PALYGORSKITE (ATTAPULGITE)

Palygorskite (also known as attapulgite) was considered by previous Working Groups in June 1986 (IARC, 1987a) and March 1987 (IARC, 1987b). New data have since become available, and these have been incorporated in the present monograph and taken into consideration in the evaluation.

'Palygorskite' is the correct mineralogical term for this substance, although 'attapulgite' has been used as a common name in much of the health effects literature (Bish & Guthrie, 1993). Samples from different regions and deposits may vary in physico-chemical characteristics and associated health effects. For purposes of this monograph, the term 'palygorskite' is generally used. When the original paper stated that the sample was from Georgia and Florida, United States, ore deposits and the authors referred to the sample as attapulgite, the monograph identifies the sample as 'palygorskite (attapulgite)'.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 12174-11-7

Deleted CAS Reg. Nos: 1337-76-4; 12174-28-6; 37189-50-7; 61180-55-0; 64418-16-2; 71396-54-8; 137546-91-9

Chem. Abstr. Name: Palygorskite

Synonym: Attapulgite

1.1.2 *Structure of typical mineral*

CAS formula: $[Mg(Al_{0.5-1}Fe_{0-0.5})]Si_4O_{10}(OH).4H_2O$

Palygorskite is a hydrated magnesium aluminium silicate with magnesium partially replaced by aluminium or, to a lesser extent, iron (Fe^{2+}, Fe^{3+}).

[The general structural formula for palygorskite is:

$$(Mg_{5-y-z}R^{3+}_{y}\square_{z})_{oct}(Si_{8-x}R^{3+}_{x})_{tet}O_{20}(OH)_2(H_2O)_4R^{2+}_{(x-y+2z)/2}.\ 4H_2O$$

(Bish & Guthrie, 1993). $R^{3+}_{y(oct)}$ is a trivalent cation, usually Al or Fe, substituting for Mg^{2+} in the octahedral sheet and originating a vacancy $\square$. $R^{3+}_{x(tet)}$ is a trivalent cation, usually Al, substituting for silicon in the tetrahedral sheet and originating an excess of negative charge. R^{2+} represents exchangeable cations, usually Ca^{2+} but also Na^{+} or K^{+},

which compensate the excess negative charge. The cation-exchange capacity of palygorskite ranges between 10 and 50 meq/100 g (Bish & Guthrie, 1993; Heivilin & Murray, 1994).]

Palygorskite has an elongated morphology and is similar in structure to minerals of the amphibole group, differing from sepiolite only in minor respects. In palygorskite, the basic sheet unit is smaller in the b-axis direction of the crystal. The units themselves are combined in an identical fashion to those of sepiolite (see the monograph in this volume); the indefinite development of these units along the c-axis of the crystal results in an amphibole-like double chain of SiO_4 tetrahedra (Harben & Bates, 1984; Bish & Guthrie, 1993). However, the structure of palygorskite is more diverse than that of sepiolite; palygorskite has one orthorhombic and three different monoclinic unit cell geometries. This diversity accounts for the long fibre forms found in Russia (which were once mistaken for asbestos), the shorter fibre gelling clay found in the southern part of Meigs–Attapulgus–Quincy district (GA, United States) and the even shorter fibre non-gelling type found in the northern part of this district (Heivilin & Murray, 1994). Cell parameters of orthorhombic samples are as follows: a = 1.27–1.29, b = 1.78–1.81, c = 0.51–0.53 nm and α = 92°14' and β = 95°46'–95°50' (Christ *et al.*, 1969). As with sepiolite, the structural arrangement of palygorskite results in long, thin or lath-like crystals (Anon., 1978).

1.1.3 *Chemical and physical properties* (from Roberts *et al.*, 1974, unless otherwise stated)

(*a*) *Description*: Occurs as elongated, lath-shaped crystals, in bundles that comprise thin sheets composed of minute interlaced fibres

(*b*) *Colour*: White, grey; translucent; dull

(*c*) *Hardness*: Soft

(*d*) *Density*: 2.2

(*e*) *Cleavage*: Easy along the {110} plane

The structure of palygorskite contains open channels, and these give it some unique properties, particularly in the sorption of various materials. Small polar molecules interact at the inner surface of these channels and non-polar organic molecules are adsorbed onto the large external surface area; surface areas in the range of 75–400 m^2/g have been reported (Bish & Guthrie, 1993; Heivilin & Murray, 1994). Another important physical property is the elongate particle shape, which makes palygorskite useful as a viscosifier and suspending agent (Heivilin & Murray, 1994).

1.1.4 *Technical products and impurities*

The chemical compositions of two palygorskite (attapulgite) ores and of one widely used commercial palygorskite (attapulgite) product are presented in **Table 1**. The distributions of fibre lengths in palygorskite (attapulgite) samples mined from various geological sources are presented in **Table 2**.

