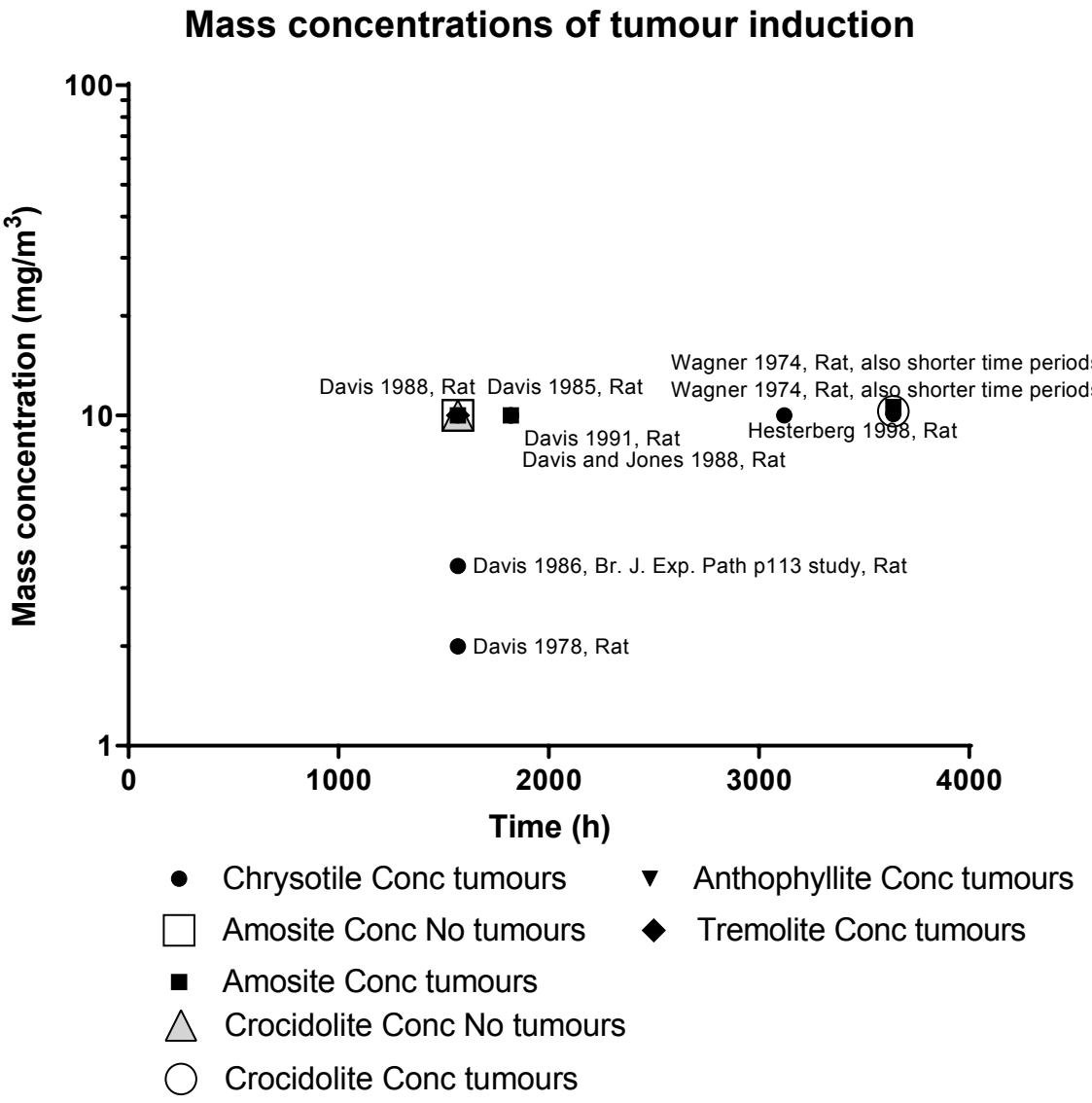
7.7.3. Animal data

Inhalation

For the inhalation studies, we reviewed animal studies and determined the mass concentrations and fibre concentrations at which the number of animals with neoplasms was increased. In addition we determined the next lower level – the highest level at which the number of animals with neoplasms was not increased (Figure 6). These numbers help determine concentrations at

[14] $K_{L(\text{Lung cancer})}$ and $K_{M(\text{mesothelioma})}$ values are the slope of a straight line when cancer risk is plotted as function of exposure. The concept is explained in detail in Section 7.7.4.

which carcinogenicity can be observed. In the section below we describe the animal studies underlying the values in Figure 6.



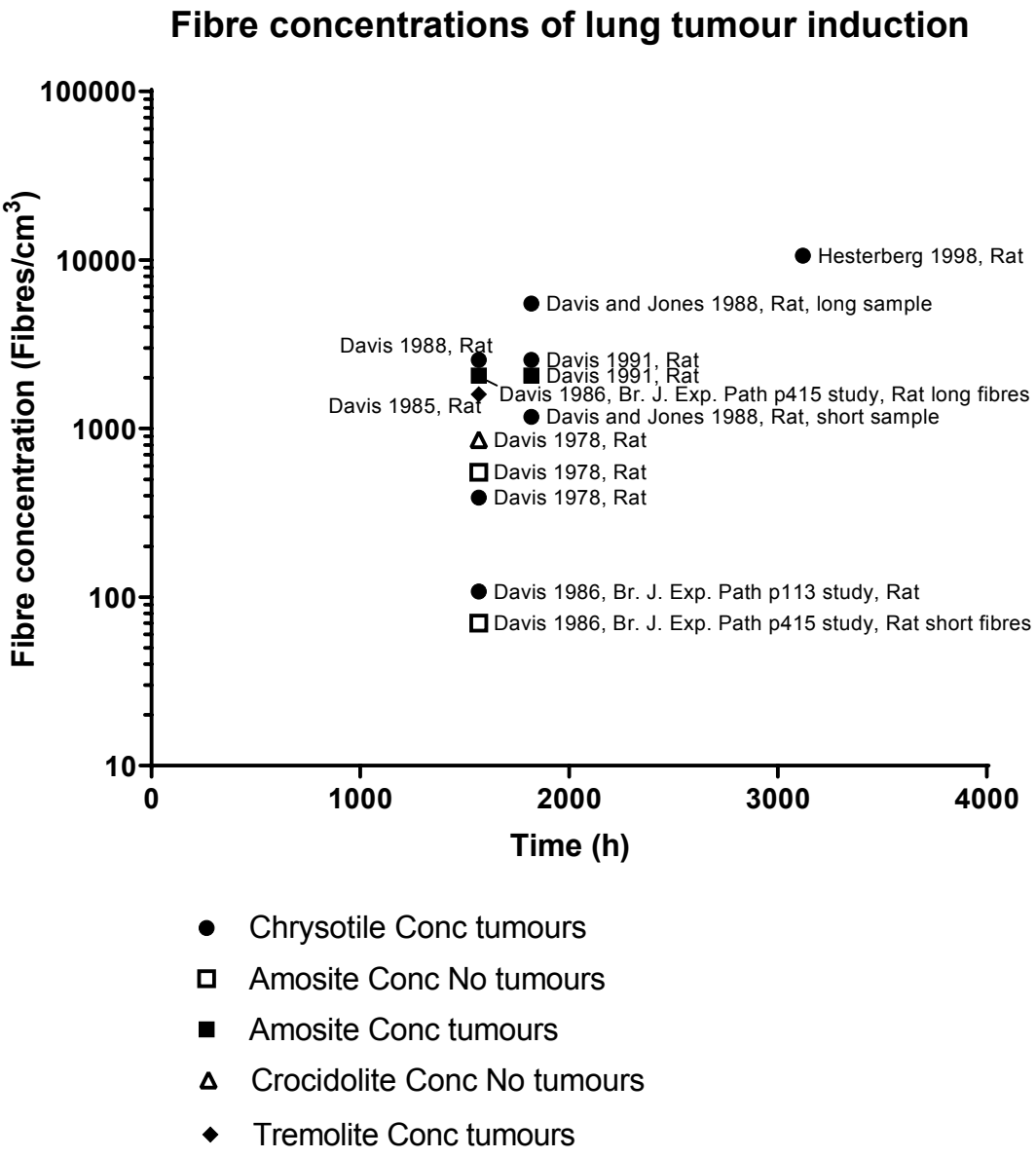


Figure 6. Mass concentrations and fibre concentrations at which carcinogenicity is absent or present. Upper panel Mass concentrations; Lower panel: Fibre concentrations.

Studies that compare chrysotile, amosite, anthophyllite, and crocidolite

Rats inhaled amosite, anthophyllite, crocidolite, Canadian chrysotile or Rhodesian chrysotile. The mass concentrations varied somewhat over a 2 year period (7h/day 5 days/week) (up to 3640 h). The mean respirable dust concentration at 24 months was reported to be 10.6 (amosite and anthophyllite), 10.3 (crocidolite) and 10.1 mg/m^3 (the two forms of chrysotile). Cumulative doses were in the range of 33200 to 33600 (mg/m^3 hours). For the amphiboles amosite, anthophyllite and crocidolite there was an increase of lung dust with dose (dose was increased in the sense of differences in exposure time), whereas for the chrysotile much less dust was observed in the lungs. The amount of dust in lungs decreased after removal of exposure at 6 months with a recovery time

up to an additional 18 months. The number of rats with lung tumours were Control 7/126 (7 rats out of a total of 126 animals in the group); amosite: 38/146, anthophyllite 50/145, crocidolite: 55/141, Chrysotile (Canadian): 45/137; Chrysotile (Rhodesian): 59/144. The number of rats with mesotheliomas were Control 0/126 (7 rats out of a total of 126 animals in the group); amosite: 1/146, anthophyllite 2/145, crocidolite: 4/141, Chrysotile (Canadian): 4/137; Chrysotile (Rhodesian): 0/144. There were also tumours in breast, pituitary and other sites, and survival times were also reported. Concerning the concentration at which tumours occurs this is not readily evaluated as there were exposure times lower than 24 months and up to 24 months ($Concentration_{tumours\ observed}$: 10.6 (amosite and anthophyllite), 10.3 (crocidolite) and 10.1 mg/m^3 (the two forms of chrysotile))(fibres/cm^3 not given) (Wagner et al., 1974). In an extension of this study, mast cell numbers were investigated and found to be increased along with increased exposure. And mast cell numbers were also associated to increasing subpleural thickening (Wagner et al., 1984).
Chrysotile, crocidolite, amosite Rats inhaled chrysotile, crocidolite, or amosite at 2 or 10 mg/m^3 (chrysotile), 5 or 10 mg/m^3 (crocidolite) or 10 mg/m^3 for amosite for 7h/day 5 days/week for 12 months (1568 h) (fibre numbers were 390 and 1950 fibres/cm^3 for chrysotile (>5 μm), and 430 and 860 fibres/cm^3 for crocidolite and 550 fibres/cm^3 for amosite). There is also recovery of asbestos in lungs 7 and 182 days. Fibrosis was most pronounced for chrysotile than it was for the amphibole asbestos types, crocidolite or amosite. Malignant pulmonary tumours were only observed following chrysotile. This was reported to have a possible explanation of a longer fibre length (Chrysotile $Concentration_{tumours\ observed}$: 2 mg/m^3 / 390 fibres/cm3; Crocidolite $Concentration_{No\ tumours\ observed}$: 10 mg/m^3 / 860 fibres/cm^3; Amosite $Concentration_{No\ tumours\ observed}$: 10 mg/m^3 / 550 fibres/cm^3) (Davis et al., 1978).[15]

Chrysotile, amosite Rats inhaled chrysotile alone, amosite alone or a mixture of amosite or chrysotile that was added either TiO_2 or quartz. The mass concentration was ~10 mg/m^3 of asbestos (plus in some cases: ~10 mg/m^3 dust) and the exposure period was for 1 year at 7h per day. But the number of days per week was not reported but estimated to be 5 days (~1820 h), with a 2-year follow-up. The addition of quartz (but not TiO_2) increased the level of fibrosis in comparison to the level observed with the fibres alone. Exposure to both quartz and TiO_2 asbestos mixtures were associated with increased numbers of pulmonary tumours and mesotheliomas as compared to only asbestos exposure. However both chrysotile and amosite had increased number of animals with tumours as compared to control (Chrysotile $Concentration_{tumours\ observed}$: 10 mg/m^3/ 2560 fibres (>5 μm)/cm^3) (Amosite $Concentration_{tumours\ observed}$: 10 mg/m^3 / 2060 fibres (>5 μm)/cm^3) (Davis et al., 1991).

Studies on only chrysotile
Rats were exposed to either normally charged or discharged chrysotile asbestos at 10 mg/m^3 for 7h/day 5days/week for 1 year (1568 h). Recovery periods were the full life time of the animals. Normally charged chrysotile produced the highest level of pulmonary fibrosis and a higher number of pulmonary tumours – but the difference to discharged seems not to be statistically significant ($Concentration_{tumours\ observed}$: 10 mg/m^3 / 2560 fibres (>5 μm)/cm^3) (Davis et al., 1988). Rats

[15] It is unknown whether the article states the number of animals with tumours or the total number of tumours of all the animals.

inhaled chrysotile at 10 mg/m^3, 7h/day, 5 days/week for 1 year (1820 h). The chrysotile asbestos was either a short (1170 fibres (>5 μm)/cm^3) or a long fibre length sample (5510 fibres (>5 μm)/cm^3). The 1 year study period was followed by a 6, and 14 to 18, month recovery periods**.** At the end of the inhalation exposure period the elimination rate of short chrysotile fibres was higher than that observed for long fibres. Rats exposed to the long-fibre chrysotile exhibited what was described as "a more advanced interstitial fibrosis (asbestosis)" and more pulmonary tumours as compared to rats exposed to the short-fibre sample; Although both fibre lengths induced increased numbers of tumours as compared to control - as evaluated by Fischer's exact test performed by us. ($LOAEC_{fibrosis}$ in the inhalation study: 10 mg/m^3) (Short sample $Concentration_{tumours\ observed}$ in the inhalation study: 10 mg/m^3 / 1170 fibres (>5 μm)/cm^3 ; Long sample $Concentration_{tumours\ observed}$: 10 mg/m^3 / 5510 fibres (>5 μm)/cm^3) (Davis and Jones, 1988).

