Kaolin

Health-based recommended occupational exposure limit

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Minister van Sociale Zaken en Werkgelegenheid

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Geachte minister,

Graag bied ik u hierbij het advies aan over de beroepsmatige blootstelling aan kaoline. Het maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige advieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Dit advies over kaoline is opgesteld door de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en aan de minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

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Dutch Expert Committee on Occupational Standards
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2007/12OSH, The Hague, December 18, 2007

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Samenvatting

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen (GBBS) van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht op de werkplek waaraan werknemers beroepsmatig kunnen worden blootgesteld.

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan kaolinestof. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór mei 2007 zijn verschenen.

Fysische en chemische eigenschappen

Kaoline (CAS 1332-58-7) is een klei-mineraal dat voornamelijk uit kaoliniet bestaat, een niet-vezelachtig aluminiumsilicaat. Kaoline bevat daarnaast kleine hoeveelheden van andere mineralen, zoals kwarts, mica en titaniumdioxide. Kaoline is een fijn verdeeld wit tot lichtgeel poeder, met een smaak van aarde. Het wordt gebruikt bij het maken van keramiek en vuurvaste materialen, als vulmiddel in plastics, papier, rubber, verven en lijmen, als coating voor hoogwaardig papier, en als middel tegen diarree.

Monitoring

Blootstelling aan kaoline vindt voornamelijk plaats door de inademing van stofdeeltjes van kaoline. De Amerikaanse instellingen ‘National Institute for Occupational Safety and Health’ (NIOSH) en ‘Occupational Safety and Health Administration’ (OSHA) hebben standaardmethoden beschreven voor de kwantitatieve bepaling van respirabel stof. Kaoline wordt aangetoond met behulp van röntgendiffractie of elektronenmicroscopie.

Grenswaarden

Nederland heeft geen grenswaarde voor beroepsmatige blootstelling aan kaolinestof. De Britse ‘Health and Safety Executive’ (HSE) en de 'American Conference of Governmental Industrial Hygienists’ (ACGIH) adviseren een grenswaarde van 2 mg/m^3 respirabel kaolinestof. De Amerikaanse instellingen NIOSH en OSHA hanteren een grenswaarde van 5 mg/m^3, achtereenvolgens als tijdgewogen gemiddelde over 10 uur en 8 uur.

Daarnaast heeft de ACGIH kaoline geclassificeerd met A4: niet classificeerbaar als kankerverwekkende stof voor de mens.

Kinetiek en toxisch werkingsmechanisme

Het is niet bekend hoe kaolinedeeltjes de longen beschadigen. Wetenschappelijke beschrijvingen van de kinetiek en het toxische werkingsmechanisme van stofdeeltjes van kaoline zijn niet gevonden.

Effecten

Uitgebreide beschrijvingen van casussen en een aantal epidemiologische onderzoeken, hoofdzakelijk uit Groot-Brittannië en de Verenigde Staten, hebben aangetoond dat chronische blootstelling aan kaoline pneumoconiose (stoflong) kan veroorzaken. Pneumoconiose veroorzaakt door kaoline, wordt ook wel kaolinose genoemd. Pneumoconiose wordt gediagnosticeerd met behulp van röntgenfoto’s van de longen. De eenvoudigste vorm van pneumoconiose (ILO categorie 1) gaat nog niet gepaard met een moeizamere ademhaling. De verminderde ademhalingsfunctie wordt voornamelijk gezien bij de gecompliceerde vorm (ILO categorie A-C). De commissie beschouwt echter de eenvoudigste

vorm van pneumoconiose al als een ongewenst effect, overeenkomstig het rapport van de Europese Commissie hierover.[1]

Over de hoeveelheid kaoline die gezondheidsproblemen oplevert, is weinig bekend. Wetenschappelijke publicaties met kwantitatieve gegevens over de blootstelling of een dosis-effectrelatie zijn schaars. De beschikbare gegevens bij dieren zijn niet bruikbaar voor het afleiden van een gezondheidskundige advieswaarde. Er is geen onderzoek gevonden dat geschikt is voor de beoordeling van de kankerverwekkendheid van kaoline, en de effecten op de vruchtbaarheid en de ontwikkeling van het nageslacht.

Er is één onderzoek met gegevens over de relatie tussen de cumulatieve dosis en ILO categorie 1 bij werknemers.[2] Volgens de onderzoekers ontwikkelt de gemiddelde niet-rokende werknemer pneumoconiose ILO categorie 1 op 60-jarige leeftijd na een 40-jarige beroepsmatige blootstelling aan 2,1 mg/m^3 respirabel kaolinestof. De betreffende publicatie bevat alleen gegevens over het niveau van de blootstelling waarbij de gemiddelde werknemer pneumoconiose ontwikkelt. Hieruit kan de commissie geen LOAEL of NOAEL afleiden. In deze publicatie ontbreken gegevens over het kwartsgehalte van het kaolinestof waaraan de werknemers waren blootgesteld. De aanwezigheid van kwarts kan het onderscheid tussen kaolinose en silicose (stoflong door blootstelling aan kwarts) bemoeilijken.

Evaluatie en advies

Volgens de commissie is overtuigend aangetoond dat beroepsmatige blootstelling aan kaolinestof schadelijke effecten heeft op de longen en uiteindelijk kan leiden tot pneumoconiose (stoflong).

De commissie is van mening dat beroepsmatige blootstelling aan 2,1 mg/m^3 respirabel kaolinestof ongewenst is omdat het een aanzienlijk risico inhoudt op het ontwikkelen van pneumoconiose ILO categorie 1. Uit de beschikbare wetenschappelijke literatuur kan de commissie echter geen NOAEL of LOAEL voor kaolinestof vaststellen. Daarom kan de commissie geen gezondheidskundige advieswaarde afleiden.

Dit advies bevat een aanvullende overweging van de commissie die betrekking heeft op de inademing van respirabel kaolinestof door werknemers.

12 Kaolin

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for chemical substances in the air in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS).

In this report, the committee discusses the consequences of occupational exposure to kaolin dust. The committee's conclusions are based on scientific papers published before May 2007.

Physical and chemical properties

Kaolin (CAS 1332-58-7) is a clay mineral that mainly consists of kaolinite, a non-fibrous aluminosilicate with small quantities of other minerals, such as quartz, mica and TiO_2. Kaolin is a fine white to light-yellow powder with an earthy taste. It is used in the manufacture of refractory materials, and ceramics; as a filler in plastics, paper, rubber, paints, and adhesives; as a coating for high quality paper; and as a gastro-intestinal adsorbent.

Monitoring

Exposure to kaolin as respirable dust particles is measured gravimetrically. The National Institute for Occupational Safety and Health (NIOSH) and the US Occupational Safety and Health Administration (OSHA) have described standard methods for the quantitative monitoring of respirable dust. Kaolin is identified by X-ray diffraction and electron microscopy.

Limit values

In the Netherlands, there is no occupational exposure limit for respirable kaolin dust. The UK Health and Safety Executive (HSE) and the American Conference of Governmental Industrial Hygienists (ACGIH) recommend 2 mg/m^3 respirable kaolin dust as the occupational exposure limit. The ACGIH threshold limit value (TLV) of 2 mg/m^3 respirable kaolin dust is only valid if it contains less than 1% quartz and no asbestos. In addition, the ACGIH has notified kaolin as an A4 substance, meaning that kaolin is not classifiable as a human carcinogen. The US NIOSH recommends a 10h-TWA exposure limit of 5 mg/m^3 and the US OSHA uses an 8h-TWA exposure limit of 5 mg/m^3.

Kinetics

No adequate studies on the kinetics and the mechanisms of action of kaolin are available.

Effects

Many reports of well-studied cases and a number of cross-sectional studies, mainly in the United Kingdom and the USA, have shown that long-term exposure to kaolin may lead to pneumoconiosis, which has been named kaolinosis. Pneumoconiosis is diagnosed by chest X-ray, and is categorized as simple pneumoconiosis (category 1-3) or complicated pneumoconiosis (category A-C) (annex D). Clinical symptoms and effects on pulmonary function are mainly observed in the complicated form. Although the mildest form of pneumoconiosis ILO category 1 is not yet associated with a decrease of pulmonary function, the committee considers pneumoconiosis category 1 as an undesired health effect, in agreement with the European Committee's report on miner's pneumoconiosis. In this report, pneumoconiosis category 1 is recognized as an occupational disease.[1]

Studies with exposure data or dose-effect relationships are scarce. The available animal data are not suitable for the derivation of a health-based recommended occupational exposure limit. Adequate studies on the carcinogenicity or reproduction toxicity of kaolin are not available.

There is one study with human data in which a dose-response relationship was reported for respirable kaolin dust.[2] According to this study, the average non-smoking worker reaches pneumoconiosis ILO category 1 at the age of 60 after 40 years of occupational exposure to 2.1 mg/m^3 respirable kaolin dust. From the data as presented in this publication, the committee can not establish a NOAEL or LOAEL. The publication does not contain information on the quartz content of the respirable dust exposures, the presence of which in kaolin can make it difficult to distinguish kaolinosis from silicosis (pneumoconiosis caused by quartz).

Evaluation and advice

According to the committee, it has convincingly been shown that occupational exposure to kaolin has adverse health effects involving the lungs and with pneumoconiosis as the clinical finding.

It is the committee's opinion that occupational exposure to 2.1 mg/m^3 respirable kaolin dust is undesired as it constitutes an substantial risk for the development of pneumoconiosis ILO category 1. However, no studies are available from which the committee can establish a NOAEL or LOAEL for kaolin dust. Therefore, the committee cannot derive a health-based recommended occupational exposure limit for kaolin dust.

In this advice, the committee gives an additional consideration on the inhalatory exposure to respirable kaolin dust in the workplace.

Chapter 1

Scope

1.1 Background

At the request of the Minister of Social Affairs and Employment (annex A), the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of chemical substances used in the workplace. The purpose of these evaluations is to recommend health-based occupational exposure limits for concentrations in the air, provided that the database allows the derivation of such values.

1.2 Committee and procedure

The present document contains the assessment of DECOS, hereafter called the committee, of the health hazard of kaolin. The members of the committee are listed in Annex B.

In 2007 the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The committee's recommendations on the health-based occupational exposure limit of kaolin have been based on scientific data which are in the public domain. Data were obtained from the online databases Toxline and Medline/PubMed. The search was performed with "kaolin? OR CAS 1332-58-7" in combination with "toxic? OR epidemio?" The last search was performed in May 2007.