Table 1. Chemical composition (%) of two palygorskite (attapulgite) ores and one commercial palygorskite (attapulgite) product

Component	Palygorskite (attapulgite) ore		Commercial product[c] (as dry weight)
	Attapulgus, GA, USA[a]	Torrejon, Spain[b]	
SiO_2	54	52	68
Al_2O_3	9	10	12
Fe_2O_3	3	2	5
FeO	0.2	0.5	NR
TiO_2	0.2	NR	0.7
CaO	2	NR	2
MgO	10	12	11
Na_2O	0.03	NR	NR
K_2O	0.4	NR	1
P_2O_5	NR	NR	1
H_2O	21	22	NR

NR, not reported
[a] From Patterson & Murray (1975)
[b] From Galan & Castillo (1984)
[c] From Engelhard Corp. (1985)

Table 2. Fibre lengths of palygorskite (attapulgite) samples

Origin of sample	No. of fibres measured	Percentage of fibres within the following size classes (%)[a]			
		< 1.0 μm	1.1–5.0 μm	5.1–10.0 μm	> 10.0 μm
Brazil	1687	71.5	26.3	1.7	0.5
Korea	1023	92.7	7.1	–	–
Australia	797	90.2	9.3	0.3	0.3
Russia	1874	78.0	21.3	0.7	0.2
Switzerland	3710	75.1	22.4	2.0	0.6
Georgia, USA	2500	91.1	8.7	0.1	0.1
NIOSH A[b]	1315	83.4	16.6	–	–
NIOSH B[b]	2500	83.1	16.8	–	–
California, USA	1995	59.4	37.5	2.6	0.6
Leicester, UK[c]	–	3.5	77.5[d]	12.6[e]	6.4

From Nolan *et al.* (1991); fibre lengths determined by transmission electron microscopy
[a] All fibres were less than 0.15 μm in diameter.
[b] Commercial palygorskite (attapulgite) specimens from the Georgia–Florida deposit (see also Waxweiler *et al.*, 1988)
[c] From Wagner *et al.* (1987)
[d] Range is 1.1–6.0 μm length (diameters of fibres, 0–0.3 μm)
[e] Range is 6.1–10.0 μm length (diameters of fibres, 0–0.3 μm)

Palygorskite is commonly found in association with smectites, amorphous silica, chert (a microcrystalline silica) and other minerals (Bish & Guthrie, 1993) (see Section 1.3.1). The purity of commercial products is dependent on that of the ore (Heivilin & Murray, 1994).

Commercial palygorskite (attapulgite) products are prepared and marketed to meet specific consumer demands. They are sold in dry sorbent grades and in dry and liquid gellant or colloidal forms. Dry grades are available in many particle sizes; one super-heated material, known as 'low volatile material', resists breakdown in water (Anon., 1978; Engelhard Corp., 1985; Russell, 1991). The most common use, that of absorbent, relies on the mineral's natural high porosity and sorptivity. Sorptive grades are produced in various mesh sizes and may be calcined to increase the absorption of larger molecules such as pigments (Haas, 1972; Jones, 1972). Gellant or colloidal grades have more free moisture, higher amounts of volatile materials and are usually finer than sorptive grades (Clarke, 1985; Engelhard Corp., 1985; Russell, 1991).

Trade names for palygorskite (attapulgite) include the following: Actapulgite; Attaclay; Attacote; Attagel; Attapulgus; Attasorb; Basco; Diasorb; Diluex; Donnagel; Fert-o-Gel; Florex; Florigel H-Y; Gastropulgite; Kaopectate; Min-U-Gel; Mucipulgite; Permagel; Pharmasorb-colloidal; Zeogel.

1.1.5 *Analysis*

Most palygorskite fibres have a diameter below the resolution limit of the light microscope (Zumwalde, 1976; Bignon *et al.*, 1980). Thus, the analysis of clays, soils and dusts for the presence of palygorskite may require the use of both X-ray diffractometry and electron microscopy. When using X-ray powder diffraction analysis, the strongest line at 1.05 nm is best suited for the identification of palygorskite (Christ *et al.*, 1969; Keller, 1979).

Single fibres may be visualized and characterized by means of transmission or scanning electron microscopy. Selected area electron diffraction or X-ray microanalysis of the characteristic magnesium, aluminium, silicon and iron contents can confirm the identity of palygorskite (Zumwalde 1976; Bignon *et al.*, 1980; Sébastien *et al.*, 1984; Murray, 1986).

1.2 Production and use

1.2.1 *Production*

In ancient times, palygorskite, as a component of various naturally occurring clays, was probably used inadvertently in pottery and for removing oil in cloth manufacture (Jones, 1972).

Palygorskite has been grouped with sepiolite and loughlinite (sodium sepiolite) into a mineral subgroup of hormitic clays. The names of generic clay products may refer to a combination of minerals. For instance, the name 'fuller's earth', a product originally used to absorb fat from wool (fulling), is used in the United States to mean palygorskite,

whereas in the United Kingdom it is applied to a certain bentonite (montmorillonite) (Anon., 1978).

The name palygorskite originates from the Palygorsk Range in the Ural mounts in Russia where it was first found in 1861. Palygorskite was first mined in the United States near the town of Attapulgus, GA; hence the origin of the common industrial name for this mineral (attapulgite), which was coined in 1935 by J. De Lapparent after studying fuller's earth samples from Attapulgus, GA, and Quincy, FL, United States, and Mormoiron, France (Grim, 1968; Nolan *et al.*, 1991).

The palygorskite (attapulgite) deposit in Georgia and Florida, United States, is over 60 km in length and may be one of the largest hormitic clay deposits in the world (Anon., 1978; Clarke, 1985). This deposit, which consists of 20–80% palygorskite (attapulgite) is thought to have resulted from marine sedimentation during the Miocene period (Harben & Bates, 1984; Clarke, 1985).