Rats were exposed to chrysotile fibres by nose-only inhalation at 10 mg/m^3 for 6 h/day, 5 days/week for 2 years (3120 h). After this exposure there was a recovery period of 23 weeks. But rats were also euthanized directly after 13, 26, 39, 52, 78, and 104 weeks of exposure. Thoracic neoplasms and pulmonary fibrosis were observed after exposure to the fibres as compared to controls, as were chronic inflammation, bronchoalveolar hyperplasia and collagen deposition ($LOAEC_{fibrosis}$ 10 mg/m^3) ($Concentration_{tumours\ observed}$ 10 mg/m^3 [16] , and 10600 WHO fibres (5 μm in length and >3 μm in diameter)/cm^3) (Hesterberg et al., 1998).

Rats were exposed by inhalation to a) yarn form wet dispersed chrysotile production process, b) dust collected from the factory air in a workshop processing only this type of wet dispersed chrysotile, c) a standard chrysotile textile yarn produced by traditional methods, or d) yarn from another chrysotile wet dispersion process. The mass concentrations were 3.5, 3.7, 3.5 and 3.5, for these groups, respectively (fibre numbers: 679, 468, 428, and 108 fibres/mL). The duration was 7h/day, 5 days/week for a total of 224 days over a period of 12 months (1568 h). Exposure to the samples resulted in all groups in fibrosis and carcinogenicity with no intergroup differences. Pulmonary carcinomas developed in 25% of the animals and in what was designated as advanced interstitial fibrosis was observed in (on average) 10% of all lung tissue. In a subsequent intraperitoneal injection study, rats were administered a dose of 25 mg/rat. This exposure resulted in all fibre dosed groups in mesotheliomas in more than 90% of the rats ($Concentration_{tumours\ observed}$: chrysotile yarn c) 3.5 mg/m^3) (Davis et al., 1986a).

Studies on only amosite

Rats inhaled 1000 fibres (longer than 5 μm)/mL, 7 h/day, 5 days/week for 12 months (1820 h). Fibrosis was observed. Concerning tumours, out of 42 exposed rats, 16 had lung tumours (7 had carcinoma, 9: adenoma) and 2 mesotheliomas were observed. Of 38 controls, two had lung tumours and none mesothelioma (no mass concentration was reported; Fibre $concentration_{tumours\ observed}$: 1000 fibres/cm^3) (Cullen et al., 2000). Rats inhaled amosite of short or long length. The mass concentration was 10 mg/m^3 and the duration was 7h/day for 5 days/week for a total of 224 days during a 12 month period (1568 h). The short fibres were almost all shorter than 5 μm (70 fibres (>5 μm)/cm^3). The long fibres consisted of dust prepared from raw amosite (2060 fibres (>5 μm)/cm^3). Exposure to the long fibre resulted in pulmonary fibrosis, and in one third of the animals, pulmonary tumours or mesotheliomas. These effects were not observed following the exposure to

[16] In the article only the total number of tumours is given, not the total number of animals with tumours.

short fibres. ($Concentration_{No\ tumours\ observed}$ short fibre 10 mg/m³ / 70 fibres (>5 μm)/cm³, $Concentration_{tumours\ observed}$ long fibre 10 mg/m³ / 2060 fibres (>5 μm)/cm³) (Davis et al., 1986b).

Studies on only tremolite
Rats inhaled tremolite at 10 mg/m³ for 7 h/day 5 days/week for 12 months (1568 h) and exhibited pulmonary fibrosis. In addition 16 cases of carcinogenesis was observed out of 39 animals as compared to no cases in 36 controls ($Concentration_{tumours\ observed}$: 10 mg/m³ / 1600 fibres (>5 μm)/cm³) (Davis et al., 1985).

Intratracheal instillation
In light of the high number of inhalation studies in animals and in light of the amount of human data intratracheal instillation studies were not considered for this endpoint.

Dermal application
Crocidolite and amosite both contain oils and also during processing, transport and storage asbestos is sometimes contaminated with such oils as jute oil. In one study both natural and contaminating oils were isolated and tested for their tumour initiating properties. Mice were exposed twice weekly with co-exposure to croton oil (a tumour promoting agent). Increased cases of papillomas for both asbestos types as well as increased carcinomas in the case of amosite were observed (Roe et al., 1966).

Oral application
Chrysotile at either short range or intermediate range was administered to Syrian golden hamsters. The dose was a concentration of 1% in pelleted diet for the whole lifetime of the hamsters, starting with mothers of the test animals. There was no adverse effect on body weight gain or survival by either fibre length. An increase in adrenal cortical adenomas was observed in male hamsters exposed to short range and intermediate range chrysotile and in females treated with intermediate range chrysotile asbestos when compared to the pooled control groups (males: pooled controls, 25/466, 5%; short range chrysotile, 26/299, 11%; intermediate range chrysotile, 24/244, 10%; females: pooled controls, 15/468, 3%; intermediate range chrysotile, 18/234, 8%). However, statistical significance was lost when these dosed groups were compared with concurrent control groups (males: short range control, 7/115, 6%; intermediate range control, 7/115, 6%; females: short range control, 4/112, 4%; intermediate range control, 6/118, 5%). Neither short range chrysotile nor intermediate range chrysotile asbestos was carcinogenic when ingested at 1% levels in the diet by male and female Syrian golden hamsters. Whereas there were increases in the rates of adrenal cortical adenomas in male and female hamsters exposed to intermediate range chrysotile asbestos compared to the pooled groups, these incidence rates were not different when compared with the concurrent control groups. Additionally, the authors of that study suggested that the biologic importance of adrenal tumours in the absence of target organ (gastrointestinal tract) neoplasia is questionable (National Toxicology Program, 1990). Rats were given chrysotile at 1% in the diet. In one study, 6 out of 10 of the rats developed malignant tumours, as compared to 1 out of 10 in the control group. Nevertheless, in a second study, 11 out of 20 rats developed malignant tumours but both in the treated and control group (Cunningham et al., 1977).

Summary of animal data on carcinogenicity

Concerning the inhalation of asbestos carcinogenicity was observed at a mass concentration of 2 mg/m^3 and above. When presenting the data as fibre concentration the carcinogenicity has been described already at 108 fibres/mL (Davis et al., 1986a). The studies showing carcinogenicity at the lowest fibre numbers (Davis et al., 1986a, 1978; McConnell et al., 1999) are further used to calculate human risk levels in the section of carcinogenic risk assessment (section 7.7.4.).

Some potential for carcinogenicity after dermal co-exposure of asbestos and croton oil cannot be excluded. Also, animal data suggest a carcinogenic potential of asbestos after oral exposure.

7.7.4. Carcinogenic risk assessment

As human data from exposed workers are available, a numerical carcinogenic risk assessment should be based on an aggregation of such data.

The current working group concludes that the hazard assessment critical endpoint is the development of cancer, and that a non-threshold mechanism cannot be ruled out. In this section the current working group discusses the evidence for setting risk estimates based on human data, but also calculate estimates based on animal data for comparison.

Concerning the structure of this section, we first present the evaluations done by DECOS; Afsset, and BAuA for the Netherlands, France and Germany. In addition, data from a study from Van der Bij *et al.* is presented. After that, we provide a calculation based on animal data that we reviewed. Finally we provide a section with our conclusions with our recommended risk estimates to be used for the setting of a health-based OEL.

DECOS

Short summary of the DECOS report

The document called "Asbestos Risk of environmental and occupational exposure" from DECOS (Dutch Expert Committee on Occupational Safety), concerns the risks associated with occupational exposure to asbestos (DECOS, 2010). In the report, DECOS calculates values corresponding to the risk levels defined in the context of environmental and occupational health policy. The values were calculated on the basis of a meta-analysis, for which a selection of epidemiologic studies was made using predefined inclusion criteria.

K values[17] were calculated for both lung cancer and mesothelioma. K_L values for lung cancer and K_M values for mesothelioma. A weighed K_L value was calculated based on 4 out of 18 available cohort studies. No difference was found between chrysotile and the amphibole types. Concerning mesothelioma a clear difference was observed in carcinogenic potential between chrysotile and the

[17] The K_L value is the increase in lung cancer risk per fibre-year of exposure (often reported as 100x KL); A K_M represents mesothelioma. For example, given a cumulative exposure of 100 years, a K_L value of 0.01 will result in a doubling of the relative risk of lung cancer.

The lung cancer risk, as established in cohort studies, is usually expressed as relative risk (RR). This is risk in the exposed population divided by the risk in the non-exposed population (the general population or a control group). RR and K_L are related according to the formula: $RR=1+K_L \times f \times d$, where f x d = cumulative exposure in fibres/mL x years and K_L is the carcinogenic potential in (fibres/mL x years)$^{-1}$. This corresponds to the mathematical formula for a straight line $Y = b + aX$.

amphiboles. Therefore two separate K_M values were calculated - one for each general asbestos type (chrysotile *vs.* amphiboles). For their meta-analysis, DECOS, selected 2 out of 12 available cohort studies, and calculated K_M values for chrysotile as well as a mixture of chrysotile and up to 20% amphibole. Also, a K_M value was calculated for 100% amphibole. The calculated K_M values indicated that amphiboles were 50 times more potent than chrysotile in terms of carcinogenic potential (mesothelioma).

The risk for occupational exposure was as detailed in Table 7 (DECOS, 2010):

Table 7. Exposure levels by asbestos type for mesothelioma and lung cancer combined, corresponding to risk levels of 4.10^{-3} and 4.10^{-5}. The values are for occupational exposure (eight hours per day, five days per week, for a period of forty years) and are expressed in fibres per m^3 (with fibres/mL between brackets), as measured by transmission electron microscopy (TEM) (DECOS, 2010).

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

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

Review of the methods and studies employed by DECOS

DECOS' assessment of a recent [recent in 2010] meta-analysis

DECOS reviewed an analysis by Hodgson and Darnton published in 2000 (Hodgson and Darnton, 2000); and also one by Berman and Crump from 2003 that was re-analysed in 2008 (Berman and Crump, 2008a, 2003). DECOS noted that neither of these studies involved the selection of studies on the basis of their quality. Also, DECOS reported that they did not agree with Hodgson and Darnton who chose not to anchor the dose-effect line at an intercept of a (RR) of 1. And for a number of studies this resulted in very high intercepts of more than 2 in RR, or of 200 in SMR. DECOS notes this would imply that at zero exposure, the mortality from lung cancer in the occupational population is more than double that seen in the general population. DECOS noted that it is normal to extrapolate to low exposure levels, near the point where the cumulative exposure is zero - and the RR is 1 (or the SMR is 100). DECOS accordingly recalculated the K_L using linear regression with fixed intercept (α=1) values for all cohorts.

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

DECOS notes that in view of these reservations, and especially concerning not selecting studies for inclusion on the basis of exposure data quality, the Dutch Committee decided that new

meta-analyses should be performed, both of the data linking asbestos with lung cancer and those linking it with mesothelioma.

(New meta-analysis performed by DECOS

The meta-analysis was conducted according to a previously published protocol (Vlaanderen et al., 2008). The meta-analysis performed by DECOS was published in the peer reviewed literature (Lenters et al., 2011). This latter article subsequently spurred criticism by Berman and Case – a criticism that was rebutted by Lenters *et al.*, who argued for the use of the truncated data set, in which poorer-quality studies were excluded (Lenters et al., 2012).

DECOS' meta-analysis of lung cancer

For the meta-analysis, DECOS searched the PubMed database for the period of 1950 to 2009 for studies with quantitative estimates of cumulative asbestos exposure and lung cancer mortality and identified original epidemiological studies. Most of these studies were already included in in the analyses by Hodgson and Darnton (Hodgson and Darnton, 2000) and Berman and Crump 2008 (Berman and Crump, 2008a). A number of these studies were excluded and a total of 18 studies were selected and included 17 cohort studies and 1 population-based case referent study (DECOS, 2010). DECOS' calculated K_L values are presented in Table 8.

Table 8. Fibre type, production method, 100×K_L[18] value and standard error (SE) for each of the studies considered for the meta-analysis (of which 18 were ultimately included). The 100×K_L values marked* with an asterisk were obtained using weighted linear regression; the others using Poisson (DECOS, 2010).

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

These 18 studies were next assessed by the DECOS panel members, who scored them on variables indicative of study quality. The process was done by three independent members who subsequently reached consensus. Studies were selected for inclusion in the meta-analysis based on the following four criteria:

"

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

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

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

[18] In order to facilitate the readability of the numbers, K_L values are often given as 100xK_L. For KM values 10^8xK_M is often used.

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

Application of these criteria ruled out 14 studies, leaving 4 studies to be considered: (Gustavsson et al., 2002; Hein et al., 2007; Peto et al., 1985; Sullivan, 2007).

There is some variability in the K_L values of the 4 studies. This was by DECOS assumed to be a consequence of differences in the quality of the exposure data, the fibre type and size distribution of the fibres involved. A 100xK_L value of 1.64 was calculated based on the 4 studies as presented in the Table 9.

Table 9. Calculated pooled K_L values (×100) for all 18 studies considered, and for the studies that passed each successive step of the selection procedure, pooled by random effects meta-analysis method. The 95% CI is given between brackets (DECOS, 2010).

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

Next exposure concentrations corresponding to the reference environmental and workplace risk levels for lung cancer were determined (Tables 10 and 11). No distinction was made between chrysotile and amphiboles.