A list of abbreviations is given in Annex H.

Chapter 2

Identity, properties and monitoring

2.1 Chemical identity

Kaolin (CAS number 1332-58-7; EEC number 310-127-6; RTECS number GF1670500) is a clay that consists primarily of kaolinite (CAS number 1318-74-7; EEC number 215-286-4), a non-fibrous aluminium silicate with the molecular formula $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$. Kaolin is a fine white to light-yellow powder with an earthy taste.[3] It usually contains small amounts of other minerals such as quartz, mica and TiO_2. The amounts differ depending on the geographic location at which the kaolin is extracted. Kaolin from Cornwall UK (purified Cornish china clay) typically consists of 89% kaolinite, 7% mica and up to 2% quartz[4], while kaolin from Georgia (USA) typically consists of 98% kaolinite, 1% TiO_2 and <1% quartz.[5,6] However, some 'kaolin-like' clays may contain substantial amounts of quartz. For example, the kaolin-like clays used in South African pottery contained 23-58% quartz.[7] In the present risk assessment, exposure to kaolin is defined as exposure to kaolin dust containing $\leq$2% quartz.

Synonyms and trade names for kaolin include Altowhites, Argilla, Bentone, Bilt-Cote, Bolus alba, China clay, Continental, Dixie, Emathlite, Fitrol, Glomax, Hydrite, Hydrated aluminium silicate, Hydrous aluminium silicate, Kaopaous, Kaophills-2, Langford, McNamee, Par clay, Peerless 2, Porcelain clay, and Snow tex.

Kaolin may be used to manufacture refractory ceramic fibres. These fibres are synthetic non-crystalline fibres produced by melting amorphous kaolin and

adding inorganic oxides. Refractory ceramic fibres are excluded from the present assessment.

2.2 Physical and chemical properties

Kaolin is insoluble in water, ether, alcohol, acids and alkaline solutions.[3] The particle size of crude kaolin ranges from 0.05 – 150 μm.[5] Processed kaolin has a particle size of <10 μm, with more than 50% of the particles being <2 μm[6], that is in the respirable range. Kaolinite has a molecular weight of 258 g/mol, a density of 2.1 – 2.6 g/cm^3, and a hardness of 2.3.[8]

Kaolinite particles are disc shaped with a diameter to thickness ratio of about 10:1. They owe their properties to the fact that the silicon atom can bind to oxygen atoms to form extensive thin flat sheets in which each silicon atom is surrounded by four oxygen atoms in a tetrahedral arrangement. These silica sheets can bind to alumina sheets of aluminium oxide (AlO(OH)) in which aluminium is surrounded by an octahedral arrangement of oxygen atoms and hydroxyl groups. The double sheet structure can be stacked in layers held together by hydrogen-bonds. This is the basic structure of kaolinite which is referred to as a 1:1 layer silicate.[9] The silanol surface groups are slightly acidic and may be negatively charged; the aluminol surface groups are amphoteric or slightly basic and may be positively charged. Flat surfaces of kaolinite thus may reveal uneven distributions of positive and negative charges.

2.3 EU Classification and labelling

No data available.

2.4 Validated analytical methods

Inhalation of dust particles is the major route of human exposure to kaolin. Quantitative methods for measuring respirable dust are gravimetric, and measure the weight of dust collected on a filter from a known volume of air.

The National Institute for Occupational Safety and Health (NIOSH) and the US Occupational Safety and Health Administration (OSHA) have described methods for sampling respirable dust (NIOSH method 0600: particulates not otherwise regulated, respirable) using an appropriate sampler with a polyvinyl chloride or equivalent filter. When sampling respirable dust, the filter is preceded by a Nylon cyclone. Kaolin is identified by X-ray diffraction or electron microscopy.

No validated methods for the determination of the amount of kaolin in biological samples were found.

Chapter 3

Sources

Kaolin is a product of the geologic weathering of feldspar, a primary constituent of granite rocks. Deposits usually consist of a soft aggregation of sand, mica and kaolinite. Commercially exploitable deposits are found in several areas around the world. In the United States, the deposits are primarily concentrated in a belt extending from central Georgia to west central South Carolina. In the UK, deposits are found in Cornwall and Devon.[4,10,11]

Kaolin is removed from the walls of the open pit by washing out the decomposed feldspar with a high pressure water jet, resulting in a kaolin slurry, or by surface strip mining, resulting in moist lumps. Mica and sand are removed from the slurry by differential sedimentation. The refined clay suspension is dried in a coal-fired open pan kiln or by filter press techniques, until the moisture content is about 10%. Then the clay is milled, bagged and loaded for transportation. The moist kaolin lumps are processed by either a ‘wet’ or a ‘dry’ method. In the wet method, the kaolin is mixed with water and contaminants are removed by differential sedimentation. Excess water is removed by vacuum filtration and spray drying before the kaolin is shipped as a rehydrated slurry or dry clay. In the dry method contact with water does not occur. The kaolin lumps are sliced, dried and pulverized by air flotation. Sand and other impurities are removed by filtering methods. Then the kaolin is bagged and loaded for transportation.[6,10,12] The dry process, which generates huge amounts of dust, was generally used before 1940 and has now been largely replaced by the wet process.

The US is the world's largest producer of kaolin with an annual production volume of about 9 million metric tons (1990-2002), of which about 3 million tons are exported. About 175,000 tons are exported to The Netherlands (2002). The UK produces about 3 million tons annually (1990-2002), which is mainly exported. The world production of kaolin in 2004 was 44 million tons, with 53 countries producing more than 1000 metric tons per year.[13]

Kaolin is used in manufacturing refractory materials and ceramics, as a filler in plastics, paper, rubber, paints and adhesives, as a coating for high quality paper, and as a gastro-intestinal adsorbent in the treatment of diarrhea.[11,14] No specific data are available on the use and origin of kaolin by Dutch industries. Therefore, the committee can not exclude that some of the kaolin used by the Dutch industries contains more than 2% quartz.

Chapter 4

Exposure

4.1 General population

Kaolin is a natural component of the soil and may occur widely in ambient air as floating dust[15]. Accordingly, exposure of the general population to kaolin is universal, albeit at low concentrations. In case examinations, both ante mortem and post mortem, kaolinite particles have been found in the lungs of men without occupational dust exposure (see WHO report[15]). In the vicinity of mines and industrial areas, kaolin is likely to be present at higher concentrations in the air than in non-mining and non-industrial sites. However, there are no measured data available on background concentrations of kaolin nor on the exposure of the general population to kaolin.

4.2 Working population

Processing of kaolin involves considerable exposure to kaolin dust. Exposure was especially significant before the 1960s.[10] After drying, nearly all work stages were carried out in high dust concentrations. Many operational changes have been introduced in the 1970s to improve airborne dust control and to reduce the amount of dust generated in the production process. More effective ventilation and closed technologies have led to a progressive reduction in airborne dust concentrations.[2,16] Data on the occupational exposure to kaolin in the Netherlands are not available.

Ambient air concentrations of kaolin and personal exposures to kaolin are usually reported as gravimetric dust concentrations. The available data are summarized in Table 4.1.

Three studies on the exposure to kaolin dust from the Georgia kaolin mines have been published.[11,12,17] A NIOSH study conducted by Sepulveda *et al.* (1983) in 1981 reported that over 50% of the dust fractions (aerodynamic particle size <10 μm) adjacent to pulverizers and to the baghouse were respirable. Other locations sampled exhibited respirable dust fractions of 10-20%. In the mill areas, dust existed of 96% kaolinite and 4% TiO_2. In all job categories (miner, car loader, bin operator, mill operator, baghouse labourer), breathing zone samples (n=44) of respirable dust showed values $\leq$5 mg/m^3. None of the personal respirable dust samples contained quartz. Total dust levels by area showed means above 10 mg/m^3 for the loading area, the milling area, and the pulverizing area.[11] All samples in this study were full-shift samples.

Altekruse *et al.* (1984) collected personal air samples (n=157) from 1977-1981 at a Georgia kaolin mine where kaolin was still being processed by the dry method. Of the dust particles, 50-80% were in the respirable range. The full-shift respirable dust concentrations were significantly higher in the processing area (2-5 mg/m^3) than in the maintenance and mining areas (0-1 mg/m^3) (p<0.025). Mineral analysis of the dust showed 94-98% kaolinite and 2-6% TiO_2.[12]

The studies described below lack data on the sampling time of exposure measurement. A study by Kennedy *et al.* (1983) at a Georgia kaolin mine reported that all processing facilities were documented by U.S. Mine Safety and Health Administration testing to be below 5 mg/m^3 (with <1% quartz) respirable kaolin dust at the time of study (1977-1980). Previous surveys of the same plant had documented maximum levels of 377 mg/m^3 in 1951, and 361 mg/m^3 in 1960.[17]

In the Cornish kaolin industry, several measurements of personal respirable dust concentrations (0.5-4.7 mg/m^3) have been reported.[2,16]

In a Polish study by Szadkowska-Stanczyk *et al.* (2001), 80% of the measurements of kaolin dust within the area of the loaders' work posts exceeded the allowable concentration of 4 mg/m^3. Quartz levels in kaolin dust were 3.2-5.1%.[18]

In a multi-centre epidemiological study, conducted by the International Agency for Research on Cancer (IARC), the exposure database reported exposure measurements from 4 paper mills. One of the 25 measurements was higher than 10 mg/m^3.[19]

Table 4.1 Available data on the occupational exposure to kaolin dust.