Palygorskite deposits are mined by opencast techniques. The stripping of layers of material is done with scrapers, dragline excavators and bulldozers and the clay is mined with power shovels, backhoes, small dragline excavators and front-end loaders. Trucks then transport the clay to processing plant. Processing involves crushing, drying, classification and pulverizing. Specific characteristics of the palygorskite product can be enhanced by certain additional processes. For example, extruding the palygorskite, to separate the elongate particles, and adding 1–2% of magnesium oxide can improve the viscosity for use as a drilling mud; alternatively, high heat drying can be used to drive the water out of the structural channels or holes in the palygorskite to improve its sorbent properties; finally, ultrafine pulverization is used to achieve the suspension properties required for certain pharmaceutical applications (Heivilin & Murray, 1994).

World production figures are difficult to ascertain because the figures for hormitic clay production are combined with those of smectites, which are used as sorbents and called fuller's earth. Palygorskite is currently mined in ten countries: Australia, China, France, India, Russia, Sénégal, South Africa, Spain, Turkey and the United States; some of this production is a mixture of palygorskite and smectites. The United States is the largest producer by far, with four companies mining the Attapulgus deposits (Clarke, 1985, 1989; Roskill Information Services Ltd, 1991; Heivilin & Murray, 1994). In 1983, the production volume of palygorskite (attapulgite) in the western world was estimated to be approximately 1.1 million tonnes. Of this total, United States mining companies produced about 84%; the market percentages of other significant producers were as follows: Sénégal, 9%; Spain, 4%; Australia, 2.5%; and South Africa, 0.5% (Clarke, 1985). In 1994, world production of palygorskite was at about the same level, and the same countries remained the major producers (Virta, 1995). Production figures for several countries from 1979 to 1994 are presented in **Table 3**.

1.2.2 *Use*

Over 80 specific uses for palygorskite have been reported (Haas, 1972). Palygorskite was probably first used inadvertently as a component of clay materials such as fuller's

Table 3. Palygorskite (attapulgite) production by country, 1979–94 (thousand tonnes)

Country	1979	1983	1989	1994
Australia	–	10	30	15[a]
Sénégal	13	100	99	112
South Africa	4	4	7	10
Spain	48	45	45	85[a]
United States	870	934	894	1080

From Ampian & Polk (1980); Ampian (1984); British Geological Survey (1985); Roskill Information Services Ltd (1986, 1991); Virta (1994, 1995)
[a]Estimated

earth. Use of fairly pure palygorskite (attapulgite) probably began in the United States (Anon., 1978). It was first sold as a drilling mud in 1941 (Patterson & Murray, 1975); in 1945, it was used primarily for processing mineral and fatty oils (Haas, 1972). Over the next 25 years, its use shifted to absorbent applications, such as incorporation in pet litter and in materials used for cleaning up liquid spillages; quantities used for various purposes in the United States in the 1980s are presented in **Table 4**. Uses have not been categorized for other countries, but market evaluations suggest that these do not differ greatly from the major uses in the United States (Anon., 1978; Clarke, 1985).

Table 4. Uses of palygorskite (attapulgite) in the United States in the 1980s (thousand tonnes)

End use	1980	1984	1989
Adhesives	1	2	–
Animal feed	–	11	–
Cosmetics, pharmaceuticals	–	–	1
Drilling muds	144	96	35
Fertilizers	56	47	46
Oil and grease absorbents	214	190	170
Pesticides and related products	98	87	97
Pet waste absorbents	154	265	297
Refining oils and greases	20	16	4
Miscellaneous	26	56	114
Total	714	770	784

From Roskill Information Services Ltd (1991)

The commercial applications of palygorskite result from its sorptive, rheological and catalytic properties (Bish & Guthrie, 1993). Absorbents, especially those used for pet wastes, are the most common current use.

Of the gellant applications of palygorskite, drilling muds are the most important, especially those used for salt-water oil drilling. In these applications, palygorskite is mixed with water, barite (barium sulfate) and other compounds to form a suspension, or mud, which is used in the drilling shaft to surround the drill bit and drill string. Palygorskite drilling muds are preferred to other clay muds in ocean drilling because they do not lose swelling capacity in salt water (Patterson & Murray, 1975; Clarke, 1985; United States Environmental Protection Agency, 1985).

The colloidal properties of palygorskite have also been exploited in paints, adhesives, sealants and catalysts (Patterson & Murray, 1975; Anon., 1978; Roskill Information Services Ltd, 1991).

Palygorskite may be used in various other consumer products, including fertilizers, pesticides, cosmetics and pharmaceutical products (Ampian, 1984).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Palygorskite occurs around the world and has been characterized as relatively rare (Jones & Galan, 1988). However, its abundance varies greatly. In clay admixtures, it often occurs at trace quantities. In contrast, in those clay deposits worked commercially, palygorskite and related fibrous minerals may account for more than 50% by weight of the clay (Callen, 1984; Galan & Castillo, 1984).

Palygorskite is commonly found in clay deposits and in calcareous soils, lake-bed sediments and shallow, warm seas in arid and semi-arid climates. These deposits occur as equatorial belts in two regions, 20°–40°N latitude and 10°–35°S latitude (Callen, 1984).

Palygorskite is mainly sedimentary in origin. It occurs in present-day marine sediments; those areas that are exploited commercially consist of ancient lagoonal or lacustrine deposits. Such deposits commonly occur with smectites, amorphous silica (see the monograph in this volume) or chert, and less frequently with kaolinite, serpentine minerals, alkali zeolites, quartz, carbonates and sulfates (Bish & Guthrie, 1993; Heivilin & Murray, 1994). As with sepiolite, palygorskite occurs as massive aggregates of fine particles; bulk specimens display a low specific gravity and high surface area (Callen, 1984; Galan & Castillo, 1984; Ovcharenko & Kukovsky, 1984; Clarke, 1985).