Table 10. Exposure concentrations corresponding to the reference environmental risk levels for lung cancer. The values relate to lifetime exposure, expressed in fibres/m^3, as measured by TEM (DECOS, 2010).

Risk level	Exposure concentration in fibres/m^3
Risk 10^{-4}	3,200
Risk 10^{-6}	32

Table 11. Workplace. Exposure concentrations corresponding to the reference workplace risk levels for lung cancer. The values relate to occupational exposure (eight hours per day, five days per week, for forty years), expressed in fibres/m³ (with fibres/mL in brackets), as measured by TEM (DECOS, 2010)**.**

Risk level	Exposure concentration in fibres/m³ (fibres/ml)
Risk 4.10^{-3}	220,000 (0.22)
Risk 4.10^{-5}	2,000 (0.0022)

This corresponds to 0.00055 fibres/mL for a risk level of 1: 100 000 and 0.0055 fibres/mL for 1:10 000.

DECOS' meta-analysis of mesothelioma

The methodology was identical to that used for lung cancer. In the first step, 13 studies were identified. These are presented in Table 12.

Table 12. Fibre type, production method, K_M value ($\times 10^{-8}$, in (fibres/mL × years⁴)$^{-1}$) and SE for each of the cohort studies considered (DECOS, 2010)

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

a Excluded because value is based on just one mesothelioma case

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

The K_M values for this meta-analysis were taken from the most recent analysis by Berman and Crump. DECOS wrote that the objections to the use of Berman and Crumps' 33 K_L values did not apply to the K_M values used in the same publication for mesothelioma, since Berman and Crump calculated the K_M value by forcing the regression line through the origin (the background mortality for mesothelioma is virtually zero).

When the four selection criteria described above were applied, only two studies were left as described in Table 13 (Hein et al., 2007; Peto et al., 1985).

Table 13. Summary of all the cohort studies considered, and the studies that passed each successive step of the selection procedure for the various types of asbestos, showing the pooled KM values and CIs for each type of asbestos (DECOS, 2010).

Inclusion	Asbestos type and study numbers (see Table 11), with the pooled K_M value ((x10^{-8} in (fibres/ml × years^4)$^{-1}$) and the confidence interval between brackets		
	Chrysotile	Mixed exposure	Amphiboles
All 12 studies (except 4 and 19a)	1a, 1b, 3, 5 0.017 (0.007-0.027)	1c, 13, 14, 18, 19b, 20 1.076 (0.330-1.821)	7.8 7.953 (0.015-15.891)
Step 1. Only studies with acceptable documentation	1a, 1b, 5 0.017 (0.006-0.029)	1c, 14, 19b, 20, 0,709 (0,101-1,316)	
Step 2. Only studies that used internal conversion factors	1a, 1b, 5 0.017 (0.006-0.029)	1c, 14, 20 0.389 (-0.047-0.825)	
Step 3. Only studies with accurate job histories	5 0.150 (-0.015-0.315)	20 1.300 (0.507-2.093)	
Step 4. Only studies with data covering >50% of the follow-up period			

Concerning Exposure concentrations corresponding to the workplace risk levels for mesothelioma these are presented in Table 14.

Table 14. Exposure concentrations corresponding to the reference workplace risk levels for mesothelioma. The values relate to occupational exposure (eight hours per day, five days per week, for forty years), expressed in fibres/m^3 (with fibres/mL in brackets), as measured by TEM (DECOS, 2010).

Risk level	Type of asbestos	Applied value of $K_M \times 10^8$	Exposure concentration in fibres/m^3 (fibres/ml)
Risk 4.10^{-3}	Chrysotile	0.15	2,800,000 (2.8)
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	320,000 (0.32)
	Amphibole	7.95	68,000 (0.068)
Risk 4.10^{-5}	Chrysotile	0.15	28,000 (0.028)
	Mixed exposure: chrysotile and up to 20% amphibole	1.3	3,200 (0.0032)
	Amphibole	7.95	680 (0.00068)

Collective values for lung cancer and mesothelioma

DECOS then calculated values pertaining to both lung cancer and mesothelioma. These values are presented in Table 15.

Table 15. 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/m³ (with fibres/mL between brackets), as measured by TEM (DECOS, 2010).

Risk level	Concentrations corresponding to reference risk level for occupational exposure measured by TEM		
	Chrysotile in fibres/m³ (fibres/ml)	Mixed exposure to up to 20% amphibole in fibres/m³ (fibres/ml)	100% amphibole in fibres/m³ (fibres/ml)
4.10^{-3}	200,000 (0.2)	130,000 (0.13)	42,000 (0.042)
4.10^{-5}	2,000 (0.002)	1,300 (0.0013)	420 (0.00042)

Notes on Table 20: The current limit value is a PCM-based value: 10,000 fibres/m³ or 0.01 fibres/ml; expressed as a TEM-based value, the current limit value is: 20,000 fibres/m³ or 0.02 fibres/ml.
NB: The current Dutch occupational exposure limit is not based on the calculation of concentrations that correspond to a given risk level.

The current working group's conclusion on the DECOS report

It is the opinion of the current working group that the assessment method employed by DECOS is sound. We agree on the selection of studies based on quality criteria. We assess that the report by DECOS is a valuable contribution to the assessment of hazard levels in the current work. We recalculated the risk levels of $4x10^{-5}$ into $1x10^{-5}$ by dividing the fibre concentrations in Table 15 with a factor of five to reach the risk levels presented below in the section: "*Overview of data from different bodies and of risk calculated by us based on animal studies*".

Our calculation on lung cancer using DECOS' K_L values

To further ensure that the estimations of DECOS are sound, we calculated the 1:10 000 risk level for lung cancer using the K_L values of DECOS and the life time risk of lung cancer in Denmark.

In Denmark, the life time risk of developing lung cancer (0 to 74 years) is 4.9% for men and 4.5% for women. The RR caused by occupational exposure to a carcinogen, which causes cancer at various risk levels (1:100, 1:1000 and 1:10 000) are given in Table 16.

Table 16. RR of lung cancer for carcinogens that cause 1%, 0.1% or 0.01% excess lung cancer risk in a population with the current Danish lung cancer incidence[19]

	Men	Women
Life time risk (0-74 years) 2011-2015 in Denmark	4.9%	4.5%
Excess lung cancer risk level	RR	RR
1:100	RR= (4.9+1)/ 4.9= 1.20	RR= (4.5+1)/4.5= 1.22
1:1000	RR= (49+1)/49= 1.02	RR= (45+1)/45=1.02
1:10 000	RR= (490+1)/490= 1.002	RR= (450+1)/450= 1.002
1:100 000	RR= (4900+1)/4900= 1.000 2	RR= (4500+1)/4500= 1.000 2

[19] http:/www-dep.iarc.fr/NORDCAN/DK/StatsFact.asp?cancer=180&country=208

Thus at a risk level of 1: 10 000 the RR has to be 1.002

We use the formula for $RR = 1 + K_L \times f \times d$

where $f \times d$ is the cumulative exposure in fibres/mL x years

a) Thus at a risk level of 1: 10 000 using a K_L value by DECOS set only on: "Step 3. Only studies with accurate histories"; and: "Step 4. Studies with data covering >50% of the follow-up period ($100xK_L = 1.64$)

$RR = 1 + K_L \times f \times d$

$1.002 = 1 + 0.0164 \times f \times d$

f x d = 0.1219 fibre-years/mL

If we then divide by 40 years

We reach a mass concentration of 0.003 fibres/mL

b) If the calculation had been done using the K_L value for all 18 studies that were considered by DECOS and for which none were excluded based on the quality criteria of DECOS ($100x\ K_L$: 0.72), then the calculation would be as follows:

$RR = 1 + K_L \times f \times d$

$1.002 = 1 + 0.0072 \times f \times d$

f x d = 0.2777 fibre-years/mL

If we then divide by 40 years

We reach a mass concentration of 0.006 fibres/mL

c) If the calculation had been done using the K_L value for the 7 studies included in: "Step 2 only studies that used internal conversion factors" by DECOS ($100x\ K_L$: 0.91), then the calculation would be as follows:

$RR = 1 + K_L \times f \times d$

$1.002 = 1 + 0.0091 \times f \times d$

F x d = 0.2197 fibre-years/mL

If we then divide by 40 years

We reach a mass concentration of 0.005 fibres/mL

All these three numbers, calculated by us, using either K_L including a) all DECOS' steps, b) none of the steps, or c) only up to step 2 are in line with the risk estimates calculated by DECOS. The current working group notes that all the risk estimates are very similar, and also very similar to the risk estimate by DECOS (Table 11), where a risk estimate of 0.0055 fibres/mL would correspond to a risk level of 1:10 000.

For mesothelioma, DECOS' calculations gives0.00068 fibres/mL at a risk level of $4x10^{-5}$; corresponding to 0.0017 fibres/mL at a risk level of 1: 10 000. The current working group notes that smoking is not a risk factor for mesothelioma. The only well-established risk factor for mesothelioma is asbestos exposure, and the current working group propose to use the risk estimates provided by DECOS, as there is no reason to suspect that the background incidence of mesothelioma or the ambient air levels of asbestos differ between Denmark and the Netherlands.

Afsset

Short summary of the Afsset report

In 2009, Afsset published a report with suggestions for risk levels of exposure to asbestos. Afsset is the *French Agency for Environmental and Occupational Health Safety* under the French Agency for Food, Environmental and Occupational Health & Safety (Afsset, 2009).

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

Thus the report dealt with the above mentioned sizes of asbestos. In the EU, countable asbestos fibres are defined as having a length >5 µm a diameter of less than 3 µm and a L/D ratio of ≥3. And thus only the *thin asbestos fibres* overlap with this definition. It was assessed by the so-called *Afsset OEL committee* (in a collective expert appraisal) that: "*The short asbestos fibres should not to be counted in the occupational exposure measurements. Indeed, due to the systematic presence of asbestos fibres with a length above 5 µm in occupational activities linked to asbestos in the workplace, the OEL that will be suggested will indirectly cover a possible health risk linked to short asbestos fibres*." In contrast the OEL committee stated that *"given the carcinogenic potential of thin asbestos fibres, this dimensional class is to be included when measuring dust levels in the workplace*".

Also concerning the size Afsset in the report concludes that: "*In the current state of knowledge establishing a dose-effect relationship for estimating the toxicity of short asbestos fibres has not been carried out experimentally*". Concerning thin asbestos fibres: "*The epidemiological and experimental studies*

agree in showing the existence of a carcinogenic potential of TAFs [thin asbestos fibres]. *Statistical analyses have linked the highest probability of tumours to the classes representative of TAFs. In the current state of knowledge, establishing a dose-effect relationship for estimating the toxicity of TAFs or a weighting attributable to the toxicity of TAFs compared with so called "WHO" fibres has not been carried out experimentally or validated epidemiologically*".

Affset then proceeds with the meta-analysis of cohort studies of asbestos fibres in general - TAFs were not included in the models used by Afsset, *the Inserm model* and *The Hodgson and Darnton model*. Afsset reached the following conclusions concerning risk levels:

"*Taking into account the current state of knowledge and the outcomes from this collective expert appraisal, when setting the new French OEL for asbestos, Afsset recommends that the following parameters be considered:*
- the effect of asbestos fibres being cumulative and with no evidence having been found of acute toxicity when performing a wide review of the literature, Afsset recommends the setting of the next OEL for asbestos over a corresponding typical 8-hour working day;
- the 8-hour OEL of 10 f/l (0.01 f/mL) is currently the lowest regulatory value of many European countries. Afsset considers that this value can constitute a relevant step in the progress towards a reduction in the risk of asbestos exposure in France. However, for this powerful carcinogen that has no threshold, Afsset recommends retaining a target value of 0.03 f/l, which corresponds to a level of risk of 10^{-6}, according to the retained model;
- given the carcinogenic potential of thin asbestos fibres, this dimensional class is to be included in the measurement of dust levels in the workplace. A modification of currently used metrological techniques is thus essential. Afsset recommends adapting the ATEM method (direct or indirect) so that it can be used as an application in the occupational environment.

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

Review of the methods and studies employed by Afsset
Concerning the discussion of different sizes of fibres the section above should be consulted. Concerning the meta-analysis, Afsset used the so-called Inserm model with the following explanation: "*In the report the so-called Inserm model is used (the 1997 Inserm model). The reason for this was that:*

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

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

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

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

When there appears to be no quantitative evidence of acute toxicity linked to asbestos fibres, the setting of a STEL is not recommended. In the absence of skin penetration data for asbestos fibres, the assigning of a "skin" notation has not been retained."

Lung cancer
Concerning lung cancer, Afsset writes they believe a linear model without cumulative exposure threshold is the most appropriate model for calculation of lung cancer risk.

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

RRp = Observed cases/Expected cases = 1 + (Kp) x (EC) where:

> *EC = $\sum$ f x d is the cumulative exposure expressed as "f/mL x year", i.e. the total products resulting from exposure levels "f" (in f/mL) observed during the career history for periods "d" (years) during which these levels prevailed.*
>
> *Kp is the slope that produces the variation of the relative risk of dying from lung cancer by additional cumulative exposure unit (1 f/mL x year). Inserm opted for practicality by adopting a single value for the Kp risk coefficient, equivalent to + 1.0% irrespective of the geological origin of the fibres*

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

Attributable extra cases = Observed cases - Expected cases = (Kp) x (EC) x (Expected cases)
"

Mesothelioma
According to Inserm, the model most suited to describing the risk of dying from mesothelioma attributable to asbestos exposure is a linear model that depends on the level of exposure in fibres/mL based on the period of

time that has elapsed since the exposure commenced, reduced by a 10-year period, and in which the excess risk of an individual remains until the end of the person's life.