Exposure group / area	Number and type of samples[a]	Kaolin dust fraction	Average dust concentrations (mg/m³)[b]	Year of sampling	Country[ref]
Miner	10, personal	respirable	~ 0.2 (0.1-0.35)[c]	1981	USA[11]
Car loader	3, personal	respirable	~ 1 (0.7-1.2)[c]		
	3, area	total	~ 10 (7-15)[c]		
Bin operator	3, personal	respirable	~ 2 (1.3-2.5)[c]		
	7, area	total	~ 20 (10-30)[c]		
Mill operator	3, personal	respirable	~ 1 (0.8-1.2)[c]		
	8, area	total	~ 20 (10-80)[c]		
Bag house labourer	5, personal	respirable	~ 2 (0.3-5)[c]		
	3, area	total	~ 5 (1.5-9)[c]		
Processing area	14, personal	respirable	~ 3.9	1977	USA[12]
	9, personal		~ 3.8	1978	
	5, personal		~ 5.3	1980	
	14, personal		~ 1.8	1981	
	68, personal		1.74	1981	
Maintenance area	15, personal		~ 0.9	1980	
	11, personal		~ 0.1	1981	
Mine	12, personal		~ 0.8	1980	
	5, personal		~ 0.1	1981	
	4, personal		0.14	1981	
Processing area	unknown	unknown	Max. value 377	1951	USA[17]
		unknown	Max. value 361	1960	
		respirable	< 5	1977-1980	
Loader/unloader	unknown	respirable	6.1-12.7	1976-1990	Poland[18]
		total	6.7-156.0	1995-1998	
Slurry maker		respirable	0.5-0.9	1976-1990	
		total	4.1-27.5	1995-1998	
Dryers	681, personal	respirable	1.9	1984-1986	UK[16]
Attritor mills	114, personal		2.7		
Calciners	63, personal		2.5		
Slurry plants	69, personal		1.1[d]		
Tube presses	5, personal		0.5		
Atritor mills		respirable	4.7 (9.32)[e]	1978	UK[2]
			2.1 (3.36)[e]	1990	
Dryers	Total of 500 personal and area samples per year		3.5 (5.41)[e]	1978	
			1.7 (2.78)[e]	1990	
Calciners			3.5 (3.93)[e]	1978	
			2.2 (3.25)[e]	1990	
Slurry plants			1.6 (mean of 2 samples)	1978	
			1.2 (2.26)[e]	1990	
Paper mills	25, unknown	unknown	0.94 (0-21.5)[e]	1950-1994	International multi-centre study[19]

[a] Sampling time was full-shift in references 4 and 39; in the other references sampling time is not given.
[b] Results from references 4 and 39 have been estimated from graphs.
[c] Average dust concentration together with range shown in parentheses.
[d] Assumed average based on regular sampling at an older, dustier plant and a small number of samples from a modern, less dusty plant.
[e] Average dust concentration together with upper deciles shown in parentheses.

Chapter 5

Kinetics

There are no data available.

Chapter 6

Mechanism of action

Many reports of well-studied cases and a number of cross-sectional studies, mainly in the United Kingdom and Georgia, USA, have shown that long-term exposure to kaolin may lead to a pneumoconiosis called kaolinosis. Pneumoconiosis is a pulmonary disease caused by the inhalation of inorganic mineral dusts (see Annex D). The toxic mechanism of action through which kaolin induces kaolinosis has not been elucidated but reactive hydroxyl radicals have been implicated.

6.1 Studies in humans

No data available.

6.2 Studies in animals

No data available.

6.3 *In vitro* studies

A few studies have examined the hypotheses that kaolin causes pneumoconiosis by catalyzing the generation of reactive oxygen species from chemical substrates supplied by the lung itself[20,21], or by distortion and lysis of the cell membrane by non-free radical surface groups[22]. Using an *in vitro* system, Kennedy *et al.*

(1989)[20] showed that kaolin catalyzes the formation of hydroxyl radicals from hydrogen peroxide in the presence of ascorbate as a reducing agent. Lipid peroxidation of membranes was studied with human erythrocyte suspensions. Kaolin (1 mg/ml) significantly increased malondialdehyde content ($p<0.05$) and caused marked *in vitro* lysis of 50% of the human red blood cells in 1 hour ($p<0.001$).[20]

Baser *et al.* (1990)[21] also showed that kaolin could generate hydroxyl radicals from hydrogen peroxide in an *in vitro* system with ascorbate as a reducing agent. Kaolinite cytotoxicity is suppressed by incubation in the presence of dipalmitoyl phosphatidylcholine, a principle lipid component of pulmonary surfactant.[22,23] Phagolysosomal enzymatic digestion can hydrolyse and remove the adsorbed surfactant molecules, and so restore kaolin dust cytotoxicity. Mineral specificity of that restoration has been postulated to be the basis for the observed difference in fibrogenic activity between kaolin and quartz.[23]

Other studies have shown kaolin-induced cytotoxicity by measuring release of lactate dehydrogenase from macrophages[24-26], and cultured cells[27]. Kaolin-induced haemolysis of sheep[23,28] and human[20] erythrocytes has also been reported.

Murphy *et al.* (1993)[27] and Banin and Meiri (1990)[29] have reported the presence of alumino-silicates in Alzheimer's senile plaques. Banin and Meiri (1990)[29] examined possible mechanisms for the interaction of kaolinite with cultured murine neuroblastoma cells. The electrical activity of differentiated cells changed when kaolinite (125 µg/ml) was added. Within minutes, the membrane permeability began to rise, the resting potential depolarized and the ability to maintain action potentials in response to stimulation was lost. Within 30 min, the cells showed clear morphological signs of deterioration. The study concluded that a layout incorporating both negative and positive charges (as on the broken edges of kaolinite), and the non-isodiametrical geometry of the particles may be necessary for the acute neurotoxic interaction. The committee considers these studies on the presence of alumino-silicates in Alzheimer plaques not relevant for the risk assessment.

6.4 Conclusions

The available *in vitro* studies do not allow conclusions on the mechanism of action of kaolin.

Chapter 7

Effects

A wide variety of respiratory effects has been reported after exposure to kaolin. Many observations, based on chest X-ray suggest that kaolin workers develop pneumoconiosis. Pneumoconiosis is a pulmonary disease caused by the inhalation of inorganic mineral dusts. These dusts cause irreversible lung lesions (fibrosis) which manifest as parenchymal opacities and pleural abnormalities on chest X-ray films. These films are used to distinguish between simple and complicated pneumoconiosis according to the classification guideline of the International Labour Office (ILO; see Annex D). Kaolin-induced pneumoconiosis is also named kaolinosis. The presence of quartz in kaolin can make it difficult to distinguish kaolinosis from pneumoconiosis caused by quartz (silicosis).

In the epidemiological studies, quantitative exposure data are limited and information on the composition of the kaolin is scarce. Lung function measurements (spirometry) are often used to detect functional changes in the respiratory system and chest X-ray films to detect pathological changes.

7.1 Observations in humans

7.1.1 Irritation and sensitisation

Although kaolin is used extensively in cosmetics, no reports have been found on the possible adverse effects of kaolin upon direct skin contact.[15]

In a study by Epstein *et al.* (1989)[30], a spray of kaolin-containing fluorocarbon aerosols was used as a topical protectant against experimental poison ivy/oak dermatitis. The composition and concentration of the kaolin in the spray was not described. It was stated that none of the compounds used in this study (including kaolin) produced evidence of primary irritation or any unexpected or abnormal systemic responses in any of the 28 healthy volunteers.

Edenfield *et al.* (1960)[5] mentioned that "exposure of workers to high concentrations of kaolin dust, such as may result from a break in a pipe line or valve, produces little or no irritation of the eyes, nasal or pharyngeal membranes, and no cough or other symptoms of bronchitis". Since this quote is not substantiated by adequate data, the committee considers this information anecdotal.

7.1.2 *Acute and short-term toxicity*

No data available.

7.1.3 *Long-term toxicity*

Many epidemiological and case studies have been conducted to detect chronic effects in populations of kaolin workers. Most of these studies did not include detailed exposure assessment. Kaolin workers in Georgia, USA, and in Cornwall, UK have been studied most extensively. Case studies are shown in the Table in annex E. Epidemiological studies without exposure data are shown in the Table in annex F. Those with exposure data are given in annex G and described in more detail below.

Epidemiological studies with exposure data

There are five cross-sectional studies on occupational exposure to kaolin dust that include information on exposure levels. Three are from kaolin workers in Georgia, USA, and two are from kaolin workers in the UK.

Kaolin workers, Georgia, USA

In a cross-sectional study (1977-1980), Kennedy et al. (1983) surveyed 459 workers for the presence of pneumoconiosis by chest X-ray (International Labour Organization (ILO) classification, 1971) and for respiratory symptoms (dyspnoea, wheezing, cough and sputum).[17] The workers were employed in three Georgia kaolin mining and processing facilities with a mean duration of employment of 12 years. The workers were categorized into the following exposure

groups: production, maintenance, laboratory/mine or administration, in decreasing order of kaolin exposure. In all categories, respirable kaolin concentrations between 1977 and 1980 were $\leq$5 mg/m^3, with < 1% quartz. It is unclear whether these concentrations are from personal or area measurements, and whether the measurements are full-shift measurements or not.

The prevalence of pneumoconiosis (ILO categories 1-3) was 9.2% (n=42), with significantly more black people (20/147=13.6%) than white people (22/312=7.1%) having pneumoconiosis. The distribution of categories of pneumoconiosis did not differ significantly between black and white workers. X-ray films of most cases manifested fine or medium irregular opacities, evenly distributed in the lungs. Eight of the 42 cases showed large opacities representing complicated pneumoconiosis. Pleural thickening was seen in two of the 42 cases. Multivariate analysis showed that the only significant predictors of the X-ray presence of pneumoconiosis were age over 55 years (p<0.005) and exposure in the production area over 15 years (p<0.001). The X-ray presence of pneumoconiosis did not correlate with respiratory symptoms, smoking history or history of tuberculosis. Pulmonary function was measured by spirometry and expressed as forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). Spirograms of the 34 workers with mild pneumoconiosis were not significantly different from workers without pneumoconiosis. Clinical impairment of pulmonary function did not occur, except for mild, insignificant impairment in advanced cases (dyspnoea on exertion). A reanalysis of the data by Baser *et al.* (1987) showed that kaoline exposure was not independently associated with pneumoconiosis and lung function, and that significant differences in FVC's among production workers existed between the plants studied.[31]

This study did not include retired workers and there was no unexposed control group outside the kaolin industry. Separate data for the different exposure groups were not available. Furthermore, no clear kaolin dust levels were identified (less than 5 mg/m^3 respirable with less than 1% free crystalline silica as documented by U.S. Mine Safety and Health Administration testing; and as high as 377 mg/m^3 and 361 mg/m^3 in processing areas of Plant 3 in 1951 and 1960, respectively). Therefore, no dose-response relationship could be derived.[17] For these reasons, the committee decided not to use this study for the risk assessment.