1.3.2 *Occupational exposure*

In 1976, about 200 dust samples were collected at the various milling operations in a United States palygorskite (attapulgite) clay production plant. During crushing, milling, drying and screening, the time-weighted average (TWA) concentrations in the workers' breathing zones ranged from 0.05 to 2.2 mg/m^3 for total dust samples and from 0.02 to 0.32 mg/m^3 for respirable dust samples. Except for some individual samples, respirable free silica exposures calculated for each job category were below 0.05 mg/m^3. As determined by transmission electron microscopy, airborne palygorskite (attapulgite) fibres had a median diameter of 0.07 μm (range, 0.02–0.1 μm) and a median length of 0.4 μm (range, 0.1–2.5 μm) (Zumwalde, 1976; Waxweiler *et al.*, 1988).

Dust concentrations were measured in several hundred air samples in two United States companies mining and milling palygorskite (attapulgite) clay (**Table 5**) (Gamble *et al.*, 1988). The mean concentrations of total dust ranged from 0.6 to 23 mg/m^3 and respirable dust ranged from 0.05 to 2.7 mg/m^3 in various areas of the two companies.

Table 5. Mean concentrations and standard deviations of total and respirable dust in two United States companies mining and milling palygorskite (attapulgite) clay

Area within company	Company A		Company B	
	Respirable dust (mg/m^3)	Total dust (mg/m^3)	Respirable dust (mg/m^3)	Total dust (mg/m^3)
Raw clay	0.65 (0.54)	4.40 (4.19)	0.15 (0.13)	0.09[b] (0)
Drying	0.66 (0.62)	5.99 (5.40)	0.37 (0.40)	13.77 (13.98)
Crushing, screening	1.82 (1.87)	13.40 (13.50)	0.79 (0.88)	4.67 (3.45)
Milling	2.03 (1.23)	22.96 (13.80)	1.10 (0.93)	11.89 (17.41)
Shipping, loading	2.71 (9.00)	9.37 (9.60)	2.64 (11.98)	9.59 (11.50)
Mining	0.05 (0.11)	0.57 (0.56)	0.40 (0.23)	3.08 (4.68)

From Gamble *et al.* (1988)

[a]Only one sample and the difference between total and respiratory dust is within measurement error.

In air samples taken from phosphate mines in Tunisia, mineral dust particles up to 10 μm were observed, 50% of which consisted of trapped and bundled palygorskite fibres of short length (< 5 μm) (Sébastien *et al.*, 1984).

1.3.3 *Non-occupational exposure*

Palygorskite fibres have been found in some United States water supplies (Millette *et al.*, 1983).

Transmission electron microscopy and X-ray diffraction analysis of selected samples of cat litter granules, art supplies and spackling compounds (powder and paste mixtures used as fillers in, for example, home decoration) identified palygorskite fibres with diameters of 0.03–0.5 μm and lengths of up to 4 μm (Méranger & Davey, 1989).

Palygorskite is available in several countries for the treatment of diarrhoea (DuPont *et al.*, 1990; Engle, 1994; Vidal, 1996). In the United States, typically, an adult dose of 1.2 g is prescribed at the onset of symptoms with repeated use up to a maximum daily dose of 8.4 g (Engle, 1994). In France, preparations containing palygorskite are available for the treatment of the symptoms of gastroduodenal ulcer or gastritis (Vidal, 1996).

1.4 Regulations and guidelines

For occupational exposures, attapulgite (palygorskite) is regulated by the United States Occupational Safety and Health Administration with the inert or nuisance dust

standard (permissible exposure limits, 15.0 mg/m^3 total dust and 5.0 mg/m^3 respirable fibres) (United States Occupational Safety and Health Administration, 1995). Exposures to crystalline silica, if present, are regulated by the relevant crystalline silica standards (see the monograph on silica in this volume).

In Germany, there is no MAK (maximal workplace concentration) value for attapulgite (palygorskite) (fibrous dust). However, palygorskite (attapulgite) is classified in Germany as a III A2 carcinogen (a substance shown to be clearly carcinogenic only in animal studies but under conditions indicative of carcinogenic potential at the workplace) (Deutsche Forschungsgemeinschaft, 1996).

In the province of Québec, Canada, an exposure standard limit has been introduced in 1994 for attapulgite (palygorskite) of 1 fibre/mL respirable dust 8 h TWA (Anon., 1995).

In the United States, attapulgite (palygorskite) is permitted for use in antidiarrhoeal products without prescription (Engle, 1994). This is probably true of many other countries.

2. Studies of Cancer in Humans

Cohort study

A cohort of 2302 men employed for at least one month between 1940 and 1975 at a palygorskite (attapulgite) mining and milling facility in Georgia and Florida, United States, was followed through to 1975 (Waxweiler *et al.*, 1988) [fibre distribution in this facility is shown in **Table 2**]. Expected deaths were calculated based on age-, calendar year- and race-specific rates for United States males. The whole cohort showed a deficit in mortality for all causes (315 deaths observed; standardized mortality ratio (SMR), 0.80 [95% confidence interval (CI), 0.71–0.89]). An increased mortality was observed for both stomach cancer (6 observed; SMR, 1.20 [95% CI, 0.44–2.61]) and lung cancer (21 observed; SMR, 1.19 [95% CI, 0.73–1.81]). No increased trends were observed for either lung cancer or stomach cancer by duration of employment, time since beginning employment or intensity of exposure (both in terms of constancy of exposure and magnitude of exposure). A deficit of mortality due to non-malignant respiratory disease was observed (9 observed; SMR, 0.43 [95% CI, 0.20–0.82]).