$I_m = K_m f [(T-10)^3 - (T-10-d)^3]$ *if* $T > 10 + d$
$I_m = K_m f (T-10)^3$ *if* $10 + d > T > 10$
$I_m = 0$ *if* $T < 10$
I_m*: incidence of mesothelioma*
K_m*: constant (*K_m *risk coefficient equivalent to 1.0 x* 10^{-8} *for "chrysotile" asbestos exposure, 1.5 times higher for combined exposures (chrysotile and amosite) and three time higher for exposure to amosite alone).*
f: exposure concentration in fibres/mL
T: time elapsed since the start of the exposure, in years
d: length of exposure, in years

Inserm retained "3" as the value to represent the increase rate of the incidence of mesothelioma and the time elapsed since the start of the exposure. Therefore, the number of mesothelioma deaths due to asbestos exposure in a given population (Nm) is expressed as:

$Nm = Im \times P$ *(Eq. 2)* [Eq. 2 is not specified in the Afsset report]"

Calculation of the lifetime risks
For the lifetime risk, the Inserm model used the all-causes mortality rates amongst the French population.

Results
The use of these methods resulted in the following results - that also form the basis for the conclusion given above:

Table 17: Chrysotile concentration, expressed in terms of f-pcm/mL, associated with an increased excess risk (designated IER by Afsset) of dying from lung cancer and/or mesothelioma, taking into consideration a sustained exposure from the age of 20 to 65, 40 hours a week for 48 weeks a year, in a population of exclusively male workers (Afsset, 2009).

Types of cancers	Lung cancer	Mesothelioma	Lung cancer and mesothelioma
F-pcm/ml concentration associated with a sustained exposure from the age of 20 to 65, 40 h/week, 48 weeks/year (occupational exposure)	$4{,}7.10^{-3}$ (IER 10^{-4})	1.10^{-2} (IER 10^{-4})	3.10^{-3} (IER 10^{-4})
	$4{,}7.10^{-4}$ (IER 10^{-5})	1.10^{-3} (IER 10^{-5})	3.10^{-4} (IER 10^{-5})
	$4{,}7.10^{-5}$ (IER 10^{-6})	1.10^{-4} (IER 10^{-6})	3.10^{-5} (IER 10^{-6})

Afsset also calculated the risks according to what they designate the Hodgson and Darnton model - taking cumulative exposure into account

Table 18: Mesothelioma risks calculated according to the nature of the asbestos fibre and the cumulative exposure (Afsset, 2009).

Cumulative exposure	Nature of the fibre	Mesothelioma IER
between 10 and 100 f/ml/year for each fibre	Crocidolite	4.10^{-3}
	Amosite	$6.5.10^{-4}$
	Chrysotile	2.10^{-5}
1 f/ml/year	Crocidolite	$6.5.10^{-3}$
	Amosite	9.10^{-4}
	Chrysotile	5.10^{-5}
0.1 f/ml/year	Crocidolite	1.10^{-3}
	Amosite	$1.5.10^{-4}$
	Chrysotile	4.10^{-5}
0.01 f/ml/year	Crocidolite	2.10^{-4}
	Amosite	3.10^{-5}
	Chrysotile	1.10^{-5}
0.005 f/ml/year	Crocidolite	1.10^{-4}
	Amosite	2.10^{-5}
	Chrysotile	Insignificant

Table 19: Lung cancer risks calculated according to the nature of the asbestos fibre and the cumulative exposure (Afsset, 2009).

Cumulative exposure	Nature of the fibre	Lung cancer IER
10 and 100 f/ml/year for each fibre	Amphiboles	$1.5.10^{-3}$
	Chrysotile	5.10^{-5}
1 f/ml/year	Amphiboles	$8.5.10^{-4}$
	Chrysotile	2.10^{-5}
0.1 f/ml/year	Amphiboles	4.10^{-5}
	Chrysotile	Insignificant
0.01 f/ml/year	Amphiboles	Insignificant
	Chrysotile	Insignificant
0.005 f/ml/year	Amphiboles	Insignificant
	Chrysotile	Insignificant

The current working group's conclusion concerning the Afsset report

It is the opinion of the current working group that the assessment method employed by Afsset is sound. We assess that the report by Afsset is a valuable contribution to the assessment of hazard levels in the current work. We support the use of the INSERM model and acknowledge estimated risk using this model: 0.003 fibres/mL corresponding to an excess risk of 1:10 000 for lung cancer and mesothelioma combined as presented in table 17.

BAuA

The document called National Asbestos Profile for Germany from BAuA – the Federal Institute for Occupational Safety and Health (BAuA, 2014) - had the aim to work as a starting point for development and enforcement of national programs for the elimination of asbestos-related diseases. In Germany, according to this document, there are two risk levels: *Acceptable Risk* and *Tolerable Risk*. In the BAuA document it is stated that:

" Work procedures defined as low-exposure work should not exceed an exposure level of a fibre-concentration of 10,000 fibres/m³ for working without respiratory protection and medical surveillance (2018 at the latest: ***1,000 fibres/m³****).* [these correspond to 0.01 fibres/cm³, and 0.001 fibres/cm³, respectively]

The limit value ***10,000 fibres/m³*** *is called* ***acceptable risk level****, which is derived by a new risk concept for carcinogenic substances developed by the Committee for Hazardous Substances (BAuA, 2013). A fibre concentration of 10,000 fibres/m³ is associated with an excess risk of lung-cancer or mesothelioma assuming a workplace exposure for a time period of over 40 years, with 240 working days per year, and exposure duration of 8 hours per day (Announcement 910 Asbestos, 2008). The upper limit, the* ***tolerable risk****, has been set at a concentration (threshold) of* ***100,000 fibres/m³*** [this corresponds to 0.1 fibres/cm³] *(Announcement 910 Asbestos, 2008). The limit value of this additional risk is not associated with a specific substance, but with respect to activities involving carcinogenic hazardous substances. Two risk levels are derived defining three ranges of exposure:*

Acceptable risk: *(interim limit) 4 : 10,000*

(not later than as of 2018) 4 : 100,000.

An exceedance of the limit values can only be tolerated, if the health risks associated with the exposure are adequately controlled by means of risk management measures complying with the specifications outlined in the catalogue of measures.

The second risk limit adopted is the
Tolerable risk: *4 : 1,000*
above which a risk is intolerable. The risk refers to a working lifetime of 40 years with a continuous exposure on every working day of 8 hours.

*The **acceptable risk** defines the additional cancer risk that is accepted meaning that, statistically, 4 out of 10,000 persons exposed to the substance throughout their working life will develop cancer. The risk does not require any additional protective measures by law, due to the low remaining occupational substance-associated cancer risk. In contrast to that, employees should not be exposed to concentrations above the threshold set by the tolerable risk. The two thresholds differentiating between three different concentration ranges based on the tolerability of the magnitude of the response (cancer cases) proposed by these definitions are in line with the ongoing national and international discussion and open up the possibility of a concept of appropriately graduated measures (Announcement 910, 2008). The tolerable risk defines the additional cancer risk of 4 : 1,000 that is tolerated, meaning that, statistically, 4 out of 1,000 persons exposed to the substance throughout their working life will develop cancer. In the case of activities in the range of medium risk (below tolerable risk, but above acceptable risk) exposure must be continuously reduced. The risk concept lists a detailed catalogue of appropriate measures (BAuA, 2013)."*

Thus this German document describes that there are two limits, the acceptable risk limit (0.001 fibres/cm^3 at latest from 2018), which is an acceptable risk of 4 : 100 000; and the Tolerable risk (0.1 fibres/cm^3) , which corresponds to a tolerable risk of 4 : 1000.

Notably, there is in the BAuA document no description of calculations or underlying data on how the acceptable risk limit was reached. This information was retrieved by personal contact to BAuA, but can also be found on the internet (BAuA, 2008).

BAuA based this calculation on the following.

"*According to the US-EPA, the unit risk for lung cancer and mesothelioma is 2.3 x 10-1 per F/mL [3]* [Reference inserted by the current working group: (US EPA, 1988)]. *This excess risk relates to an exposure of 24 hours per day for 70 years and a respiratory volume of 20 m³ per day. In accordance with the "Guide for the quantification of cancer risk figures after exposure to carcinogenic hazardous substances for establishing limit values at the workplace" [4], this results in a specific workplace risk (40 years; 240 working days per year; 8 hours per day; respiratory volume 10 m³ / 8 hours) of 0.43 x 10-1 per F/mL. Since the additional cancer risk is frequently expressed as a function of cumulative asbestos exposure in the form of fibre years (fibre year = F/mL x years), the result is a workplace-specific additional*
lung cancer and mesothelioma risk of 4.3% per 40 fibre years or approx. 0.1% per fibre year. The tolerable risk of 4:1000 is therefore around 4 fibre years and the acceptable risk of 4:10000 (2018 at the latest:

4:100000) is around 0.4 fibre years (2018 at the latest: 0.04 fibre years). Given an exposure time of 40 years, 240 working days per year and an exposure duration of 8 hours per working day, the tolerable risk works out at a concentration of 100000 fibres/m3 and the acceptable risk at 10000 fibres/m³ (2018 at the latest: 1000 fibres/m³)".

Our conclusion concerning the BAuA report

The current working group briefly reviewed the US EPA document (US EPA, 1988), and the Inhalation Unit Risk is indeed reported to be 2.3E-1 per (fibre/mL). The current working group notes that the US EPA document is of an older date (1988) and is based on a range of epidemiological studies published in the period before 1988. Notably the assessment is less conservative as compared to the evaluations by Afsset and DECOS, but as mentioned above the data underlying the BAuA conclusions are more than 30 years old, providing an argument that the assessments of Afsset and DECOS are more relevant for the current assessment.

Van der Bij Study

Van der Bij *et al.* stated that existing estimated lung cancer risks per unit of asbestos exposure are based mainly on, and applicable to, high exposure levels. Van der Bij *et al.* therefore assessed the risk at low cumulative exposure by fitting flexible meta-regression models. The selection criteria of relevant studies was that lung cancer risk per cumulative asbestos exposure was reported for at least two exposure categories. From a selected 19 studies the following was extracted: 104 risk estimates over a cumulative exposure range of 0.11 to 4,710 fibre-years/mL. Linear and natural spline meta-regression models were fitted to the data. The authors stated that: A natural spline allows risks to vary nonlinearly with exposure, such that estimates at low exposure are less affected by estimates in the upper exposure categories. Associated RRs were calculated for several low cumulative asbestos exposures. A natural spline model fitted the data best. With this model, the relative lung cancer risks for cumulative exposure levels of 4 and 40 fibre-years/mL were estimated to be between 1.013 and 1.027, and 1.13 and 1.30, respectively. After stratification by fibre type, a non-significant three- to fourfold difference in RRs between chrysotile and amphibole fibres was found for exposures below 40 fibre-years/mL. Fibre-type-specific risk estimates were strongly influenced by a few studies. In conclusion, the natural spline regression model indicated that at lower asbestos exposure levels, the increase in RR of lung cancer due to asbestos exposure may be larger than expected from previous meta-analyses. The authors of that study also noted that observed potency differences between different fibre types were lower than the generally held consensus (van der Bij et al., 2013).

Table 20 Data from van der Bij *et al.* in tabulated form

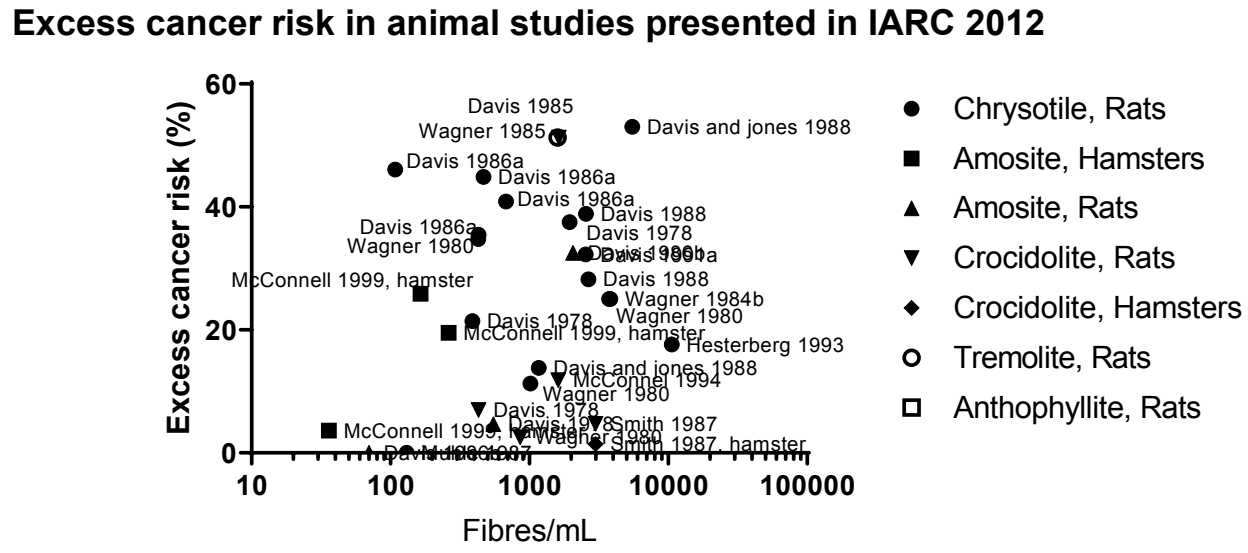
Model for predicted lung cancer	RR 4 fibre-years/mL = 0.1 fibres/mL over 40 years of work life	Excess cases per 1000	Excess cases per 10 000	Excess cases per 100 000
Natural spline corrected for intercept	1.013	13	130	1300
Natural spline without intercept	1.027	27	270	2700

The current working group notes that - based on the data from van der Bij presented in Table 20 - *a risk level of 1:100 000 would be obtained at a (0.1 fibres/mL / 1300) = 0.000077 fibres/mL* when done by linear extrapolation by us. This number is close to the risk estimates calculated by Afsset and DECOS in 2008 and 2010.