In 1981, a cross-sectional health study was conducted by Sepulveda *et al.* (1983)[11] at a Georgia kaolin mine and mill among 39 current workers and 16 ex-workers, all with over 5 years of exposure, and among 10 current workers with less than 5 years of kaolin exposure. The workers were divided in five job cate-

gories, namely miners, car loaders, bin operators, mill operators and bag-house workers. An external non-kaolin exposed reference group (n=189) for the analysis of pulmonary function included workers from soft drink bottling companies, candy factories, a power tool company, the fabric department of a tire manufacturer, and shipping clerks in a poultry packing plant. Personal respirable dust and area total dust was sampled during full shifts. The airborne dust contained 96% kaolinite, 4% TiO_2 and no quartz. At processing areas, respirable dust fractions (aerodynamic particle size <10 μm) of over 50% were found, while at other locations respirable dust fractions of 10-20% were reported. Total dust levels exceeded 10 mg/m^3 in the car loading, bin and mill areas, while in none of the working areas respirable dust exceeded 5 mg/m^3.

Based on chest X-ray (ILO classification, 1971), 5 of 39 current workers and 3 of 16 ex-workers with 5 years or more of exposure were identified with pneumoconiosis (prevalence 8/55=15%). These included four cases of simple and four cases of complicated pneumoconiosis. In one current worker with simple pneumoconiosis, previous exposure to asbestos was discovered. Among the current workers with less than 5 years of kaolin exposure (n=8), none had pneumoconiosis. There were no X-ray data for the non-exposed comparison group. Kaolin workers in this study showed significantly lower values ($p<0.05$) for FVC, FEV_1 and peak flow rate than non-kaolin workers, when the values were adjusted for age, height, race, and pack-years of smoking. No relationship between pneumoconiosis and history of smoking or abnormalities of lung function was observed. The size of the subgroups with different job categories was small in this study. Because of the absence of historical air sampling data, this study could not provide reliable estimates of past exposure to kaolin nor a clear relationship between kaolin exposure and pneumoconiosis. Therefore, the committee could not use this study for the risk assessment.

In a cross-sectional study of a Georgia kaolin mine and processing plant, Altekruse *et al.* (1984)[12] examined pulmonary function and chest X-ray films from the entire work force of 65 men. In the study, personal air samples (n=157) collected between 1977-1981 were included. Workers were divided into three working area subgroups: production and processing area (continuous dust exposure), mining area (no dust exposure), plant and vehicle maintenance area (intermittent dust exposure). In the dry processing area, 50-80% of the dust was in the respirable range. Between 1977 and 1981, respirable kaolin dust concentrations (containing 94-98% kaolinite, 2-6% TiO_2 and no quartz) were significantly higher ($p<0.025$) in the processing area (2-5 mg/m^3) than in the maintenance and mining areas

($\leq$1 mg/m^3). The mean concentration of respirable kaolin dust in 1981 was 0.14 mg/m^3 in the mining area, and 1.74 mg/m^3 in the processing area.

X-ray (ILO classification, 1980) revealed pneumoconiosis in 5 of the 65 workers (prevalence 7.7%), all of whom had worked in the processing area for 7-36 years and all of whom had symptoms of bronchitis. Four of these five had simple, and one had complicated pneumoconiosis. The mean FVC and FEV_1 of the 5 workers with pneumoconiosis was mildly but significantly ($p<0.05$) reduced compared to the other 19 processing workers. The FVC and FEV_1 showed a small but significant ($p<0.05$) decline with increasing length of employment at the processing area. However, overall no differences in lung function values (FVC, FEV_1) and lung volumes were reported between working area subgroups. According to the authors, the study indicated that kaolin inhalation alone can lead to pneumoconiosis because of the complete absence of quartz in the dust, and that kaolin pneumoconiosis was associated with significant though mild effects on pulmonary function.[12] Because of the small number of workers included, the committee decided not to use this study for the risk assessment.

Kaolin workers, UK

In 1985, a cross-sectional study by Ogle *et al.* (1989)[16] examined chest X-ray films (ILO classification, revised 1980) of 3,400 current and 289 retired kaolin workers. Pneumoconiosis prevalence was 8.5%, with 271 cases in category 1, 39 in category 2, and 5 in category 3. Of the small opacities observed, 60% were rounded in shape, and 40% were irregular. Pleural thickening was shown in 87 cases, and pleural calcification in 17 cases. Smoking status did not statistically affect the X-ray results. Average personal respirable dust concentrations (1984-1986) ranged from 0.5 – 2.7 mg/m^3 depending on location. Information on the sampling time and on the composition of the dust (non-kaolin dust and quartz content) was not given. Employment was categorized into groups with similar dust exposure levels (Table 7.1). The investigators carried out regression analysis yielding regression coefficients (RC) describing the size of the effect of one exposure year on 1000 x Ln (X-ray score). This regression coefficient is a measure of the effect of one exposure year on the X-ray score for the average worker. Employment in attritor mills, china stone mills and as dryers was found to have the greatest effect on the X-ray diagnosed pneumoconiosis classification. Compared to the effects before 1971, the effects post 1971 - with improved working conditions installed in the early seventies - were about 50% lower as reflected by the regression coefficients for all workers in Table 7.1 (fourth column; values printed in bold). When workers in dusty jobs before 1971 were excluded, the

effects post 1971 were about 60-70% lower as reflected by the regression coefficients for the workers excluding those with pre-1971 dust exposure (seventh column, values printed in bold) compared with those for all workers pre-1971 (fourth column, pre-1971). This shows the effect of the improved working conditions since 1971.

Ventilatory capacity (FVC, FEV_1) was independent of employment history, but highly dependent on age and radiological score. The probability of exhibiting symptoms (cough, phlegm, breathlessness, wheeze) was dependent on the level of ventilatory capacity for each of the 3 smoking classes (current, ex- and non-smokers). Age, exposure to dust and X-ray category made no additional contribution.

The study lacks accurate exposure data from before 1978 and an unexposed control group, and therefore conclusions on the exposure-concentration dependent health effects of kaolin exposure are limited. Nevertheless, the investigators found the greatest effect of employment on X-ray category for attritor mill workers and china stone mill workers, and were able to show a major effect of the improved working conditions since the early 1970s. The authors noted that of the post-1971 group, 99 of 123 subjects whose X-ray score was greater than 0 had worked in jobs with little (n=51) or no (n=48) dust exposure. They explained this by the poor quality of the X-ray films (102/123), the higher age (61% being over 50) or by signs of disease other than pneumoconiosis.[16]

Table 7.1 Regression coefficients of 1000 x Ln (X-ray film score) on years of exposure.[16]

Job classification	Average dust concentration (mg/m^3)[a]	All workers		Workers excluding those with pre-1971 dust exposure	
		Number of subjects[d]	RC (SE)[e]	Number of subjects[d]	RC (SE)[e]
Non-dusty life[b]	not available	3689	6 (0.4)	2925	6 (0.4)
Dryers					
- pre-1971	not available	522	**25** (2)	-	-
- post-1971	1.9 (n=681)	997	**14** (1)	519	**10** (2)
Attritor mills					
- pre-1971	not available	138	**44** (4)	-	-
- post-1971	2.7 (n=114)	73	**23** (4)	16	**12** (11)
Slurry plants	1.1 (n=69)[c]	325	8 (1)	255	7 (1)
China stone mills	not available	37	51 (6)	-	-
Pan kilns	not available	248	13 (2)	-	-

[a] Average personal respirable dust concentrations (mg/m^3) measured between January 1984 - March 1986, with total number of samples shown in parentheses. Data on sampling time are not available.
[b] Defined as the sum of the time before employment, the time after retirement, and the time in jobs with the level of respirable dust < 0.3 mg/m^3, summed for all workers.
[c] This is an assumed average based on regular sampling at the older, more dusty plant, and a small number of samples at the modern, less dusty plants.
[d] Number of subjects at the time of study (1985)
[e] RC: regression coefficient describing the size of the effect of one exposure year on 1000 x Ln (X-ray score); SE : standard error

Table 7.2 Regression coefficients of 1000 x Ln (X-ray film score) on years of exposure.[2]

Job classification	Average dust concentration (mg/m^3)[a]			Number of subjects[d]	RC (SE)[e]
	1978	1990			
Non-dusty life[b]	not available	not available		4112	7.7 (0.4)
Dryers	not available	not available	pre-1971:	456	29.2 (2.2)
	3.5 (5.41)	1.7 (2.78)	post-1971:	1218	13.0 (1.1)
Attritor mills					
- pre-1971	not available	not available	pre-1971:	82	46.9 (6.1)
- post-1971	4.7 (9.32)	2.1 (3.36)	post-1971:	151	21.1 (3.3)
Slurry plants and tube presses	1.6[c]	1.2[c] (2.26)		493	8.9 (1.2)
China stone mills	not available	not available		37	30.6 (5.3)
Pan kilns	not available	not available		202	22.7 (2.6)

[a] Average personal respirable dust concentrations (mg/m^3), with upper deciles shown in parentheses.
[b] Defined as the sum of the time before employment, the time after retirement, and the time in jobs with the level of respirable dust < 0.3 mg/m^3, summed for all workers.
[c] Based on two samples; for slurry plants only
[d] Number of subjects at the time of study (1990)
[e] RC: regression coefficient describing the size of the effect of one year of exposure on 1000 x Ln (X-ray score); SE: standard error

In a cross-sectional study by Rundle *et al.* (1993)[2] in 1990, 4112 current and retired UK kaolin workers were studied using an X-ray film survey (ILO classification, 1980), spirometry (FVC, FEV_1), and a questionnaire (occupational and smoking history, respiratory symptoms). The study population was partly identical to that of Ogle *et al.* (1989). Respirable and total dust samples had been regularly taken since 1978 (Table 7.2) and these provided representative dust concentrations for each location from 1978. Dust concentrations before 1978 were based on estimates. No data are presented on the amount of quartz and the amount of non-kaolin dust in the samples. According to the WHO Environmental Health Criteria (no. 231) document on kaolin, UK china clay workers are exposed to kaolin clay containing less than 1.1% quartz.[15] The total occupational respirable dust dose (TODD in $mg/m^3 \cdot$years) for each worker was calculated by adding together the average respirable dust concentration (mg/m^3) for each year based on his employment in that year. In this study, 60% of the workers had TODD values of 10 $mg/m^3 \cdot$years or less, 88% of the workers had values of 30 $mg/m^3 \cdot$ years or less, and 1.1% had values greater than 80 $mg/m^3 \cdot$years.

Of the 4112 X-ray films, 9.2% showed simple pneumoconiosis category 1, 0.75% showed category 2, and 0.05% showed category 3. Two cases showed complicated pneumoconiosis (large opacities). Of the opacities found, 50% were rounded in shape. X-ray films showed pleural calcification in 9 cases and pleural thickening in 39 cases.