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

Rat: Two groups of 20 male and 20 female Fischer 344 rats, six weeks of age, were exposed by inhalation in chambers to 10 mg/m^3 of one of two types of palygorskite dusts for 6 h per day, on five days a week for 12 months. One sample came from a deposit in Lebrija, Spain; all fibres were found to be < 2 μm in length [diameter unspecified]. The second sample was from a quarry in Leicester, United Kingdom; 20% of the fibres were > 6 μm in length and < 0.5 μm in diameter; the number of fibres (length ≥ 6 μm,

diameter < 0.5 μm) was 36.5×10^5 per μg respirable dust. All fibres from both samples were respirable. After three, six, 12 and 24 months, two animals of each sex from each group were killed and the lungs were examined to assess the severity of fibrosis. The remaining animals were allowed to live out their normal life span [exact survival unspecified]. Animals were subjected to a full necropsy; lungs, liver, spleen, kidneys and other relevant organs were examined histologically. In the group treated with palygorskite from Lebrija, animals killed up to 24 months had a score for fibrosis of 3.2 (early interstitial reaction); 3/40 rats developed bronchoalveolar hyperplasia and 1/40 had a peritoneal mesothelioma. In the group treated with palygorskite from Leicester, the fibrosis score at 12 months was up to 4.0 (first signs of fibrosis); 8/40 rats had bronchoalveolar hyperplasia, 2/40 had benign alveolar tumours, 1/40 had a malignant alveolar tumour and 3/40 had mesotheliomas, one of which was a peritoneal mesothelioma. In a positive control group treated with 10 mg/m^3 UICC crocidolite, 3/40 rats developed bronchoalveolar hyperplasia and one rat had a lung adenocarcinoma. In an unexposed control group of 40 rats, no tumour or hyperplasia was found (Wagner *et al.*, 1987). [The Working Group noted that the positive control group treated with crocidolite showed no increased tumour incidence. This limits the value of the findings for the inhaled palygorskite fibres. Also, as 12 animals per group were removed for serial killings, the effective group size was reduced to 28 rats.]

3.2 Intrapleural administration

Rat: Two groups of 30–50 female Osborne-Mendel rats, 12–20 weeks of age, received a single application directly on the left pleural surface by open thoracotomy of 40 mg/animal of one of two palygorskite (attapulgite) samples dispersed uniformly in hardened gelatin. The palygorskite (attapulgite) was obtained from sources in Attapulgus, GA, United States, and both samples were considerably refined. The samples consisted of short fibres of small diameter and were > 90% pure, the remainder being quartz. One sample contained no fibres > 4 μm in length. The other had 130×10^3 fibres per μg that were > 4 μm in length and < 0.1 μm in diameter, which corresponded to a total dose of 5.2×10^9 fibres of this size in 40 mg. The rats were followed for two years and the survivors were then killed. In each of the two palygorskite (attapulgite)-treated groups, pleural sarcomas were seen in 2/29 rats. The incidences of pleural sarcomas from historical controls were 3/491 in untreated rats and 17/615 in rats receiving pleural implants of 40 mg/animal 'non-fibrous materials' described by the authors as 'non-carcinogenic'. In a group treated with 40 mg/animal UICC crocidolite, 14/29 rats developed pleural mesotheliomas (Stanton *et al.*, 1981). [The Working Group noted the lack of data on mortality and that adequate statistical analysis is precluded by the use of historical controls.]

A group of 36 male non-inbred Sprague-Dawley rats, at two months old, received an intrapleural administration of 20 mg palygorskite obtained from a deposit in Mormoiron, France in 1 mL saline. All fibres were < 4 μm in length (mean, 0.77 μm) and < 1.5 μm in diameter (mean, 0.06 μm); the mean aspect ratio was 12.6. The dust sample contained 0.26×10^{10} fibres/mg. Rats were allowed to live out their normal life span or were killed

when moribund; the mean survival time was 788 days. A full necropsy was performed on every animal. No mesothelioma was observed in 36 rats. In another group, which was treated with 20 mg amosite asbestos, 20/35 rats had mesotheliomas (Jaurand *et al.*, 1987).

Three groups of 20 male and 20 female Fischer 344 rats, about five weeks of age, received a single intrapleural injection of 20 mg/animal of one of three palygorskite samples suspended in 0.4 mL saline. The first and second samples came from Lebrija, Spain, and from Leicester, United Kingdom, respectively and were also used in an inhalation experiment (see Section 3.1 for fibre dimensions, etc.). The third sample originated from Torrejon, Spain. In the suspension of this sample injected after mild dispersion, 0.5% of the fibres were longer than 6 μm, and the number of fibres with a length ≥ 6 μm and a diameter < 0.5 μm was 0.085×10^6 per μg (0.54%). After treatment, the animals were allowed to live out their natural life span but were killed if moribund. A full necropsy and histological examination was carried out on both lungs, any pleural nodules, liver and spleen. In the group treated with palygorskite from Lebrija, 2/40 rats had mesotheliomas, one of which was a peritoneal mesothelioma. [It should be noted that in this sample no fibres were > 2 μm in length]. In the group treated with palygorskite from Torrejon, 14/40 rats had pleural mesotheliomas. In the group treated with palygorskite from Leicester, 30/32 had pleural mesotheliomas; in this group, only 32 rats were treated. The incidences of pleural mesotheliomas were 1/40 in a saline control group and 19/39 in rats treated with 20 mg of UICC chrysotile (Wagner *et al.*, 1987). [The Working Group noted that no information was given on the survival of the rats.]