Risk calculated based on animal studies

The current working group finds evidence in support of non-threshold mechanisms of asbestos-induced cancer. Figure 7 gives an overview of carcinogenic animal studies described in IARC 2012. In panel B of the figure - three studies with the lowest fibre concentration and still inducing tumours are located to the left on the curve. Risk levels are calculated based on these three investigations, two on chrysotile (Davis et al., 1986a, 1978) and one on amosite (McConnell et al., 1999). The risk estimates of these studies are given in Table 25.

A:



B:

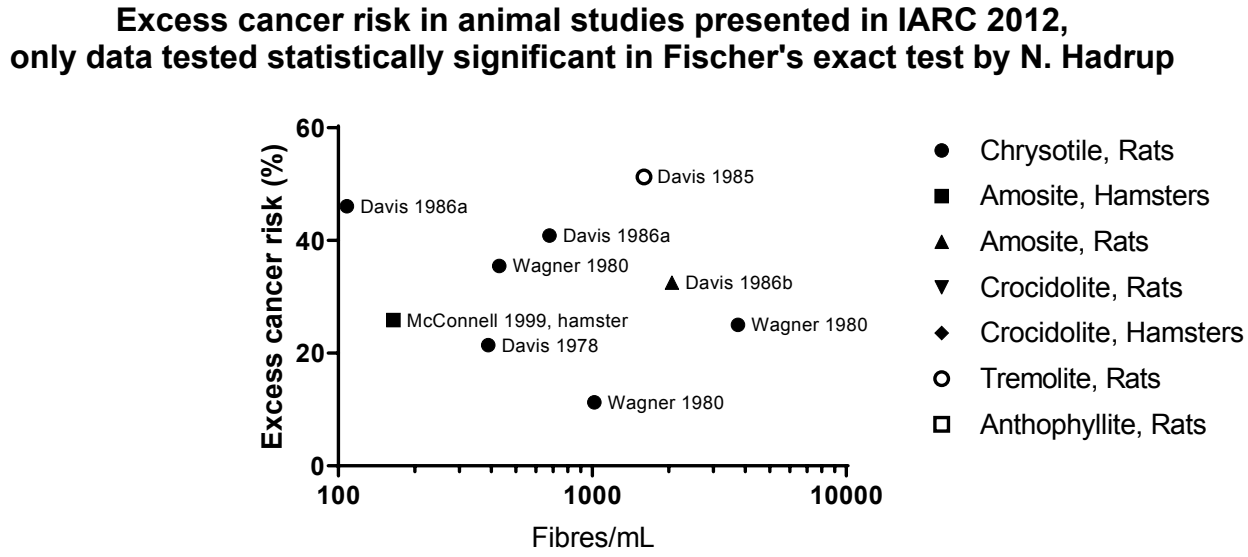


Figure 7. Excess cancer risk in animal studies presented in IARC 2012. The cancer risk is adjusted for the tumour incidence in the control group by use of the formula: *Excess cancer risk = ((number of animal with tumours in treated group/total number of animals in the treated group)-(number of animals with tumours in the control group/number of animals in the control group))/(1-(number of animals with tumours in the control group/number of animals in the control group))*100.* Panel A presents all studies regardless of whether the number of animals in the treated group was significantly different from the control group. Panel B presents only studies in which the number of animals with tumours was found to be statistically different from the number of animals with tumours in the control group (Fischer's exact test conducted by N. Hadrup).

As a calculation example the following is based on (Davis et al., 1986a). The OEL is derived based on the chronic inhalation study of female mice and rats by Davis and co-workers (Davis et al., 1986a) (Table 20). The lowest effect level for lung cancer was observed in the investigated rats, where increased thoracic tumour incidence including mesotheliomas was found at 3.5 mg/m^3 / 108 fibres/mL; the only tested dose in the study. The rats inhaled the dose for 12 months. Lung cancer incidence (number of animals with thoracic tumours according to IARC) in chrysotile exposed rats was 49% (21/43), while the cancer incidence in control rats was 5% (2/39).

In our assessment we include both malignant and non-malignant tumours in accordance with the REACH guideline stating that: *"malignant tumours as well as benign tumours that are suspected of possibly progressing to malignant tumours are taken into account in obtaining the dose-descriptor values"* (ECHA, 2012).

Table 21. Data from Davis 1986 used for calculation. Data are given based on the presentation provided by IARC (IARC, 2012).

Type	**Mass concen-tration**	**Fibre numbers**	**Animal species and exposure duration and follow up period**	**Number of pleural mesothe-liomas**	**number of animals with thoracic tumour in the treated group**	**Number of animals with thoracic tumour in control group**	**%tumours**
Chrysotile experimental WDC	3.5 mg/m^3	108 fibres/mL	Wistar rats, Exposure period: 7h/day, 5 days per week for 12 months. Follow up period: lifetime	4	21 out of 43 animals	2 out of 39	49%

Calculation of Excess cancer risk
This value is calculated based on the one-year chrysotile inhalation study in rats by (Davis et al., 1986a) (values summarised in Table 21):

Excess cancer risk:

Observed excess cancer incidence at 108 fibres/mL:

Formula used:

Observed excess cancer incidence = ((treated animals with thoracic tumours/total treated animals)-(control animals with thoracic tumours/total control animals)) / (1-(control animals with thoracic tumours/total control animals)

And with the numbers from Table 21 inserted into the formula:

Observed excess cancer incidence = (21/43- 2/39) / (1-2/39) = 0.46 = 46 %

Correction of dose metric for humans during occupational exposure (8 h/day):

$$108 \text{ fibres/mL} \times (7 \text{ h/day}) / (8 \text{ h/day}) \times (6.7 \text{ m}^3/10 \text{ m}^3) = 63.3 \text{ fibres/mL}$$

The risk at 1% is then calculated by

63.3 fibres/mL / 46% = 1.4 Fibres/mL

Calculation of dose levels corresponding to risk level of 10^{-5} (1: 100 000), 10^{-4} (1: 10 000) and 10^{-3} (1: 1 000) - under the assumption of linear extrapolation.

Table 22. Calculated excess thoracic tumour incidence at different chrysotile fibre concentrations (8h-TWA)

Excess lung cancer incidence	Chrysotile Air concentration
1: 1 000	0.14 fibres/mL
1: 10 000	0.014 fibres/mL
1: 100 000	0.0014 fibres/mL

Considerations on the potential differences in potencies among the asbestos types.

Concerning animal studies, as can be seen on Figure 4 illustrating the NOAEC and LOAEC values of non-carcinogenic endpoints, it is not possible to assess that one type is more potent than the other. Looking at fibre concentrations of lung tumour induction as illustrated in Figure 6, there is some indication that, concerning thoracic tumours, the serpentine asbestos chrysotile is more potent than the amphibole asbestos amosite.

IARC in 2012 reported that there was evidence from epidemiological studies that exposure to the serpentine asbestos, chrysotile, is less potent in the development of these cancers, in particular for mesothelioma, as compared to the amphibole asbestos types. There IARC also reported that there however was a debate on whether this was the case for lung cancer (IARC, 2012). More details of this debate are given in section 7.7.1. DECOS wrote that – for mesothelioma – a clear difference in carcinogenic potential was discernible between chrysotile asbestos and the amphiboles, which is why DECOS has two different risk estimates for chrysotile and for amphiboles. As presented in Table 23, the excess cancer risk differs by a factor of 5 for lung cancer and mesothelioma combined, with amphiboles being the most potent. Finally Afsset concluded that: *"All known and commercialised mineral varieties of asbestos are likely to cause cancer in humans by inhalation. A single value will be recommended to protect from the effects of all mineral varieties"* (Afsset, 2009). Afsset thus did not distinguish between the different asbestos types.

Notably, the various asbestos types are in virtually all cases cross-contaminated with each other suggesting that it is difficult to pinpoint that Danish workers would only be exposed to single types.

Overall, it is the assessment of the current working group that it cannot be excluded that amphiboles are more potent carcinogens than the serpentine asbestos, chrysotile; on the other hand, occupational exposure to asbestos will likely include mixed exposures and the current working group therefore recommends to use the estimates by DECOS on amphiboles for the setting of a health-based OEL.

Overview of data from different bodies - and of risk calculated by the current working group based on animal studies

The exposure levels *leading to excess cancer risk* by different bodies and articles are given in Table 23.

Table 23 Overview of *exposure levels (8h-TWA) leading to excess cancer risk* by different bodies

Risk estimates taken from reports and articles										
Excess cancer incidence (specified whether lung cancer and/or mesothelioma)	Meta-analysis of Human studies *For lung cancer* (DECOS, 2010) Asbestos type: Concerning lung cancer, no distinction was made between chrysotile and amphiboles	Meta-analysis of Human studies *For mesothelioma* (DECOS, 2010) Asbestos type: Chrysotile	Meta-analysis of Human studies *For mesothelioma* (DECOS, 2010) Asbestos type: Amphiboles	Meta-analysis of Human studies *For mesothelioma and lung cancer combined* (DECOS, 2010) Asbestos type: Chrysotile	Meta-analysis of Human studies *For mesothelioma and lung cancer combined* (DECOS, 2010) Asbestos type: Amphiboles	Meta-analysis of Human studies *Lung cancer* (Afsset, 2009) Asbestos type: Chrysotile	Meta-analysis of Human studies *mesothelioma* (Afsset, 2009) Asbestos type: Chrysotile	Meta-analysis of Human studies *Lung cancer and mesothelioma* (Afsset, 2009) Asbestos type: Chrysotile	Meta-analysis of Human studies (BAuA) BAuA based their risk levels on the US EPA unit risk for the general public *for lung cancer and mesothelioma* (2.3 x 10-1) per fibre/mL. And converted this to $0.43x10^{-1}$ per fibre/mL for the working life. And found a risk of 0.1 % per fibre year. Asbestos type: Designated as "asbestos"	Calculations based on Van der Bij (van der Bij et al., 2013) based on *lung cancer*. Asbestos type: Based on studies on chrysotile, amphiboles, and so-called mixed
1:1000	0.055 fibres/mL	0.7 fibres/mL	0.017 fibres/mL	0.05 fibres/mL	0.01 fibres/mL	0.047 fibres/mL	0.1 fibres/mL	0.03 fibres/mL	1 fibre/mL	0.0077 fibres/mL
1:10 000	0.0055 fibres/mL	0.07 fibres/mL	0.0017 fibres/mL	0.005 fibres/mL	0.001 fibres/mL	0.0047 fibres/mL	0.01 fibres/mL	0.003 fibres/mL	0.1 fibres/mL	0.00077 fibres/mL
1:100 000	0.00055 fibres/mL	0.007 fibres/mL	0.00017 fibres/mL	0.0005 fibres/mL	0.0001 fibres/mL	0.00047 fibres/mL	0.001 fibres/mL	0.0003 fibres/mL	0.01 fibres/mL	0.000077 fibres/mL

The recommendation from Afsset is given as f-pcm/mL: an abbreviation for fibres-measured by phase contrast microscopy/mL.

The current working group ensured the calculations of DECOS by re-calculating the risk levels for lung cancer using values for lung cancer risk in Denmark (Table 24). The estimates by the current working group, detailed in the table, based on DECOS, are in line with those calculated by DECOS itself. The DECOS value on the risk level for lung cancer – when no distinction was made between chrysotile and amphiboles – was 0.00055 fibres/mL (risk level 1: 100 000) (Table 24). Smoking is not a risk factor for mesothelioma. Therefore, the current working group is of the opinion that the risk assessment for asbestos-induced mesothelioma based on epidemiological data by DECOS is also valid for Denmark.

Table 24 ***Exposure levels leading to excess cancer risk*** **calculations by the current working group based on Danish numbers for lung cancer risk and DECOS' K_L values.** For comparison DECOS' own calculation is inserted in the last column.

Risk estimates calculated by us (NFA) based on the DECOS report				**DECOS' own result**
Excess cancer incidence	Calculations by the current working group based on a K_L value for lung cancer set by DECOS based on quality Criteria "Step 3. Only studies with accurate histories"; and "Step 4. Studies with data covering >50% of the follow-up period (100xKL = 1.64). Asbestos type: Concerning lung cancer, no distinction was made between chrysotile and amphiboles.	Calculations by the current working group using the K_L value for all 18 studies that were considered by DECOS and for which none were excluded based on the quality criteria of DECOS (100x K_L: 0.72). Asbestos type: Concerning lung cancer, no distinction was made between chrysotile and amphiboles.	Calculations by the current working group using the K_L value for the 7 studies fulfilling DECOS' Step 2 only studies that used internal conversion factors (100x K_L: 0.91),) Asbestos type: Concerning lung cancer, no distinction was made between chrysotile and amphiboles.	Meta-analysis of Human studies *For lung cancer* (DECOS, 2010) Asbestos type: Concerning lung cancer, no distinction was made between chrysotile and amphiboles.
1:1000	0.03 fibres/mL	0.06 fibres/mL	0.05 fibres/mL	0.055 fibres/mL
1:10 000	0.003 fibres/mL	0.006 fibres/mL	0.005 fibres/mL	0.0055 fibres/mL
1:100 000	0.0003 fibres/mL	0.0006 fibres/mL	0.0005 fibres/mL	0.00055 fibres/mL

Concerning animal data, the current working group regards the risk levels calculated based on animal studies (Table 25) as being less conservative – compared to the risk estimates based on epidemiological data. The current working group recommends to use epidemiological data for setting the health based OEL.