For regression analysis, each X-ray subcategory was transformed in a score drawn from a continuum. In this way, major X-ray category 0 ranged from –2.718 to 0.754; major X-ray category 1 from 1.162 to 1.920; major X-ray category 2 from 2.061 to 2.713; and major X-ray category 3 from 2.865 to 3.044. With regression analysis of X-ray film score on years of exposure, working in mills, pan kilns and dryers was found to have the greatest effect on X-ray score, which is consistent with the respirable dust concentrations in mills and dryers (Table 7.2). From the results of the regression analysis of X-ray film score on TODD, the authors plotted a graph for an average 60-year old non-smoker, ex-smoker and current smoker, showing the relations between X-ray film category and TODD (Figure 1). The average non-smoking worker would reach X-ray film category 1 at the age of 60 after 85 mg/m^3·years of exposure (*e.g.*, working for 40 years at an average dust concentration of 2.1 mg/m^3). In the average smoker, the total exposure would need to be 65 mg/m^3·years (*e.g.*, working for 40 years at an average dust concentration of 1.6 mg/m^3). Regression analysis of lung function values on X-ray film score , age, and smoking class was performed. Regardless of age and smoking class, FEV_1 and FVC decreased with 210 and 356 ml, respectively, with an increase of X-ray film score with one major category.

The study by Rundle *et al.* (1993)[2] is the only human study available with data on a relationship between total occupational respirable dust dose and major X-ray category. In this study, the TODD to reach ILO category 1 is given for the average worker, only, at the age of 60. This study does not present data on the TODD at which the smallest number of workers develop pneumoconiosis ILO category 1 at the age of 60. No NOAEL or LOAEL can be derived from this type of data presentation. Nevertheless, according to the authors exposure to 2.1 mg/m^3 respirable kaolin dust for 40 years causes ILO category 1 in the average worker at the age of 60. This may involve a large number of workers. Like in the study by Ogle *et al.* (1989)[16], the non-exposed group contained workers with pneumoconiosis category $\geq$1. Of the 413 cases whose median X-ray category was 1 or above, 136 had had no dust exposure, of whom 21 were non-smokers. The authors did not give an explanation for this.

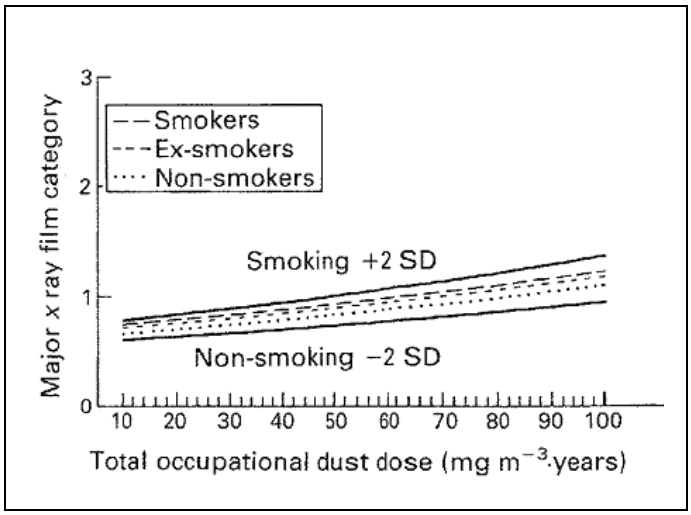

Figure 1. Estimates of X-ray film category for different smoking classes at age 60.[2]

7.1.4 *Carcinogenicity*

No adequate studies are available.

Lung tumours have been found incidentally in epidemiological or case studies. Lapenas *et al.* (1984)[14] described a case of widely disseminated intraparenchymous lung carcinoma found at autopsy, next to complicated pneumoconiosis, after kaolin exposure. The authors did not discuss this further. Sheers *et al.* (1964)[10] mentioned one case of carcinoma of the bronchus in a survey of 1394 kaolin workers.

In the study by Szadkowska-Stanczyk *et al.* (2001)[18], 79 cases of lung cancer were investigated in a mortality study among pulp and paper workers. The study was part of a cohort study of 10,575 male and female workers employed for at least one year in a large pulp and paper mill between 1968 and 1990, and observed until 1996. The study had a nested case-control design and for each case, three control subjects were selected and matched according to sex, year of birth, and year of hire. Two cases and one control had been exposed to kaolin dust (concentration unknown). The risk of mortality, adjusted for smoking, from lung cancer for these two cases was six times higher compared to the non-exposed. However, because of the small number of cases, the odds ratio value of 5.64 was not statistically significant (95% confidence interval adjusted for smok-

ing: 0.5-63.4). Subsequent measurements of kaolin dust concentrations in the period 1995-1998 revealed respirable kaolin dust levels in the mill under study, ranging from 6.1 to 12.7 mg/m^3 and containing 3.2 to 5.1% free crystalline silica.

7.1.5 Reproduction toxicity (fertility and development)

No data available

7.1.6 Immunological effects

No data available

7.1.7 Neurological effects

No data available.

7.1.8 In vitro effects

Kennedy et al. (1989)[20] studied lipid peroxidation of membranes in human erythrocytes suspensions. They found that kaolin (1 mg/ml) significantly increased malondialdehyde content ($p<0.05$), and caused marked in vitro lysis of 50% of the human red blood cells within 1 hour ($p<0.001$).

7.1.9 Miscellaneous

No data available.

7.2 Animal experiments

7.2.1 Irritation and sensitization

No data available

7.2.2 Acute toxicity

A sterilized suspension of 0 or 5 mg/animal Indian kaolin (99% kaolinite, no quartz; particle size <5 µm) in 0.1 ml NaCl (0.15 M) was given once intratracheally to 70 albino Swiss mice of either sex. In this study by Sahu et al. (1978)[32], two animals per group were killed periodically at various time points up to 210

days after treatment, and the lungs were examined. Macroscopically, white patches were observed from day 30 onwards, which increased in area, becoming prominent at termination of the experiment on day 210. The tracheobronchial lymph nodes became enlarged from day 90 onwards, and appeared quite prominent at day 210. Microscopically, an inflammatory response involving leucocytes and dust-laden macrophages in alveolar tissue was observed from the first day onwards. Subsequently, fibroblast proliferation increased and became marked at day 120. Lymph nodes contained many small foci of vacuolated macrophages and little reticulin reaction at day 210. The lungs and lymph nodes of the animals in the control group were normal.[32]

In a study by Martin *et al.* (1975)[33], ten female Sprague-Dawley rats were given a single intratracheal injection of 50 mg of kaolin per animal (no data available on composition). After three months, an increase in the collagen content was observed, but no increase in the weight of the lungs. Kaolin did not produce lesions of alveolar proteinosis, but most of the kaolin was present in the bronchiolo-vascular lymphatic sheaths. Compared to quartz, which was also tested in this study, kaolin has a considerably less fibrogenic (but not negligible) capacity.[33]

Cornish coating grade kaolin, with >98% of the particles in the range of 0.8-6.6 µm, was used as a negative control in intrapleural implantation studies by Wagner *et al.* (1987).[34] Forty Fischer F344 rats, 20 of each sex, at about 5 weeks of age, were inoculated intrapleurally with a single injection of kaolin in saline (dose not given). The animals were allowed to live for their natural life span. On death, no mesotheliomas were found.[34]

7.2.3 *Short-term toxicity*

In the study by Patterson and Staszak (1977)[35], diet containing 0% or 20%* kaolin (Georgia, USA; 97% kaolinite, no quartz) was fed to different groups of four female Sprague-Dawley rats during different time periods before conception and through gestation. The time intervals were: 37 to 68 days, 69 to 95 days, or 96 to 117 days. The authors did not observe significant weight differences between the groups during the first 13 days of gestation. A significant reduction ($p<0.01$) in all measured maternal blood values (red blood cell count, haematocrit and haemoglobin concentration) was observed in the kaolin group for all three exposure periods compared to the control group.[35]

* Using standard values for body weight (female rat: 0.35 kg) and daily diet consumption (female rat: 50 g), the 20% dose was recalculated to a daily kaolin concentration of 28.6 g/kg body weight.

Groups of twenty male and twenty female Fischer F344 rats inhaled a dose of 10 mg/m^3 kaolin dust for 6 hours/day, 5 days/week, for 12 months. In this study by Wagner *et al.* (1987)[34], Cornish coating grade kaolin with >98% of the particles in the range of 0.8-6.6 µm was used. Two rats of each sex were killed at 3, 6, 12 and 24 months. Mean fibrosis gradings of the lungs were 2.8, 2.75, 2.4 and 2.1, respectively (grade 1 normal; grade 2 dust in macrophages; grade 3 early interstitial reaction). After living out their lifespan, the other rats were subjected to a full necropsy and histopathology of the lung, liver, spleen and kidney. In two of these rats, broncho-alveolar hyperplasia was found. Of the 40 rats exposed, 38 rats had no proliferative lesions, nor were any lung carcinomas observed.[34]

7.2.4 *Long-term toxicity and carcinogenicity*

In a study by Mossman and Craighead (1982), four to six-week old female Golden Syrian hamsters were implanted with tracheal organ cultures.[36] These organ cultures had been exposed in vitro for one hour to 200 mg Georgia kaolin (particle diameter: 3-5 µm), and then maintained in vitro for four weeks. Tumours did not appear in tracheal tissues within 2 years after implantation.

Pott and Roller (2003)[37] and Mohr *et al.* (2006)[38] found increased lung tumour incidences in female rats after repeated (10 or 20 times) intratracheal instillation of 6 mg kaolin fine (mean particle diameter 2.0 µm) per animal. Tumour formation in rats was also observed after intratracheal instillation of other dusts, including previously considered inert dusts. Lung tumour formation by intratracheal instillation of dusts is supposed to be caused by particle overload which may occur when the volume of particles in the lungs markedly impairs pulmonary clearance mechanisms.[39,40] Internationally, the relevance of intratracheal instillation is under debate and several investigators consider particle deposition by intratracheal instillation different from particle deposition by chronic inhalation.[41] For kaolin, this view is supported by the lack of epidemiological data showing increased lung tumour incidence in kaolin workers. Lung tumours have only been found incidentally in epidemiological or case studies. Therefore, the committee concludes that there is insufficient epidemiological evidence for carcinogenicity of kaolin dust under occupational exposure conditions.