Six groups of 25 Fischer 344 rats [sex unspecified], four to six weeks of age, received a single intrapleural injection of 0.5, 2, 4, 8, 16 or 32 mg/animal of palygorskite (attapulgite) (from Attapulgus, GA–FL, United States) in saline. Ninety-nine percent of the fibres in this sample were < 1 μm in length and < 0.1 μm in diameter. [The number of fibres given to the animals is not stated.] The median life span was 839 days compared to 729 days in a control group. Mesotheliomas were observed in 2/140 rats; the incidence in the control group was 1/79. In a group treated with erionite, 137/144 rats developed mesothelioma (Coffin *et al.*, 1992). [The Working Group noted the lack of information on the dose to which animals bearing mesotheliomas were exposed.]

3.3 Intraperitoneal administration

Rat: A group of 40 female Wistar rats, eight to 12 weeks of age, received three intraperitoneal injections of 25 mg/animal palygorskite [origin unspecified] (30% of fibres > 5 μm in length) [diameter unspecified] suspended in 2 mL saline at one-week intervals. Average survival time for rats given palygorskite was 46 weeks after the first injection. Of the 34 rats treated with palygorskite and necropsied, 26 (77%) had developed malignant tumours of the abdominal cavity (24 diagnosed as mesotheliomas and two as sarcomas). In similar groups of 40 female rats receiving a single injection of 6.25 or 25 mg/animal UICC chrysotile A, 24/35 and 21/31 developed mesotheliomas of the abdominal cavity, respectively (Pott *et al.*, 1976).

Three groups of female Wistar rats [initial numbers unspecified], nine weeks of age, received five weekly intraperitoneal injections of 12 mg/animal of three different samples of palygorskite (the fibre characteristics of these samples were reported by Rödelsperger *et al.* (1987)) in 2 mL saline. The first group received a sample that originated from Mormoiron, France, and was the drug 'Gastropulgite', which contains 83% palygorskite (median length, 0.7 μm; median diameter, 0.07 μm; aspect ratio, 11; number of fibres ≥ 5 μm in length, 60×10^3 per mg). The second group received a sample originating from Lebrija, Spain (median fibre length, 0.5 μm; median fibre diameter, 0.07 μm; aspect ratio, 7; number of fibres ≥ 5 μm in length, 340×10^3 per mg). The third group received a sample from Georgia, United States (median fibre length, 0.8 μm; median fibre diameter, 0.04 μm; aspect ratio, 20; number of fibres ≥ 5 μm in length, 610×10^3 per mg). After treatment, the median life span of the three groups was 116, 116 and 108 weeks, respectively. The abdominal cavity of each rat was examined after death, and parts of any tumours observed were examined histopathologically. Sarcomas, mesotheliomas or carcinomas in the abdominal cavity, excluding tumours of the uterus, were listed. According to this classification, tumours were observed in 4/114 rats treated with palygorskite from Mormoiron, in 4/115 rats treated with palygorskite from Lebrija, in 4/112 rats treated with palygorskite (attapulgite) from Georgia and 6/113 control rats treated with a total of 90 mg granular titanium dioxide (Pott *et al.*, 1987).

A group of 30 female Wistar rats, five weeks of age, received three intraperitoneal injections of 2, 4 and 4 mg/animal (total, 10 mg) palygorskite from Caceres, Spain (median fibre length, 1.3 μm; median fibre diameter, 0.07 μm; aspect ratio, 19; number of fibres ≥ 5 μm in length, 240×10^6 per mg (3%); Rödelsperger *et al.*, 1987). [The Working Group noted that this latter figure is a factor of about 1000 more than that for the other three palygorskite samples mentioned in the previous experiment.] The median life span was 109 weeks. Abdominal tumours described as 'sarcoma, mesothelioma or carcinoma', excluding tumours of the uterus, were reported in 12/30 rats. In a positive control group treated with 1 mg/animal UICC chrysotile B, the abdominal tumour rate was 27/32. In a negative control group treated with 10 mg/animal granular titanium dioxide, no abdominal tumour was found in 32 rats (Pott *et al.* 1987).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Deposition, distribution, persistence and biodegradability

No data were available to the Working Group.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Kinetics

(*a*) *Oral administration*

A histochemical study was carried out to evaluate the changes occurring in mucins secreted by the rat stomach and intestine following a seven-day treatment with palygorskite. The results show that the polysaccharide components of the gastrointestinal glycoproteins are modified by palygorskite; this mechanism may be involved in its protective effects (More *et al.*, 1992).

(*b*) *Intratracheal instillation*

Bégin *et al.* (1987) exposed the tracheal lobes of groups of 16 sheep to a single instillation of either saline, 100 mg UICC chrysotile B from Canada in saline (42% of fibres > 5 μm), 100 mg short chrysotile fibres from Canada (98% < 3 μm mean length) in saline or 100 mg palygorskite (attapulgite) from Florida (mean length, 0.8 μm) in saline. The animals were studied by bronchoalveolar lavage (BAL) at days 2, 12, 24, 40 and 60 and by autopsy at day 60. In the sheep exposed to either UICC chrysotile B or palygorskite (attapulgite), significant and sustained cellular changes in lavage fluids were observed, which was in contrast to that found for either the short chrysotile- and saline-exposed sheep. Lung histology revealed peribronchiolar fibrosing alveolitis in the sheep exposed to UICC chrysotile B. Macrophage inflammatory responses with minimal airway distortion were observed in the sheep exposed to short chrysotile and in all but three of the sheep exposed to palygorskite (attapulgite).