Table 25 Risk estimates by the current working group based on animal studies

Excess cancer incidence (specified whether lung cancer and/or mesothelioma)	**Chrysotile** Rat inhalation study of 3.5 mg/m^3 / 108 fibres/mL (L>5 µm) Method II ECHA** (Davis et al., 1986a), used to calculate fibres/mL at 1% risk At 1% = 1.4 fibres/mL	**Chrysotile** Rat inhalation study of 2 mg/m^3 / 390 fibres/mL (L>5 µm) Method II ECHA** (Davis et al., 1978), used to calculate fibres/mL at 1% risk At 1% = 10.7 fibres/mL	**Amosite,** Hamster inhalation study of 3.7 mg/m^3 / 165 fibres/cm^3 (L>5 µm, and 38 of these were longer than 20 µm/cm^3) Method II ECHA** (McConnell et al., 1999), used to calculate fibres/mL at 1% risk At 1% risk = 3.2 fibres/mL
1:1000	0.14 fibres/mL	1.07 fibres/mL	0.32 fibres/mL
1:10 000	0.014 fibres/mL	0.107 fibres/mL	0.032 fibres/mL
1:100 000	0.0014 fibres/mL	0.0107 fibres/mL	0.0032 fibres/mL

The animal studies selected were the two with the lowest chrysotile fibres/mL and the one with the lowest amosite while still increasing neoplasms in rats/hamsters. There were studies described by IARC who did not report fibre numbers, but none of these had a mass concentration below the studies included in this table.

Based on the considerations above, the current working group recommends that DECOS' values are used for hazard assessment and suggest using the most conservative value for amphiboles, for lung cancer and mesothelioma combined. The value is: 0.0001 fibres/mL, corresponding to a risk level of 1: 100 000 (Table 26).

Table 26 Recommendation by the current working group on: ***exposure levels (8-h- TWA) leading to excess cancer risk***

Excess cancer incidence of lung cancer or mesothelioma	Risk levels (8h-TWA) based on a meta-analysis conducted by DECOS on Human studies of mesothelioma and lung cancer combined – calculated based on exposure to amphibole asbestos
1:1000	0.01 fibres/mL
1:10 000	0.001 fibres/mL
1:100 000	0.0001 fibres/mL

Summary and conclusion

The two risk assessments by DECOS (2010) and Afsset (2008) lead to practically identical risk estimates for excess human lung cancer risk mortality – in relation to asbestos exposure. Taking both assessments together, a mean 8h-TWA asbestos exposure over 40 working years of about 0.0001 fibres/mL would lead to an excess mesothelioma and lung cancer mortality rate of 1×10^{-5}. Our calculations using Danish numbers for asbestos-induced lung cancer and based on the K_L value for lung cancer set by DECOS based on a) DECOS' own quality criteria; and b) DECOS' K_L value for their initially selected 18 studies – were all in line with the number on lung cancer given by DECOS itself, suggesting that the risk estimates are quite robust. Notably, risk estimates based on animal data did not indicate that animal studies would provide a lower risk estimate for lung cancer. The current working group recommends using human data in setting risk levels for a health-based OEL.

The current working group suggests that the following *exposure levels leading to excess cancer risk* are used:

Excess cancer incidence of lung cancer or mesothelioma	Risk levels (8h-TWA) based on a meta-analysis conducted by DECOS on Human studies of mesothelioma and lung cancer combined – calculated based on exposure to amphibole asbestos
1:1000	0.01 fibres/mL
1:10 000	0.001 fibres/mL
1:100 000	0.0001 fibres/mL

7.8. Reproductive toxicity

7.8.1. Human data

It is clear that if asbestos has a genotoxic effect the risk of teratogenicity exists. A key question, however, is whether there is translocation of asbestos fibres to the germ cells, or to the foetus. The tissues and placentas of autopsied stillborn infants were investigated for the presence of asbestos fibres. Asbestos fibres were detected in 50% of the foetal digests and 23% of the placental digests of 82 stillborn infants. Various asbestos types were present: 88% were chrysotile, 10% were tremolite, and 2% were actinolite and anthophyllite. The organs in which the fibres were most frequently present were: Lungs (50%), muscle (37%), placenta (23%), and liver (23%). However, the number of fibres were highest in the liver (58 736 fibres/g), placenta (52 894 fibres/g), lungs (39 341 fibres/g), and in skeletal muscle (31 733 fibres/g). Concerning placentas from liveborn foetuses asbestos fibres were detected in 15% of these, but only in small numbers. In placentas of the stillborn the fibre count was 52 894 fibres/g whereas in liveborn foetuses it was only 19 fibres/g. The fibre presence in the stillborn foetuses was associated with the history of previous abortions and with placental diseases (Haque et al., 1998). In a study by the same group in 1996 similar results were obtained studying 40 stillborn infants and placental digests of 45 liveborn infants (Haque et al., 1996), and similar data were reported by the same group in 1992 (Haque et al., 1992).

A group of women and girls exposed to crocidolite at Wittenoom consisted of 2968 individuals and included 3 cases of choriocarcinoma and 3 cases of hydatidiform mole. In 4 of

these cases the females had lived with asbestos company workers who brought their dusty work-clothes home for washing (Reid et al., 2009).

Talc is chemically related to asbestos. The association between genital exposure to talc and the occurrence of ovarian cancers was assessed in in 215 females having this cancer form. A control population of 215 women was matched by age, race, and residence. Ninety-two (42.8%) of the women with cancer regularly used talc either as a dusting powder. This was used on the perineum or on sanitary napkins. The number in the control group was 61 (28.4%). This gave an RR of 1.92 having a P-value of less than 0.003 for ovarian cancer. Women who had had regularly engaged in both practices had an RR of 3.28 P-value of less than 0.001 as compared to women who had done neither of the practices. The authors of that article suggest that "this provides some support for an association between talc and ovarian cancer" (Cramer et al., 1982).

A literature review of mesothelioma in children, suggested that mesothelioma has a relatively short latency period in children (Wassermann et al., 1980).

7.8.2. Animal data

Having reviewed the inhalation toxicity data of asbestos in animal models, we found no reproductive effects to be reported in these. However from a gavage study there is data concerning the trans-placental transfer of asbestos in pregnant mice. Pregnant mice were orally administered chrysotile asbestos by gavage. The mice were given two doses of 50 μg chrysotile. After mating 2 days later, the mice received two additional doses. The lungs and liver of pups were found to contain chrysotile fibres at 780 fibres/g lung and 214 fibres/g liver. Weight gain and mortality was not different from that of pups in a control group (Haque et al., 2001). This aspect was also investigated in a previous study from the same group (Haque and Vrazel, 1998). Teratogenicity was investigated in mice receiving crocidolite, chrysotile, or amosite at 40 mg/kg bw by intraperitoneal injection. In comparison with a control group, the percentage of live foetuses was increased after crocidolite, whereas the number of dams with early dead foetuses was increased in the chrysotile and amosite groups. The incidence of external malformations (mainly reduction deformity of limb) was increased in the amosite group. And the incidences of skeletal malformation (mainly fusion of vertebrae) were increased in all three asbestos groups (Fujitani et al., 2014).

Collectively the data on animal studies suggest the transfer of asbestos from mother to foetus and suggest a potential for teratogenicity at an intraperitoneal dose of 40 mg/kg bw in mice.

7.8.3. In vitro data

No relevant in vitro data were identified.

7.9. Mode of action considerations

The mutagenic/genotoxic mode of action of asbestos likely involves at least two modes of action a) frustrated phagocytosis – the inability of macrophages to fully engulf long fibres leading to chronic inflammation and oxidative stress; and b) the genotoxic effects of iron – iron is a pronounced constituent of some asbestos types. Also pertaining to the size and rigidity of the asbestos fibres is c) the hypothesis of a needle-like mode of action in the mammalian tissues potentially causing the widespread distribution of asbestos fibres in various tissues and potentially interfering with chromosome alignment during cell division.

7.10. Lack of specific scientific information

The toxicology of asbestos in general has been well investigated, although notably some types of asbestos have been investigated more than others. In general for all types, it is noted that the literature on sensitisation and asbestos is lacking.

8. Groups at extra risk

It has been reported that there is interaction between the exposure to asbestos and to tobacco smoke in relation to the induction of lung cancer (Markowitz et al., 2013; Ngamwong et al., 2015; Selikoff et al., 1968). Mesothelioma has been reported to develop in children with a faster onset as compared to adults; and also the maternal transfer of asbestos to the foetus raises concern (Haque et al., 1996, 1992).

REFERENCES

Afsset. Opinion of the French Agency for Environmental and Occupational Health Safety. Relating to the proposed occupational exposure limits of chemicals in the workplace Asbestos fibres: Assessment of the health effects and methods used to measure exposure levels. Maisons-Alfort, France: French Agency for Environmental and Occupational Health Safety, 2009.

Anderson HA, Lilis R, Daum SM, Fischbein AS, Selikoff IJ. Household-contact asbestos neoplastic risk. Ann NY Acad Sci 1976;271:311–23.

Arbejdstilsynet. At-vejledning juli 2005 – Opdateret oktober 2016 - Erstatter At-meddelelse nr. 3.01.6 af oktober 1999, At-meddelelse nr. 4.02.2 af oktober 1987, At-cirkulæreskrivelse nr. 4/1987 og At-cirkulæreskrivelse nr. 1/1997 Stoffer og materialer – C.2.2-1. København: Arbejdstilsynet, 2016.
ATSDR. Toxicological Profile for Asbestos (TP-61). Agency for Toxic Substances and Disease Registry, 2001.

Auerbach O, Conston AS, Garfinkel L, Parks VR, Kaslow HD, Hammond EC. Presence of asbestos bodies in organs other than the lung. Chest 1980;77:133–7.

Baris I, Simonato L, Artvinli M, Pooley F, Saracci R, Skidmore J, Wagner C, Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: A four-year study in the Cappadocian region of Turkey. Int J Cancer 1987;39:10–7.

Barry BE, Wong KC, Brody AR, Crapo JD. Reaction of rat lungs to inhaled chrysotile asbestos following acute and subchronic exposures. Exp Lung Res 1983;5:1–21.

BAuA. National Asbestos Profile for Germany. Dortmund: Federal Institute for Occupational Safety and Health, 2014.

BAuA. Exposure-risk relationship for asbestos. Federal Institute for Occupational Safety and Health, 2008.

Bégin R, Gauthier JJ, Desmeules M, Ostiguy G. Work-related mesothelioma in Québec, 1967-1990. Am J Ind Med 1992;22:531–42.

Berman DW, Crump KS. A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol 2008a;38(Suppl 1):49–73.

Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 2008b; 38(Suppl 1):1–47.

Berman DW, Crump KS. Final draft: Technical support document for a protocol to assess asbestosrelated risk. Prepared for Office of Solid Waste and Emergency Response. EPA, 2003.

Bernstein DM, Chevalier J, Smith P. Comparison of Calidria chrysotile asbestos to pure tremolite: Final results of the inhalation biopersistence and histopathology examination following short-term exposure. Inhal Toxicol 2005;17:427–49.

Bernstein DM, Rogers R, Smith P. The biopersistence of brazilian chrysotile asbestos following inhalation. Inhal Toxicol 2004;16:745–61.

Bernstein DM, Rogers R, Smith P, Chevalier J. The toxicological response of Brazilian chrysotile asbestos: A multidose subchronic 90-day inhalation toxicology study with 92-day recovery to assess cellular and pathological response. Inhal Toxicol 2006;18:313–32.

Bernstein DM, Rogers RA, Sepulveda R, Donaldson K, Schuler D, Gaering S, Kunzendorf P, Chevalier J, Holm SE. Quantification of the pathological response and fate in the lung and pleura of chrysotile in combination with fine particles compared to amosite-asbestos following short-term inhalation exposure. Inhal Toxicol 2011;23:372–91.

Bernstein DM, Rogers RA, Sepulveda R, Kunzendorf P, Bellmann B, Ernst H, Creutzenberg O, Phillips JI. Evaluation of the fate and pathological response in the lung and pleura of brake dust alone and in combination with added chrysotile compared to crocidolite asbestos following short-term inhalation exposure. Toxicol Appl Pharmacol 2015;283:20–34.

Berry G, Gilson JC, Holmes S, Lewinsohn HC, Roach SA. Asbestosis: A study of dose-response relationships in an asbestos textile factory. Br J Ind Med 1979;36:98–112.

BéruBé KA, Quinlan TR, Moulton G, Hemenway D, O'Shaughnessy P, Vacek P, Mossman BT. Comparative proliferative and histopathologic changes in rat lungs after inhalation of chrysotile or crocidolite ssbestos. Toxicol Appl Pharmacol 1996;137:67–74.

Boffetta P, Donato F, Pira E, Luu HN, La Vecchia C. Risk of mesothelioma after cessation of asbestos exposure: a systematic review and meta-regression [Epub ahead of print]. Int Arch Occup Environ Health 2019.

Bolt HM, Foth H, Hengstler JG, Degen GH. Carcinogenicity categorization of chemicals—new aspects to be considered in a European perspective. Toxicol Lett 2004;151:29–41.

Boorman GA, Dean JH, Luster MI, Adkins B, Brody A, Hong HL. Bone marrow alterations induced in mice with inhalation of chrysotile asbestos. Toxicol Appl Pharmacol 1984;72:148–58.

Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol 2000;9:165–9.

Bourgault M-H, Gagné M, Valcke M. Lung cancer and mesothelioma risk assessment for a population environmentally exposed to asbestos. Int J Hyg Environ Health 2014;217:340–6.

Brody AR, Hill LH. Interstitial accumulation of inhaled chrysotile asbestos fibers and consequent formation of microcalcifications. Am J Pathol 1982;109:107–14.

Brody AR, Hill LH, Adkins B, O'Connor RW. Chrysotile asbestos inhalation in rats: deposition pattern and reaction of alveolar epithelium and pulmonary macrophages. Am Rev Respir Dis 1981;123:670–9.

Camus M, Siemiatycki J, Meek B. Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Engl J Med 1998;338:1565–71.

Carter RE, Taylor WF. Identification of a particular amphibole asbestos fiber in tissues of persons exposed to a high oral intake of the mineral. Environ Res 1980;21:85–93.