7.2.5 *Mutagenicity and genotoxicity*

No data available

7.2.6 *Reproduction toxicity*

In the study by Patterson and Staszak (1977)[35] described above, a diet containing 0% or 20% kaolin (Georgia, USA) was fed to different groups of four Sprague-Dawley female rats, at time intervals 37 to 68 days, 69 to 95 days, or 96 to 117 days prior to conception and through gestation. The authors did not observe significant weight differences between the groups during the first 13 days of gestation. All measured maternal blood values (red blood cell count, haematocrit and haemoglobin concentration) were significantly reduced ($p<0.01$) in the kaolin group compared to the control group for all three time periods. The mean weight of pups from the kaolin diet group was significantly less ($p<0.01$) than those from the control group (9.4% lower than control). No effects were observed on mean length of pups, litter size, or on morphology of the pups.[35]

7.2.7 *Immunological effects*

Sluiter et al. (1987)[42] intraperitoneally injected random-bred female Swiss mice (number of animals unknown) once with kaolin (0.5% w/v in saline; no data available on composition). This evoked a substantial increase in the number of granulocytes in the peripheral blood (6-12 hours after injection), and the peritoneal cavity (6-24 hours after injection).[42]

Lewis *et al.* (1976)[43] used kaolin to produce a local inflammatory response (oedema) in the rat hind paw in order to screen new anti-inflammatory drugs, and to investigate the inflammatory process. Male Wistar rats (10/group) were administered 50, 100 and 150 mg/ml kaolin (no data available on composition) in 0.9% w/v saline by subplantar injection. Kaolin produced dose-related increases in paw volume.[43]

7.2.8 *Neurological effects*

Kaolin induction of hydrocephalus in animals (rat, sheep, rhesus monkey) by injecting kaolin into the cisterna magna, is one of the most studied models of congenital hydrocephalus in the literature.[44,45]

7.2.9 *Miscellaneous*

No data available.

7.3 Summary

The majority of case studies and epidemiological studies have been focussed on pneumoconiosis in kaolin workers. Pneumoconiosis is a pulmonary disease caused by the inhalation of inorganic mineral dusts which cause irreversible lung lesions (fibrosis). Pneumoconiosis is identified by chest X-ray, thereby using the classification guideline from the International Labour Office (see Annex D). Simple pneumoconiosis is defined as small opacities throughout the lung; complicated pneumoconiosis is defined as the presence of large opacities and progressive massive fibrosis in the lung.

In most of the studies, the radiological score was independent of smoking, but dependent on age, time of employment, and type of job. In some studies, a small decrease in lung function (FEV_1 and/or FVC) with increasing radiological score was found. Only in the case of complicated pneumoconiosis, a significant decrease was found. Respiratory symptoms, such as dyspnoea, cough or sputum production, were more frequently reported in cases of complicated pneumoconiosis than in cases of simple pneumoconiosis.

In the greater part of the human studies no data on occupational kaolin exposure levels were given. It is assumed that in the past, especially before 1970, occupational exposure to kaolin at undefined concentrations (but probably under very dusty conditions that no longer exist now) was associated with cases of pneumoconiosis.

In most of the available studies with exposure data, mean respirable concentrations were below 5 mg/m^3. However, most of the studies presenting health effects, reflect exposures in periods for which measurements were not available, and in which strict control on dust levels was lacking. This makes it difficult to derive long-term dose-response relationships.

The amount of quartz in kaolin may also be an important confounding factor, since occupational exposure to quartz is associated with silicosis, lung cancer, and pulmonary tuberculosis. Purified Cornish china-clay typically contains 2% quartz. Georgia kaolin typically contains < 1% quartz, and is therefore considered as pure kaolin. The presence of quartz in kaolin can make it difficult to distinguish between silicosis and kaolin-induced pneumoconiosis.

Rundle *et al.* (1993)[2] presented data on a dose-response relationship for kaolin-induced lung effects. However, the amount of non-kaolin dust and the amount of quartz in the dust samples are not described in this study. A total occupational respirable dust dose (TODD) of 65 mg/m^3·years (*e.g.*, 40 years exposed to 1.6 mg/m^3) was necessary to reach pneumoconiosis ILO category 1 in an average

smoking male worker, 60 years of age. For an average non-smoking male worker, 60 years of age, a TODD of 85 mg/m^3·years (*e.g.*, 40 years exposed to 2.1 mg/m^3) was needed to reach ILO category 1. A NOAEL or a LOAEL cannot be established from the data as presented in this study. Regression analysis of lung function values on X-ray film score, age, and smoking class yielded that, regardless of age and smoking class, FEV_1 and FVC decreased 210 and 356 ml, respectively, with an increase of the X-ray film score with one major category. In this study, pneumoconiosis was also identified in non-exposed workers.

Most animal studies are of little relevance in the context of human occupational exposure. In most studies, the purity of kaolin was not established nor its contaminants determined, and limited endpoints were investigated. At 10 mg/m^3, fibrosis of the lungs was reported in rats exposed for 12 months. Lung tumour incidence in rats was increased after repeated intratracheal instillation (10 or 20 times 6 mg/animal) of kaolin fine with mean particle diameter of 2.0 µm. Lung tumour formation by intratracheal instillation of dusts is supposed to be caused by particle overload which may occur when the volume of particles in the lungs markedly impairs pulmonary clearance mechanisms.[39,40] Internationally, the relevance of intratracheal instillation is under debate and several investigators consider particle deposition by intratracheal instillation different from particle deposition by chronic inhalation.[41] For kaolin, this view is supported by the lack of epidemiological data showing increased lung tumour incidence in kaolin workers. Lung tumours have only been found incidentally in epidemiological or case studies. Therefore, the committee concludes that there is insufficient epidemiological evidence for carcinogenicity of kaolin dust under occupational exposure conditions.

No evidence of teratogenic effects was found. Slight decreases in pup weight were seen after exposure of the dams to 20% kaolin in the diet (approximately 28.6 g/kg bw/days) for up to 117 days.

Chapter 8

Existing guidelines, standards and evaluations

8.1 General population

For the general population no guidelines exist.

8.2 Working population

The available standards for occupational exposure to kaolin are summarized in Table 8.1. The American Conference of Governmental Industrial Hygienists (ACGIH) has established a TLV (threshold limit value as an 8-hour time-weighted average) of 2 mg/m^3 respirable kaolin dust.[46] In addition, the ACGIH noted kaolin as an A4 substance, meaning that kaolin is not classifiable as a human carcinogen.

Table 8.1 Established limits for occupational exposure to kaolin dust in various countries.

country - organisation	occupational exposure limit (mg/m^3)	dust fraction	time-weighted average	note[a]	ref.
Denmark	2	respirable	8 h	OEL	47
The Netherlands - Ministry of Social Affairs and Employment	-				48
Germany - AGS	-				49
- DFG	-				50
UK - HSE	2	respirable	8 h	WEL	51
USA - ACGIH	2[b]	respirable	8 h	TLV; A4[c]	46
- NIOSH	10	total	10 h	REL	52
	5	respirable	10 h	REL	
- OSHA	15	total	8 h	PEL	53
	5	respirable	8 h	PEL	
European Union - SCOEL	-				54

[a] Abbreviations OEL: occupational exposure limit; PEL: permissible exposure limit; REL: recommended exposure limit; TLV: threshold limit value; WEL: workplace exposure limit;
[b] The value is for particulate matter containing no asbestos and < 1% crystalline silica.
[c] A4: not classifiable as a human carcinogen because of lack of data.

Chapter 9

Hazard assessment

9.1 Assessment of the health risk

Kaolin is a clay that consists primarily of kaolinite, a non-fibrous silicate of aluminium. Crude kaolin has a particle size of 0.05 – 150 µm; the particle size of processed kaolin is less than 10 µm with more than 50% of the particles being less than 2 µm, that is in the respirable range. In this document, the health risk assessment of exposure to kaolin is limited to exposure to kaolin dust containing $\leq$2% quartz.

Case reports and cross-sectional studies, mainly in the United Kingdom and the USA, have shown that long-term exposure of humans to kaolin dust can lead to kaolin-induced pneumoconiosis, also called kaolinosis. Pneumoconiosis is a pulmonary disease caused by the inhalation of inorganic mineral dusts. These dusts cause irreversible lung lesions (fibrosis) which manifest as parenchymal opacities and pleural abnormalities by chest X-ray radiography. Pneumoconiosis is diagnosed by chest X-ray radiography and can be categorized as simple pneumoconiosis (ILO category 1-3) or complicated pneumoconiosis (ILO category A-C) (annex D). The mildest form of pneumoconiosis category 1 is not yet associated with decreased pulmonary function. Clinical symptoms (cough, sputum, dyspnoea) and effects on pulmonary function (decreased FVC and/or FEV_1) are mainly observed in the complicated form. Nevertheless, the committee considers simple pneumoconiosis of ILO category 1 as an undesired health effect because of lung pathology (found in X-ray radiography) which may be the onset of

decreased lung function. This is in line with a report of the European Committee in which miners' pneumoconiosis category 1 is recognized as an occupational disease.[1] It should be noted that the scoring of pneumoconiosis, based on the ILO guidelines (annex D), is a matter of subjective assessment. Due to inter-rater differences in scoring and interpreting of the X-ray films, it can not be ruled out that cases of ILO category 1 have been missed.

Occupational exposure to kaolin has gradually decreased over the years. In the USA, dry processing of kaolin, inducing large amounts of dust, was gradually replaced by the wet method after 1940. After the 1960s, dust control was significantly improved. In the UK, many operational changes have been introduced, mainly in the 1970s, to improve airborne dust control. The older drying processes in pan kilns were phased out in 1971. Several studies from kaolin industries in the USA and the UK, between 1977 and 1990, showed average respirable dust levels below 5 mg/m^3.

According to the committee, it has convincingly been shown that the critical effects of kaolin exposure involve the lungs, with pneumoconiosis as the most important clinical observation. In case studies, kaolin particles have been found in lung macrophages present in areas of fibrosis. Epidemiological studies have shown that the radiological category of pneumoconiosis is dependent on age, years of exposure to kaolin, and job type. A few studies have found a correlation between increasing pneumoconiosis category and lung function (decreased FVC and/or FEV_1) or respiratory symptoms (*e.g.*, cough, sputum, dyspnoea), especially for complicated pneumoconiosis.

Studies with quantitative exposure data or dose-effect relationships in humans are scarce. These studies provide information on adverse-effect levels only and not on no-effect levels of kaolin. In some studies also non-exposed, non-smoking subjects had small opacities in the lungs, consistent with simple pneumoconiosis.