Wagner *et al.* (1987) exposed 20 male and 20 female Fischer 344 rats to milled [method not stated] samples of palygorskite from Torrejon, Spain (0.54% > 6 μm length) and from Leicester, United Kingdom (19.9% > 6 μm length) and to UICC crocidolite, UICC chrysotile B and kaolin. Exposure was through inhalation at 10 mg/m^3 for 6 h per day, on five days per week for six months. Animals were killed and evaluated at sequential time periods. The palygorskite samples produced fibrosis and bronchoalveolar hyperplasia similar to or more severe than those produced by UICC crocidolite. Palygorskite from Torrejon produced an early interstitial reaction and bronchoalveolar hyperplasia.

To evaluate the inflammatory and fibrogenic potentials of palygorskite (attapulgite), UICC chrysotile B, short chrysotile 4T30, and man-made mineral fibres, xonotlite (a calcium silicate) and Fiberfrax (an aluminium silicate), groups of five male Wistar rats were exposed to 1, 5 or 10 mg of the various particulates by intratracheal instillation. The average lengths of the fibre samples were approximately 1.0 μm, except for the Fiberfrax sample (8.3 μm) and the UICC chrysotile B sample [not given]. One month after the treatment, histopathology and BAL were performed on each animal. The highest dose of palygorskite (attapulgite) produced minimal reactions, which were characterized by mononuclear cell infiltration in alveoli. In contrast, at all doses tested, Fiberfrax caused significant granulomatous reactions and the appearance of early fibrosis, and UICC chrysotile B induced fibrotic lesions in bronchiolar tissues. Short chrysotile caused focal accumulation of inflammatory cells in lung parenchyma without apparent fibrosis.

Xonotlite caused minimal inflammatory reactions, detectable only at the high dose (10 mg). Overall, the order of lung response observed for the various silicates was xonotlite < palygorskite (attapulgite) < short chrysotile < Fiberfrax < UICC chrysotile B (Lemaire *et al.*, 1989).

Using a similar protocol and the same fibre types as described above, Lemaire (1991) investigated alveolar macrophages and their interleukin-1 (IL-1) activity and production of macrophage-derived growth factor for fibroblast proliferation during chronic inflammatory reactions leading to either granuloma formation or fibrosis. One month after intratracheal instillation of fibre samples, the various treatments induced either no change (xonotlite), granuloma formation (palygorskite (attapulgite) and short chrysotile) or fibrosis (UICC chrysotile B). Eight months after exposure, however, the granulomatous reactions had resolved or greatly diminished, whereas the fibrosis persisted; examination of cell populations recovered by BAL revealed that multinucleated giant cells were present in the lavage fluids of animals with resolving granulomatous reactions but absent in those obtained from animals with lung fibrosis. In an evaluation of cytokines, IL-1 activity was detected associated with both granuloma formation and fibrosis, but production of macrophage-derived growth factor for fibroblast proliferation was observed only in animals with lung fibrosis.

(*c*) *In-vitro studies*

Jaurand *et al.* (1987) investigated the biochemical and cytotoxic effects of palygorskite and various forms of asbestos. Palygorskite was found to be cytotoxic to rabbit alveolar macrophages at concentrations ≥ 4 μg/cm^2. However, using rat pleural mesothelial cells, palygorskite was found to have low toxicity at concentrations ≥ 10 μg/cm^2.

In an in-vitro study using cultures of pleural mesothelial cells exposed to palygorskite, short chrysotile from Canada and UICC chrysotile from Rhodesia, Renier *et al.* (1989) found that neither palygorskite nor short chrysotile altered cell growth or were toxic, except at concentrations of 10 μg/cm^2. In contrast, UICC chrysotile was highly cytotoxic at a concentration of 1 μg/cm^2.

Garcia *et al.* (1989) exposed cultures of human umbilical vein and bovine pulmonary artery endothelial cell monolayers to 125, 250 and 500 μg/mL of the following fibres [dimensions not given]: palygorskite, amosite and chrysotile; fibreglass and latex beads were used as controls. The test particles were found to be rapidly phagocytized by endothelial cells. Using sodium [^{51}Cr]chromate-labelled cells, observations were made on time-dependent and concentration-dependent endothelial cell injury (measured by ^{51}Cr release). Amosite and palygorskite were found to be markedly toxic, whereas chrysotile and fibreglass were much less toxic; latex beads were not significantly injurious at any time or dose examined. The responses of both bovine and human endothelial cells to fibre phagocytosis and fibre-induced injury were similar. ^{51}Cr release from human and bovine cells treated with either palygorskite or amosite was inhibited by several oxygen scavengers or inhibitors (superoxide dismutase, catalase and the iron chelator, desferrioxamine). In human endothelial cell monolayers, the fibres mediated the stimulation of prostacyclin, an arachidonate metabolite, in a pattern similar to their effects on endothelial cells — amosite and palygorskite were stimulatory, whereas fibreglass and

latex beads did not significantly increase prostacyclin generation; these responses were not examined in the bovine cells.