Chang LY, Overby LH, Brody AR, Crapo JD. Progressive lung cell reactions and extracellular matrix production after a brief exposure to asbestos. Am J Pathol 1988;131:156–70.

Coin PG, Osornio-Vargas AR, Roggli VL, Brody AR. Pulmonary fibrogenesis after three consecutive inhalation exposures to chrysotile asbestos. Am J Respir Crit Care Med 1996;154:1511–1519.

Cole SR, Richardson DB, Chu H, Naimi AI. Analysis of occupational asbestos exposure and lung cancer mortality using the g formula. Am J Epidemiol 2013;177:989–96.

Courtice MN, Wang X, Lin S, Yu ITS, Berman DW, Yano E. Exposure-response estimate for lung cancer and asbestosis in a predominantly chrysotile-exposed Chinese factory cohort. Am J Ind Med 2016;59:369–78.

Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: A case-control study. Cancer 1982;50:372–6.

Crapo JD, Barry BE, Brody AR, O'Neil JJ. Morphological, morphometric and x-ray microanalytical studies on lung tissue of rats exposed to chrysotile asbestos in inhalation chambres. IARC Sci Publ 1980:273–83.

Cullen MR, Baloyi RS. Chrysotile asbestos and health in Zimbabwe: I. Analysis of miners and millers compensated for asbestos-related diseases since independence (1980). Am J Ind Med 1991;19:161–9.

Cullen RT, Searl A, Buchanan D, Davis JM, Miller BG, Jones AD. Pathogenicity of a special-purpose glass microfiber (E glass) relative to another glass microfiber and amosite asbestos. Inhal Toxicol 2000;12:959–77.

Cunningham HM, Moodie CA, Lawrence GA, Pontefract RD. Chronic effects of ingested asbestos in rats. Arch Environ Contam Toxicol 1977;6:507–13.

Cyphert JM, Carlin DJ, Nyska A, Schladweiler MC, Ledbetter AD, Shannahan JH, Kodavanti UP, Gavett SH. Comparative long-term toxicity of Libby amphibole and amosite asbestos in rats after single or multiple intratracheal exposures. J Toxicol Environ Health A 2015;78:151–65.

Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD. Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. Br J Exp Pathol 1986a;67:113–29.

Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD, Miller BG. Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 1985;6:667–74.

Davis JM, Addison J, Bolton RE, Donaldson K, Jones AD, Smith T. The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br J Exp Pathol 1986b;67:415–30.

Davis JM, Beckett ST, Bolton RE, Collings P, Middleton AP. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. Br J Cancer 1978;37:673–88.

Davis JM, Beckett ST, Bolton RE, Donaldson K. A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. IARC Sci Publ 1980a;285–92.

Davis JM, Beckett ST, Bolton RE, Donaldson K. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. Br J Exp Pathol 1980b;61:272–80.

Davis JM, Bolton RE, Douglas AN, Jones AD, Smith T, 1988. Effects of electrostatic charge on the pathogenicity of chrysotile asbestos. Br J Ind Med 1988;45:292–9.

Davis JM, Jones AD. Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. Br J Exp Pathol 1988;69:717–37.

Davis JM, Jones AD, Miller BG. Experimental studies in rats on the effects of asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. Int J Exp Pathol 1991;72:501–25.

DECOS. Asbestos: Risks of environmental and occupational exposure. The Hague: Health Council of the Netherlands, 2010

Dement JM, Brown DP. Lung cancer mortality among asbestos textile workers: A review and update. Ann Occup Hyg 1994;38:525–32, 412.

Dement JM, Kuempel ED, Zumwalde RD, Smith RJ, Stayner LT, Loomis D. Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. Occup Environ Med 2008;65:605–12.

Deng Q, Wang X, Wang M, Lan Y. Exposure-response relationship between chrysotile exposure and mortality from lung cancer and asbestosis. Occup Environ Med 2012;69:81–6.

DGUV/IFA. GESTIS Substance Database. 2018. URL: http://gestis.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates&fn=default.htm&vid=gestiseng:sdbeng

Doll R. Mortality from lung cancer in asbestos workers 1955. Br J Ind Med 1993;50:485–90.

Dufresne A, Bégin R, Massé S, Dufresne CM, Loosereewanich P, Perrault G. Retention of asbestos fibres in lungs of workers with asbestosis, asbestosis and lung cancer, and mesothelioma in Asbestos township. Occup Environ Med 1996;53:801–7.

Durnev AD, Daugel-Dauge NO, Korkina LG, Seredenin SB. Peculiarities of the clastogenic properties of chrysotile-asbestos fibers and zeolite particles. Mutat Res 1993;319:303–8.

ECHA. Guidance on information requirements and chemical safety assessment. Part E: Risk characterisation. European Chemicals Agency, 2016.

ECHA. Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. European Chemicals Agency, 2012.

Elliott L, Loomis D, Dement J, Hein MJ, Richardson D, Stayner L. Lung cancer mortality in North Carolina and South Carolina chrysotile asbestos textile workers. Occup Environ Med 2012;69:385–90.

EU Commission. Commission Directive 1999/77/EC of 26 July 1999 adapting to technical progress for the sixth time Annex I to Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrict. European Commission, 1999.

EU. Directive 2009/148/EC of the European Parliament andof the Council of 30 November 2009 on the protection of workers from the risks related to exposure to asbestos at work. European Union, 2009.

EU. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC). European Union, 2008.

EU. Council Directive 87/217/EEC of 19 March 1987 on the prevention and reduction of environmental pollution by asbestos. European Union, 1987.

Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect 2007;115:1401–5.

Ferrante D, Chellini E, Merler E, Pavone V, Silvestri S, Miligi L, Gorini G, Bressan V, Girardi P, Ancona L, Romeo E, Luberto F, Sala O, Scarnato C, Menegozzo S, Oddone E, Tunesi S, Perticaroli P, Pettinari A, Cuccaro F, Mattioli S, Baldassarre A, Barone-Adesi F, Cena T, Legittimo P, Marinaccio A, Mirabelli D, Musti M, Pirastu R, Ranucci A, Magnani C, The working group. Italian pool of asbestos workers cohorts: Mortality trends of asbestos-related neoplasms after long time since first exposure. Occup Environ Med 2017;74:887–898.

Ferrante D, Mirabelli D, Tunesi S, Terracini B, Magnani C. Pleural mesothelioma and occupational and non-occupational asbestos exposure: A case-control study with quantitative risk assessment. Occup Environ Med 2016;73:147–53.

Finkelstein MM. Asbestosis in long-term employees of an Ontario asbestos-cement factory. Am Rev Respir Dis 1982;125:496–501.

Fortunato L, Rushton L. Stomach cancer and occupational exposure to asbestos: A meta-analysis of occupational cohort studies. Br J Cancer 2015;112:1805–15.

Fujitani T, Hojo M, Inomata A, Ogata A, Hirose A, Nishimura T, Nakae D, 2014. Teratogenicity of asbestos in mice. J Toxicol Sci 2014;39:363–70.

Gavett SH, Parkinson CU, Willson GA, Wood CE, Jarabek AM, Roberts KC, Kodavanti UP, Dodd DE. Persistent effects of Libby amphibole and amosite asbestos following subchronic inhalation in rats. Part Fibre Toxicol 2016;13:17.

Gloyne S. Two cases of squamous carcinoma of the lung occurring in asbestosis. Tubercle 1935;17:5–10.

Griffis LC, Pickrell JA, Carpenter RL, Wolff RK, McAllen SJ, Yerkes KL. Deposition of Crocidolite asbestos and glass microfibers inhaled by the beagle dog. Am Ind Hyg Assoc J 1983;44:216–222.

Gustavsson P, Nyberg F, Pershagen G, Schéele P, Jakobsson R, Plato N. Low-dose exposure to asbestos and lung cancer: Dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. Am J Epidemiol 2002;155:1016–22.

Hallenbeck WH, Patel-Mandlik KJ. Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. Environ Res 1979;20:335–40.

Hamra GB, Loomis D, Dement J. Examining the association of lung cancer and highly correlated fibre size-specific asbestos exposures with a hierarchical Bayesian model. Occup Environ Med 2014;71:353–7.

Hamra GB, Richardson DB, Dement J, Loomis D. Lung cancer risk Associated with regulated and unregulated chrysotile asbestos fibers. Epidemiology 2017;28:275–280.

Han JH, Park JD, Sakai K, Hisanaga N, Chang HK, Lee YH, Kwon IH, Choi BS, Chung YH, Kim HY, Yang JS, Cho MH, Yu IJ. Comparison of lung asbestos fiber content in cancer subjects with healthy individuals with no known history of occupational asbestos exposure in Korea. J Toxicol Environ Health Part A 2009;72:1292–1295.

Haque AK, Ali I, Vrazel DM, Uchida T. Chrysotile asbestos fibers detected in the newborn pups following gavage feeding of pregnant mice. J Toxicol Environ Health A 2001;62:23–31.

Haque AK, Mancuso MG, Williams MG, Dodson RF. Asbestos in organs and placenta of five stillborn infants suggests transplacental transfer. Environ Res 1992;58:163–75.

Haque AK, Vrazel DM. Transplacental transfer of asbestos in pregnant mice. Bull Environ Contam Toxicol 1998;60:620–5.

Haque AK, Vrazel DM, Burau KD, Cooper SP, Downs T. Is there transplacental transfer of asbestos? A study of 40 stillborn infants. Pediatr Pathol Lab Med 1996;16:877–92.

Haque AK, Vrazel DM, Uchida T. Assessment of asbestos burden in the placenta and tissue digests of stillborn infants in South Texas. Arch Environ Contam Toxicol 1998;35:532–8.

Hasanoglu HC, Bayram E, Hasanoglu A, Demirag F. Orally ingested chrysotile asbestos affects rat lungs and pleura. Arch Environ Occup Health 2008;63:71–5.

Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: Cohort mortality and exposure-response. Occup Environ Med 2007;64:616–25.

Hesterberg TW, Hart GA, Chevalier J, Miiller WC, Hamilton RD, Bauer J, Thevenaz P. The importance of fiber biopersistence and lung dose in determining the chronic inhalation effects of X607, RCF1, and chrysotile asbestos in rats. Toxicol Appl Pharmacol 1998;153:68–82.

Hesterberg TW, Miiller WC, Musselman RP, Kamstrup O, Hamilton RD, Thevenaz P. Biopersistence of man-made vitreous fibers and crocidolite asbestos in the rat lung following inhalation. Fundam Appl Toxicol 1996;29:269–79.

Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 2000;44:565–601.

Huang JQ. A study on the dose-response relationship between asbestos exposure level and asbestosis among workers in a Chinese chrysotile product factory. Biomed Environ Sci 1990;3:90–8.

IARC. Arsenic, metals, fibres and dusts. A Review of Human Carcinogens. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Volume 100 C. International Agency for Research on Cancer, 2012.

IARC. Silica and Sorne Silicates. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Volume 42. International Agency for Research on Cancer, 1987.
IOM. Asbestos: Selected Cancers. Institute of Medicine, 2006.

Ishihara Y, Kyono H, Kohyama N, Otaki N, Serita F, Toya T, Kagawa J. Acute biological effects of intratracheally instilled titanium dioxide whiskers compared with nonfibrous titanium dioxide and amosite in rats. Inhal Toxicol 1999;11:131–49.

Järvholm B, Aström E. The risk of lung cancer after cessation of asbestos exposure in construction workers using pleural malignant mesothelioma as a marker of exposure. J Occup Environ Med 2014;56:1297–301.

Johnson NF. Asbestos-induced changes in rat lung parenchyma. J Toxicol Environ Health 1987;21:193–203.

Kaczenski JH, Hallenbeck WH. Migration of ingested asbestos. Environ Res 1984;35:531–51.

Kociok N, Unfried K, Roller M, Dehnen W. DNA fingerprint analysis reveals differences in mutational patterns in experimentally induced rat peritoneal tumors, depending on the type of environmental mutagen. Cancer Genet Cytogenet 1999;111:71–6.

Lacourt A, Gramond C, Rolland P, Ducamp S, Audignon S, Astoul P, Chamming's S, Gilg Soit Ilg A, Rinaldo M, Raherison C, Galateau-Salle F, Imbernon E, Pairon JC, Goldberg M, Brochard P. Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma. Thorax 2014;69:532–9.

Langhoff MD, Kragh-Thomsen MB, Stanislaus S, Weinreich UM. Almost half of women with malignant mesothelioma were exposed to asbestos at home through their husbands or sons. Dan Med J 2014;61:A4902.

Larson TC, Antao VC, Bove FJ. Vermiculite worker mortality: Estimated effects of occupational exposure to Libby amphibole. J Occup Environ Med 2010;52:555–60.

Lash TL, Crouch, EA, Green LC. A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Occup Environ Med 1997;54:254–63.

Lavappa KS, Fu MM, Epstein SS. Cytogenetic studies on chrysotile asbestos. Environ Res 1975;10:165–73.

Lazarus AA, Philip A. Asbestosis Dis Mon 2011;57:14–26.

Lenters V, Burdorf A, Vermeulen R, Stayner L, Heederik D. Quality of evidence must guide risk assessment of asbestos. Ann Occup Hyg 2012;56:879–87.

Lenters V, Vermeulen R, Dogger S, Stayner L, Portengen L, Burdorf A, Heederik D. A meta-analysis of asbestos and lung cancer: is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? Environ Health Perspect 2011;119:1547–55.

Leonard SS, Mowrey K, Pack D, Shi X, Castranova V, Kuppusamy P, Vallyathan, V. In vivo bioassays of acute asbestosis and its correlation with ESR spectroscopy and imaging in redox status. Mol Cell Biochem 2002;234–235:369–77.

Li B, Tang SP, Wang KZ. Esophagus cancer and occupational exposure to asbestos: Results from a meta-analysis of epidemiology studies. Dis Esophagus 2016;29:421–8.