Despite the extensiveness of the epidemiological studies, only Rundle *et al.* (1993)[2] tried to identify a dose-response relationship for kaolin exposure and pneumoconiosis. No data were presented on the amount of quartz and non-kaolin dust in the samples but according to the WHO Environmental Health Criteria 231 report[15], UK china clay workers were exposed to clay containing less than 1.1% quartz. By regression analysis of the logarithm of the X-ray film score on the total occupational respirable dust dose (TODD), Rundle *et al.* (1993) found a relation between the pneumoconiosis category and the personal TODD.[2] The lower limit of major pneumoconiosis ILO category 1 was reached by the average non-smoking worker at the age of 60 after a TODD of 85 mg/m^3·years, that is after being exposed for 40 years to 2.1 mg/m^3, and by the average smoking

worker after a TODD of 65 mg/m^3·years, that is after exposure for 40 years to 1.6 mg/m^3. These TODD levels are for the 'average worker' only, and from such levels a NOAEL or a LOAEL cannot be established. Nevertheless, the committee considers exposure to 2.1 mg/m^3 respirable kaolin dust for 40 years undesired as ILO category 1 is undesired and the development of ILO category 1 in the average worker may involve a large number of workers.

In the WHO Environmental Health Criteria 231 report[15], an international group of experts estimated that kaoline is at least an order of magnitude less potent than quartz in inducing pneumoconiosis. This conclusion was based on a comparison of the Rundle data with the estimated ranges of silicosis prevalence as a consequence of exposure to quartz: 2-30% of ILO category $\geq$1/1 silicosis after a 45-year exposure to quartz at 0.05 mg/m^3 (*i.e.*, a cumulative exposure to 2.25 mg/m^3·years); and 3-90% of ILO category $\geq$1/1 silicosis after a 45-year exposure to quartz at 0.10 mg/m^3 (*i.e.*, a cumulative exposure to 4.5 mg/m^3·years). The health-based recommended occupational exposure limit (HBROEL) for respirable quartz is 0.075 mg/m^3, as an 8-hour time-weighted average.[55]

Several studies in animals support the respiratory effects observed in humans. Three studies were found that indicated that kaolin has fibrogenic activity and is able to induce an inflammatory response and fibrosis in the lungs of rats and mice. Based on the available studies, it is the committee's opinion that there is insufficient evidence for carcinogenicity and no evidence for teratogenicity of kaolin, and that kaolin does not need to be classified as a carcinogen or as a substance with reproductive toxicity.

9.2 Recommendation of the health-based occupational exposure limit

The committee concludes that the toxicological database does not contain any studies from which a NOAEL or a LOAEL can be established. Therefore, the database does not allow the derivation and recommendation of a health-based occupational exposure limit for kaolin.

9.3 Additional consideration

Although the mildest form of pneumoconiosis is not yet associated with a decrease of pulmonary function, the committee considers ILO category 1 an undesired health effect in line with the European Committee report on the classification of miners' pneumoconiosis.[1]

The results of the Rundle study[2] indicate that cumulative exposure to 85 mg/m^3·years of respirable kaolin dust is able to induce simple pneumoconiosis ILO category 1 in the average non-smoking worker at the age of 60, that is after 40 years of exposure to 2.1 mg/m^3. According to the committee, this exposure level may affect a large number of workers and constitutes an undesired health risk. Therefore, the HBROEL for respirable kaolin dust must be lower than 2.1 mg/m^3. On the other hand, kaolin is estimated to be an order of magnitude less potent than quartz in inducing pneumoconiosis. This indicates that the HBROEL for respirable kaolin dust is approximately ten-fold the HBROEL for respirable quartz dust. Taking these considerations into account, it is the committee's opinion that an occupational exposure level of 0.5 mg/m^3 for respirable kaolin dust, as an 8-hour time-weighted average concentration, is not associated with pneumoconiosis and might be used as an upper exposure limit for workers.

The committee adds that this consideration is only applicable to kaolin with the particle size distribution and the amount of quartz (typically $\leq$2% w/w)[4] as present in the UK china clay industry at the time of the measurements.

9.4 Groups at extra risk

Based on the Rundle study[2], smokers are at higher risk than non-smokers. Another group at higher risk may be workers with decreased lung function or chronic lung disease.

Chapter 10

Recommendations for research

The composition including the particle size distribution and the quartz content of kaolin dust in the workplace needs to be defined more accurately in future studies. Accurate exposure data including personal air monitoring and quartz analysis, and objectively obtained effect data should be used to obtain more and better exposure-response relationships. Predisposed workers, like asthmatics, should be distinguished in future studies.

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Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as

part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the committee is given in Annex B.

Annex **B**

The committee

- G.J. Mulder, *chairman*
  emeritus professor of toxicology, Leiden University, Leiden
- R.B. Beems
  toxicologic pathologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  toxicologist, Shell International BV, The Hague
- J.J.A.M. Brokamp, *advisor*
  Social and Economic Council, The Hague
- D.J.J. Heederik
  professor of risk assessment in occupational epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- L.A.L.M. Kiemeney
  professor of cancer epidemiology, University Medical Centre St Radboud, Nijmegen
- H. van Loveren
  professor of immunotoxicology, Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  occupational physician, Netherlands Center for Occupational Diseases, Amsterdam

- A.H. Piersma
  professor of reproductive toxicology, National Institute for Public Health and the Environment, Bilthoven
- H.P.J. te Riele
  professor of molecular biology, VU University Amsterdam, Amsterdam
- I.M.C.M. Rietjens
  professor of toxicology, Wageningen University and Research Centre, Wageningen
- H. Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T. Smid
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- G.M.H. Swaen
  epidemiologist, Dow Benelux N.V., Terneuzen
- R.A. Woutersen
  toxicologic pathologist, TNO Quality of Life, Zeist
- P.B. Wulp
  occupational physician, Labour Inspectorate, Groningen
- E.J.M. Pennings, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of this report was prepared in 2005 by R.H.M.M. Schreurs and W.M.L.G. Gubbels-Van Hal from NOTOX BV, 's-Hertogenbosch, The Netherlands, by contract with the Dutch Health Council.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship

will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2007 for public review. The following organisations and persons have commented on the draft report:

- E. González-Fernández, Ministerio de Trabajo y Asuntos Sociales, Spain
- E.L.J. van Hal and J.A.J. Kemps, Koninklijk Verbond van Nederlandse Baksteenfabrikanten, Nederlandse Dakpannencorporatie en Algemene Vereniging voor de Nederlandse Aardewerkindustrie, The Netherlands
- R.T.H. van Welie, Nederlandse Cosmetica Vereniging, The Netherlands
- R.D. Zumwalde, National Institute for Occupational Safety and Health, USA

Annex **D**

Classification of pneumoconiosis

A series of guidelines on the classification of chest X-ray films (radiographs) for persons with pneumoconiosis has been published by the International Labour Office (ILO) since 1950. The goal of this process was to describe and codify the radiographic abnormalities of pneumoconiosis in a simple, reproducible manner.

In the present manifestation of the ILO system (2002)[56], the reader is first asked to grade film quality. Parenchymal abnormalities are then divided in small opacities (simple pneumoconiosis) and large opacities (complicated pneumoconiosis). Pleural abnormalities (pleural thickening or pleural calcification) are also assessed.

Small opacities (simple pneumoconiosis) are characterized according to:

- shape and size:
  round opacities: p (< 1.5 mm), q (1.5 – 3 mm), r (3 – 10 mm)
  irregular opacities: s (< 1.5 mm), t (1.5 – 3 mm), u (3 – 10 mm)
- profusion (frequency):
  classification according to a 12-point scale into one of four major categories (0,1, 2 or 3); if during the reading the major category above or below is seriously considered as an alternative, this is recorded as the second digit.

Normal (**category 0**)	0/-	0/0	0/1
Mild (**category 1**)	1/0	1/1	1/2
Moderate (**category 2**)	2/1	2/2	2/3
Severe (**category 3**)	3/2	3/3	3/+

- zone:
  the lung zones in which the opacities occur: RU (right upper), RM (right middle), RL (right lower), LU (left upper), LM (left middle), LL (left lower)

Large opacities (complicated pneumoconiosis) are classified as:

- **category A**:
  greatest diameter exceeding 1 cm and up to 5 cm; or several opacities each greater than 1 cm with the sum of the diameters not exceeding 5 cm;
- **category B**:
  one or more large opacities with combined diameter greater than 5 cm but not exceeding the equivalent of the right upper zone;
- **category C**:
  one or more large opacities whose combined area exceeds the equivalent of the right upper zone.

Annex **E**

Occupational exposure to kaolin: case studies

Studied population	Findings	Ref
2 kaolin workers from Georgia, USA a) 23 years in milling area b) 17 years in loading area	Both had large areas of fibrosis in the lungs and kaolinite particles were identified in alveolar macrophages.	5
5 kaolin workers from Georgia, USA age 37-84; 3 had died	Cases had complicated pneumoconiosis, showing small irregular opacities, conglomerate masses and multiple large, well-delineated opacities on the chest radiograph (ILO classification 1980). Respiratory failure was a contributing factor to death in two of the subjects. Particles in the lung were kaolinite.	14
54 Cornish kaolin workers (post mortem 1968-1981) a) china clay group (n=22; 17-55 years of exposure); lung specimens (n=16): ≥90% kaolinite, ≤1.0% quartz; b) miscellaneous group (n=10; 10-52 years of exposure); lung specimens (n=10): 33-91% kaolinite, ≤5% quartz;	Radiographs: available from 26 cases (ILO classification 1971). Smoking histories: unavailable. a) radiographs (n=21) showed simple (n=11) and complicated (n=10) pneumoconiosis; round and irregular radiological opacities and pathologically slight to severe nodular and interstitial fibrosis. Dust concentrations in the lungs: 7.6-289.3 (median 40) mg per gram lung tissue. b) radiographs (n=5) showed 3 cases of simple pneumoconiosis (irregular opacities); pathologically slight to moderate nodular and interstitial fibrosis. Dust concentrations in the lungs: 1.6-28.7 (median 6.5) mg per gram lung tissue. Nodular fibrosis was related to a high quartz content of the lung dust (statistically significant); interstitial fibrosis seemed to be related to a high kaolinite content of lung dust (not statistically significant).	57
2 U.S. kaolin processing workers Both had died at age 35-36 with 17-21 years of employment.	Both had advanced pneumoconiosis, one with pulmonary thrombosis and infarct of the lung; massive nodular fibrosis was observed; one had symptoms of dyspnoea, cough, sputum and ankle oedema.	58
4 Scottish shale miners Age 69-83; 32-49 years of employment; 2 had died.	All cases developed complicated pneumoconiosis, and 2 were found at autopsy also to have peripheral squamous lung cancer. The lung dust in 3 cases was found to contain kaolinite (19–36%), mica (13–16%), and quartz (9–18%).	59
6 workers from a kaolin processing plant in Ayyat, United Arabic Republic Age 46-57; 15-25 years of employment.	Chest radiographs (ILO classification 1950) showed simple pneumoconiosis (n=3 category 1, 2 and 3). Two of the three with complicated pneumoconiosis and symptoms (dyspnoea on exertion, cough with sputum) showed progressive massive fibrosis.	60

Annex **F**

Occupational exposure to kaolin: epidemiological studies without exposure data

Studied population	Data collected	Findings	Remarks	Ref
1130 current kaolin workers (Georgia, USA)	Chest radiographs, medical and occupational histories, physical examination.	Radiographs showed 44 workers (prevalence 3.9%) with pneumoconiosis. Stage I pneumoconiosis (n=31): fine discrete nodulation in lungs; no symptoms; no progression over 3-12 years. Stage II pneumoconiosis (n=7): fine discrete nodulation in lungs; no symptoms; little tendency to progression. Stage III pneumoconiosis (n=6) nodulation with massive conglomerate fibrosis in the lungs (upper lobes); cough and dyspnea; gradual progression over the years (emphysema). Exposure time > 20 years.	- Data on smoking not available. - Exposure times from workers in stage I and II are unknown.	5
350 current kaolin workers (Georgia, USA)	Chest radiographs (ILO classification 1980), medical and employment records, symptoms and occupational history (questionnaire)	Abnormal radiographs (n=32) were clinically evaluated. Nineteen workers had pulmonary changes consistent with kaolinosis (prevalence 5.4%). Computed tomography of the chest in 12 subjects (exposure time 12-35 years) proved kaolinosis (11 mild, 1 complicated), but without evident pleural abnormalities on radiographs.	- No dry-processing workers included. - Most workers were employed in kaolin products manufacturing, after appearance of strict controls on respiratory dust levels	61
553 current kaolin workers (Cornwall, UK)	Chest radiographs (ILO classification 1959), occupational history, symptoms.	Total kaolinosis prevalence: 9% (48 cases: 36 simple, 12 complicated); < 5 years of exposure: 0% < 15 years of exposure: 4% > 25 years of exposure: 19% men < 25 years of age: 0% men > 65 years of age: 24%	- > 5 years of continuous (millers, baggers, loaders) or intermittent (kiln workers, drymen) exposure to clay dust. - No smoking history available.	10
1676 current kaolin workers (Cornwall, UK)	Chest radiographs (ILO classification 1980), questionnaire (symptoms, smoking history), occupational history, spirometry (FVC, FEV_1).	Pneumoconiosis: category 0: 77.4% category 1: 17.9% categories 2 and 3: 4.7% Advanced pneumoconiosis was detected in 19 workers (1.1%). FVC showed a small significant reduction with increasing radiological score No relationship between symptoms and past exposure to kaolin was detected.	- Exclusively exposed to kaolin. - No statistical *p*-values were calculated - Radiological score was unrelated to smoking, but related to the period spent in dusty jobs, and to age - Exposure times unknown.	62
914 workers from a kaolin processing plant in Ayyat, United Arabic Republic (1959)	Chest radiographs (ILO classification 1950), occupational history, symptoms.	Pneumoconiosis prevalence: < 10 years (n=264) exposure: 0% 10-15 years (n=133) exposure: 0% 15-20 years (n=326) exposure: 1.2% with symptoms: dyspnoea on exertion, cough with sputum in 2 cases. > 20 years (n=191) exposure: 1% with progressive massive fibrosis and symptoms (cough, sputum and dyspnoea).	Dust from the mill contained 83-86% $K_4Al_2Si_2O_9$ and 1-2% quartz. Particles < 3.4 μm	60

Annex G

Occupational exposure to kaolin: epidemiological studies with exposure data

Studied population	Kaolin exposure	Data collected	Findings	Remarks	Ref
459 current kaolin mine and processing workers (Georgia, USA)	Current exposure (1977-1980): Respirable kaolin dust: <5 mg/m³ (<1% quartz) Mean exposure: 12 years. Exposure in the past: 1951: 377 mg/m³ 1960: 361 mg/m³	Chest X-ray films (ILO classification 1971), spirometry (FEV_1, FVC), questionnaire (symptoms, smoking history), occupational history.	Simple pneumoconiosis prevalence: Category 0: 90.9% (white 93.0%, black 86.4%) Category 1: 6.3% (white 5.1%, black 8.9%) Category 2: 1.8% (white 1.3%, black 2.7%) Category 3: 1.1% (white 0.7%, black 2.0%) Complicated pneumoconiosis: 1.7% (n=8) In most cases fine or medium irregular opacities. Age >50 years ($p<0.005$) and exposure > 15 years ($p<0.001$) significantly related to pneumoconiosis. Lower FEV_1 and FVC only in cases of complicated pneumoconiosis. More frequent dyspnea in cases of pneumoconiosis.	No unexposed control group. No exposure data from different job categories. Type of sampling (area or personal) unknown.	17
47 current and 16 former kaolin mine and mill workers (Georgia, USA) 189 external controls.	96% kaolinite, 4% TiO_2 and 0% quartz. Respirable dust (pers.): Mine: 0.1-0.35 mg/m³ Loader: 0.7-1.2 mg/m³ Bin: 1.3-2.5 mg/m³ Mill: 0.8-1.2 mg/m³ Baghouse: 0.3-5 mg/m³ Total dust (area): Loader: 7-15 mg/m³ Bin: 10-30 mg/m³ Mill: 10-80 mg/m³ Baghouse: 1.5-9 mg/m³	Chest X-ray films (ILO classification 1971), spirometry (FEV_1, FVC, peak flow rate), questionnaire (symptoms, smoking and occupational history)	Pneumoconiosis prevalence: - Current workers <5 years exposure (n=8): 0% - Current workers ≥5 years exposure (n=39): 4/39 simple (15-39 years exposure) and 1/39 complicated pneumoconiosis (35 years exposure) - Former workers ≥5 years exposure (n=16): 3/16 complicated pneumoconiosis (26-35 years exposure) Small rounded opacities. Seven cases were mill workers, one was miner. All were (ex-)smokers. Abnormal spirometric values in three cases. Reduced spirometric values in kaolin workers compared to controls ($p<0.05$).	No control group data. No data on different exposure groups. No historical exposure data. Small group sizes.	11
65 current kaolin mine and processing workers (Georgia, USA)	94-98% kaolinite, 2-6% TiO_2 and 0% quartz. Respirable dust (pers.): Mine: 0.1-0.8 mg/m³ Maintenance area: 0.1-0.9 mg/m³ Processing area: 1.7-5.3 mg/m³	Chest X-ray films (ILO classification 1980), spirometry (FEV_1, FVC), questionnaire (symptoms, smoking and occupational history)	Simple pneumoconiosis: 4/25 processing workers (7-13 years exposure). Complicated pneumoconiosis: 1/25 (36 years exposure). All five had symptoms of bronchitis, and mildly lower spirometric values ($p<0.05$) compared to other processing workers.	No control group. Small group sizes. No historical exposure data.	12

3400 current and 289 former kaolin workers (UK).	Average respirable dust (pers.) (1984-1986): Dryers: 1.9 mg/m^3 Mills: 2.7 mg/m^3 Calciners: 2.5 mg/m^3 Slurry plants: 1.1 mg/m^3 Tube press: 0.5 mg/m^3	Chest X-ray films (ILO classification 1980), spirometry (FEV_1, FVC), questionnaire (symptoms, smoking history)	Simple pneumoconiosis prevalence: Category 0: 3374/3689 (91.5%) (age: ≤20-80) Category 1: 271/3689 (7.3%) (age: 21-80) Category 2: 39/3689 (1.1%) (age: 41-80) Category 3: 5/3689 (0.1%) (age: 51-80) Complicated pneumoconiosis: 16/3689 (0.4%) Both rounded and irregular small opacities were observed. Pleural thickening (n=87) and calcification (=17) was also noted. Ventilatory capacity was related to age and radiological score. The extent of phlegm, cough, wheeze and breathlessness was dependent on the level of ventilatory capacity.	No control group. No historical exposure data. 99/123 subjects with little or no exposure had pneumoconiosis category 1or higher. Quartz content and non-kaolin dust content unknown.	16
4112 current and former kaolin workers (UK).	Average respirable dust (pers.): (1978) Dryers: 3.5 mg/m^3 Mills: 4.7 mg/m^3 Slurry plants: 1.6 mg/m^3 (1990) Dryers: 1.7 mg/m^3 Mills: 2.1 mg/m^3 Slurry plants: 1.2 mg/m^3	Chest X-ray films (ILO classification 1980), spirometry (FEV_1, FVC), questionnaire (symptoms, smoking and occupational history)	Simple pneumoconiosis prevalence: Category 0: 3699/4112 (90%) (age: <20-80) Category 1: 378/4112 (9.2%) (age: 21-80) Category 2: 33/4112 (0.75%) (age: 41-80) Category 3: 2/4112 (0.05%) (age: 51-70) Complicated pneumoconiosis: 2/4112 (0.05%) Both rounded and irregular small opacities were observed. Pleural thickening (n=39) and calcification (n=9) was also noted. Working in dusty jobs had greatest effect on X-ray score. Ventilatory capacity was related to age and radiological score. The incidence of symptoms was related to the level of ventilatory capacity.	No historical exposure data. 136 subjects with no exposure had pneumoconiosis category 1 or higher. Quartz content and non-kaolin dust content unknown.	2

Annex **H**

Abbreviations

General terms

bw	body weight
FEV_1	forced expiratory volume at 1 second
FVC	forced vital capacity
HBROEL	health-based recommended occupational exposure limit
LOAEL	lowest observed adverse effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
OES	occupational exposure standard
PEL	permissible exposure limit
REL	Recommended exposure limit
tgg	tijdgewogen gemiddelde
TLV	threshold limit value
TODD	total occupational dust dose
TWA	time-weighted average
WEL	workplace exposure limit

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ILO	International Labour Office
INRS	Institut National de Recherche et de Sécurité
NIOSH	National Institute for Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council
WHO	World Health Organisation

Statistical terms

RC	regression coefficient
SE	standard error