Liddell FD, McDonald AD, McDonald JC. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: Development from 1904 and mortality to 1992. Ann Occup Hyg 1997;41:13–36.

Lim H-S, Kim JY, Sakai K, Hisanaga N. Pulmonary asbestos and non-asbestos fiber concentrations in autopsied inhabitants in Pohang, Korea. Ind Health 2004;42:163–70.

Lippmann M. Effects of fiber characteristics on lung deposition, retention, and disease. Environ Health Perspect 1990;88:311–7.

Loomis D, Dement J, Richardson D, Wolf S. Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. Occup Environ Med 2010;67:580–4.

Luce D, Bugel I, Goldberg P, Goldberg M, Salomon C, Billon-Galland MA, Nicolau J, Quénel P, Fevotte J, Brochard P. Environmental exposure to tremolite and respiratory cancer in New Caledonia: A case-control study. Am J Epidemiol 2000;151:259–65.

Lynch KM, Smith WA. Pulmonary Asbestosis III: Carcinoma of Lung in Asbesto-Silicosis. Am J Cancer 1935;24:56–64.

Magnani C, Agudo A, González CA, Andrion A, Calleja A, Chellini E, Dalmasso P, Escolar A, Hernandez S, Ivaldi C, Mirabelli D, Ramirez J, Turuguet D, Usel M, Terracini B. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. Br J Cancer 2000;83:104–11.

Magnani C, Dalmasso P, Biggeri A, Ivaldi C, Mirabelli D, Terracini B. Increased risk of malignant mesothelioma of the pleura after residential or domestic exposure to asbestos: A case-control study in Casale Monferrato, Italy. Environ. Health Perspect 2001;109:915–9.

Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. Am J Respir Crit Care Med 2013;188:90–6.

McConnell EE, Axten C, Hesterberg TW, Chevalier J, Miiller WC, Everitt J, Oberdörster G, Chase GR, Thevenaz P, Kotin P. Studies on the inhalation toxicology of two fiberglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of chronic exposure. Inhal Toxicol 1999;11:785–835.

McConnochie K, Simonato L, Mavrides P, Christofides P, Pooley FD, Wagner JC. Mesothelioma in Cyprus: The role of tremolite. Thorax 1987;42:342–7.

McDonald AD, Case BW, Churg A, Dufresne A, Gibbs GW, Sébastien P, McDonald JC. Mesothelioma in Quebec chrysotile miners and millers: Epidemiology and aetiology. Ann Occup Hyg 1997;41:707–19.

McDonald AD, Fry JS, Woolley AJ, McDonald J. Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 1983;40:361–7.

McDonald JC, Harris J, Armstrong B. Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup Environ Med 2004;61:363–6.

McDonald JC, McDonald AD. Chrysotile, tremolite, and mesothelioma. Science 1995;267:776–7.

Muhle H, Pott F. Asbestos as reference material for fibre-induced cancer. Int Arch Occup Environ Health 2000;73(Suppl):S53-9.

Mzileni O, Sitas F, Steyn K, Carrara H, Bekker P. Lung cancer, tobacco, and environmental factors in the African population of the Northern Province, South Africa. Tob Control 1999;8:398–401.

National Toxicology Program. NTP lifetime carcinogenesis studies of Chrysotile Asbestos (CAS No. 12001-29-5) in Syrian golden hamsters (Feed Studies). Natl Toxicol Program Tech Rep Ser 1990;246:1–192.

Ngamwong Y, Tangamornsuksan W, Lohitnavy O, Chaiyakunapruk N, Scholfield CN, Reisfeld B, Lohitnavy M. Additives synergism between asbestos and smoking in lung cancer risk: A systematic review and meta-analysis. PLoS One 2015;10:e0135798.

NTP. Report on Carcinogens (11th edition): Appendix B. National Toxicology Program, 2005.

Oddone E, Ferrante D, Tunesi S, Magnani C. Mortality in asbestos cement workers in Pavia, Italy: A cohort study. Am J Ind Med 2017;60:852–866.

Offermans NSM, Vermeulen R, Burdorf A, Goldbohm RA, Kauppinen T, Kromhout H, van den Brandt PA. Occupational asbestos exposure and risk of pleural mesothelioma, lung cancer, and laryngeal cancer in the prospective Netherlands cohort study. J Occup Environ Med 2004a;56:6–19.

Offermans NSM, Vermeulen R, Burdorf A, Goldbohm RA, Keszei AP, Peters S, Kauppinen T, Kromhout H, van den Brandt PA. Occupational asbestos exposure and risk of esophageal, gastric and colorectal cancer in the prospective Netherlands Cohort Study. Int J Cancer 2014b;135:1970–7.

Oghiso Y, Kagan E, Brody AR. Intrapulmonary distribution of inhaled chrysotile and crocidolite asbestos: Ultrastructural features. Br J Exp Pathol 1984;65:467–84.

Omland Ø, Meyer HW, Lauridsen HL, Bønløkke JH, Sherson DL. [Work-up of asbestosis and estimation of asbestos exposure in an occupational context]. Ugeskr Laeger 2018;180 (22):V10170739.

Padilla-Carlin DJ, Schladweiler MCJ, Shannahan JH, Kodavanti UP, Nyska A, Burgoon LD, Gavett SH. Pulmonary inflammatory and fibrotic responses in Fischer 344 rats after intratracheal instillation exposure to Libby amphibole. J Toxicol Environ Health A 2011;74:1111–32.

Pan X, Day HW, Wang W, Beckett LA, Schenker MB. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med 2005:172:1019–25.

Peng W, Jia X, Wei B, Yang L, Yu Y, Zhang L. Stomach cancer mortality among workers exposed to asbestos: A meta-analysis. J Cancer Res Clin Oncol 2015;141:1141–9.

Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T. Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 1985;29:305–55.

Pinkerton KE, Pratt PC, Brody AR, Crapo JD. Fiber localization and its relationship to lung reaction in rats after chronic inhalation of chrysotile asbestos. Am J Pathol 1984;117:484–98.

Piolatto G, Negri E, La Vecchia C, Pira E, Decarli A, Peto J. An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. Br J Ind Med 1990;47:810–4.

Pira E, Romano C, Donato F, Pelucchi C, Vecchia C, Boffetta P. Mortality from cancer and other causes among Italian chrysotile asbestos miners. Occup Environ Med 2017;74:558–563.

Platek SF, Groth DH, Ulrich CE, Stettler LE, Finnell MS, Stoll M. Chronic inhalation of short asbestos fibers. Fundam Appl Toxicol 1985;5: 327–40.

Plato N, Martinsen JI, Sparén P, Hillerdal G, Weiderpass E. Occupation and mesothelioma in Sweden: Updated incidence in men and women in the 27 years after the asbestos ban. Epidemiol Health 2016;38:e2016039.

Pollice L, Molinini R, Paoletti L, Batisti D, Caruso G, Di Nunno C, Gentile A. [Asbestos fiber count in extra-pulmonary tissues]. G Ital Med Lav Ergon 1997;19:39–41.

Rees D, Myers JE, Goodman K, Fourie E, Blignaut C, Chapman R, Bachmann MO. Case-control study of mesothelioma in South Africa. Am J Ind Med 1999;35:213–22.

Rees DKB, Du Toit RSJ, Rendall R. Tremolite in Southern African chrysotiles. S Afr J Sci 1992;88:468–469.

Reid A, de Klerk NH, Magnani C, Ferrante D, Berry G, Musk AW, Merler E. Mesothelioma risk after 40 years since first exposure to asbestos: A pooled analysis. Thorax 2014;69:843–50.

Reid A, Heyworth J, de Klerk N, Musk AW. Asbestos exposure and gestational trophoblastic disease: A hypothesis. Cancer Epidemiol Biomarkers Prev 2009;18:2895–2898.

Repp K, Lorbeer R, Ittermann T, Gläser S, John U, Hoffmann W, Völzke H. Occupational exposure to asbestos is associated with increased mortality in men recruited for a population-based study in Germany. Int J Occup Med Environ Health 2015;28:849–62.

Rihn B, Coulais C, Kauffer E, Bottin MC, Martin P, Yvon F, Vigneron JC, Binet S, Monhoven N, Steiblen G, Keith G. Inhaled crocidolite mutagenicity in lung DNA. Environ Health Perspect 2000;108:341–6.

Robinson BWS, Creaney J, Lake R, Nowak A, Musk AW, de Klerk N, Winzell P, Hellstrom KE, Hellstrom I. Mesothelin-family proteins and diagnosis of mesothelioma. Lancet (London, England) 2003;362:1612–6.

Roe FJ, Walters MA, Harington JS. Tumour initiation by natural and contaminating asbestos oils. Int J Cancer 1966;1:491–5.

Roggli V, Gibbs AR, Attanoos R, Churg A, Popper H, Corrin B, Franks T, Galateau-Salle F, Galvin J, Hasleton P, Honma K. Pathology of asbestosis: An update of the diagnostic criteria response to a critique. Arch Pathol Lab Med 2016;140:950–2.

Roggli VL, Brody AR. Changes in numbers and dimensions of chrysotile asbestos fibers in lungs of rats following short-term exposure. Exp Lung Res 1984;7:133–47.

Roggli VL, George MH, Brody AR. Clearance and dimensional changes of crocidolite asbestos fibers isolated from lungs of rats following short-term exposure. Environ Res 1987;42:94–105.

Selikoff IJ, Hammond EC, Churg,J. Asbestos exposure, smoking, and neoplasia. JAMA 1968;204:106–12.

Shvedova AA, Yanamala N, Kisin ER, Tkach AV, Murray AR, Hubbs A, Chirila MM, Keohavong P, Sycheva LP, Kagan VE, Castranova V. Long-term effects of carbon containing engineered nanomaterials and asbestos in the lung: One year postexposure comparisons. Am J Physiol Lung Cell Mol Physiol 2014;306:L170-82.

Stayner L, Kuempel E, Gilbert S, Hein M, Dement J. An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. Occup Environ Med 2008;65:613–9.

Stayner L, Smith R, Bailer J, Gilbert S, Steenland K, Dement J, Brown D, Lemen R, 1997. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. Occup Environ Med 1997;54:646–52.

Stayner LT, Dankovic DA, Lemen RA. Occupational exposure to chrysotile asbestos and cancer risk: A review of the amphibole hypothesis. Am J Public Health 1996;86:179–86.

Sullivan PA. Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: Update of a cohort mortality study. Environ Health Perspect 2007;115:579–85.

Topinka J, Loli P, Georgiadis P, Dusinská M, Hurbánková M, Kováciková Z, Volkovová K, Kazimírová A, Barancoková M, Tatrai E, Oesterle D, Wolff T, Kyrtopoulos SA. Mutagenesis by asbestos in the lung of lambda-lacI transgenic rats. Mutat Res 2004;553:67–78.

Truhaut R, Chouroulinkov I. Effect of long-term ingestion of asbestos fibres in rats. IARC Sci Publ 1989;(90):127–33.

Unfried K, Schürkes C, Abel J. Distinct spectrum of mutations induced by crocidolite asbestos: clue for 8-hydroxydeoxyguanosine-dependent mutagenesis in vivo. Cancer Res 2002;62:99–104.

US EPA. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure. United States Environmental Protection Agency, 1988.

Van den Borre L, Deboosere P. Asbestos in Belgium: An underestimated health risk. The evolution of mesothelioma mortality rates (1969-2009). Int J Occup Environ Health 2014;20:134–40.

Van der Bij S, Koffijberg H, Lenters V, Portengen L, Moons KGM, Heederik D, Vermeulen RCH. Lung cancer risk at low cumulative asbestos exposure: Meta-regression of the exposure-response relationship. Cancer Causes Control 2013;24:1–12.

Varga C, Horváth G, Timbrell V. In vivo studies on genotoxicity and cogenotoxicity of ingested UICC anthophyllite asbestos. Cancer Lett 1996a;105:181–5.

Varga C, Pocsai Z, Horváth G, Timbrell V. Studies on genotoxicity of orally administered crocidolite asbestos in rats: Implications for ingested asbestos induced carcinogenesis. Anticancer Res 1996b;16:811–4.

Villeneuve PJ, Parent M-É, Harris SA, Johnson KC, Canadian Cancer Registries Epidemiology Research Group. Occupational exposure to asbestos and lung cancer in men: Evidence from a population-based case-control study in eight Canadian provinces. BMC Cancer 2012;12:595.

Vlaanderen J, Vermeulen R, Heederik D, Kromhout H, ECNIS Integrated Risk Assessment Group, European Union Network Of Excellence. Guidelines to evaluate human observational studies for quantitative risk assessment. Environ Health Perspect 2008;116:1700–5.

Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. Br J Cancer 1974;29:252–69.

Wagner JC, Pooley FD. Mineral fibres and mesothelioma. Thorax 1986;41:161–6.

Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 1960;17:260–71.

Wagner MM, Edwards RE, Moncrieff CB, Wagner JC. Mast cells and inhalation of asbestos in rats. Thorax 1984;39:539–44.

Wang X, Yano E, Lin S, Yu ITS, Lan Y, Tse LA, Qiu H, Christiani DC. Cancer mortality in Chinese chrysotile asbestos miners: Exposure-response relationships. PLoS One 2013;8:e71899.

Warnock ML. Lung asbestos burden in shipyard and construction workers with mesothelioma: Comparison with burdens in subjects with asbestosis or lung cancer. Environ Res 1989;50:68–85.

Wassermann M, Wassermann D, Steinitz R, Katz L, Lemesch C. Mesothelioma in children. IARC Sci Publ 1980;253–7.

Wu W-T, Lin Y-J, Li C-Y, Tsai P-J, Yang C-Y, Liou S-H, Wu T-N. Cancer attributable to asbestos exposure in shipbreaking workers: A matched-cohort study. PLoS One 2015;10:e0133128.

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