Woodworth *et al.* (1983) observed the effects of palygorskite (4 and 16 mg/mL; fibre length, ≤ 5 μm) and crocidolite (1–8 mg/mL) on squamous metaplasia in Syrian hamster tracheal explants. Crocidolite induced a significant effect, but palygorskite did not. Tritiated thymidine incorporation was statistically significantly increased by crocidolite but not by palygorskite.

Chamberlain *et al.* (1982) found palygorskite to be toxic to Swiss mouse peritoneal macrophages, as determined by the release of lactate dehydrogenase. In a comparison of short-fibre and long-fibre palygorskite, it was found that short-fibre palygorskite caused the release of more of the enzyme than long-fibre palygorskite following treatment with 150 μg/mL for 18 h. In human lung carcinoma cells (A549), treatment for five days with 200 μg/mL of the short-fibre palygorskite did not induce giant cell formation; the colony formation of Chinese hamster lung fibroblasts (V79-4) was not modified following incubation for six days with several concentrations of the short fibres. However, when these latter cells were treated with long fibres (52 μg/mL), cloning efficiency was reduced by 50%. [The Working Group noted that fibre dimensions were not given.]

Reiss *et al.* (1980) studied the colony formation of human embryo intestinal cells (I-407). Palygorskite (attapulgite) from Georgia, United States (of length generally 2 μm) did not modify colony formation at 0.001–1 mg/mL. At higher doses, colony formation was inhibited (35% reduction with 2.5 mg/mL and 43% with 5.0 mg/mL).

The potential of palygorskite to lyse red blood cells was investigated by Perderiset *et al.* (1989). Some of these fibres, from Sénégal, were pre-treated with either dipalmitoyl phosphatidylcholine or bovine serum albumin. These, and untreated fibres, were then incubated with human red blood cells. The coating of the palygorskite with either dipalmitoyl phosphatidylcholine or bovine serum albumin was shown to protect against haemolysis, indicating that haemolysis is dependent on the surface properties of particulates.

Nadeau *et al.* (1987) carried out a number of in-vitro assays to determine the cytotoxicity of respirable fibres. These fibres included palygorskite (attapulgite) from Florida, chrysotile and Fiberfrax and xonotlite. All of the fibres had an average length of 1.0 μm, with the exception of Fiberfrax which was longer [mean length not reported]. The primary endpoints were haemolysis studies with rat erythrocytes and in-vitro alveolar macrophage cytotoxicity studies (from Long Evans rats) with lactate dehydrogenase and β-galactosidase. The Fiberfrax fibres were found to be non-haemolytic while chrysotile had the strongest haemolytic potential followed very closely by xonotlite; palygorskite (attapulgite) was significantly less haemolytic than chrysotile. In-vitro cytotoxicity assays, using rat pulmonary alveolar macrophages, showed that all four fibres caused similar levels of cell damage at 250 μg; at 50 μg, however, the intensity of the effect was as follows: Fiberfrax > palygorskite (attapulgite) > chrysotile > xonotlite.

Lung natural killer (NK) cell cytotoxicity is significantly suppressed, in a dose-dependent manner, by alveolar macrophages freshly obtained from male Wistar rats by BAL. This alveolar macrophage-mediated suppression of NK activity was found to be

enhanced by intratracheal instillation of palygorskite (attapulgite) (Lemaire & St-Jean, 1990).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group on the genetic effects of palygorskite in exposed humans.

4.4.2 *Experimental systems*

Achard *et al.* (1987) tested a sample of palygorskite from Sénégal (fibres < 2 μm in length) for the induction of sister chromatid exchange in rat pleural mesothelial cell cultures. Cells were treated with 10 or 20 μg/mL (2 or 4 μg/cm^2) palygorskite for 48 h. Thirty metaphases were scored for induction of sister chromatid exchange. UICC crocidolite was used as a positive control and produced a weak effect. No increase in sister chromatid exchange was shown for palygorskite.

A sample of palygorskite from Mormoiron, France, with a mean fibre length of 0.77 μm, was tested for induction of unscheduled DNA synthesis in rat pleural mesothelial cell cultures, as measured by liquid scintillation counting [this technique is no longer considered to be valid]. Confluent cell cultures were treated with 2, 4 or 10 μg/cm^2 palygorskite for 24 h; UICC crocidolite was used as a positive control and produced a significant effect. Palygorskite did not increase unscheduled DNA synthesis in rat pleural mesothelial cells (Renier *et al.*, 1990).

Denizeau *et al.* (1985) tested a sample of palygorskite from the Institut de Recherche et de Développement sur l'Amiante, Sherbrooke, Canada (average fibre length, 0.8 μm; 96% of fibres 0.01–0.1 μm in diameter) for the induction of unscheduled DNA synthesis, as measured by liquid scintillation counting [this technique is no longer considered to be valid]. Primary rat hepatocyte cultures were incubated with 1 or 10 μg/mL palygorskite for 20 h alone or in combination with 2-acetylaminofluorene (0.05 or 0.25 μg/mL). Palygorskite did not induce unscheduled DNA synthesis, nor did it enhance the activity of 2-acetylaminofluorene.

[The Working Group noted that in the above three studies palygorskite samples contained fibres with an average length of 2 μm or less and that complete information about fibre size distribution was lacking. If the endpoints tested depended on fibre length, these samples may not have had a sufficient number of fibres longer than 5 μm to produce a positive result. In two studies, UICC crocidolite was used as a positive control. It is not known whether the fibre size distribution of the test palygorskite samples and the positive control fibre are comparable.]

4.5 Mechanistic considerations related to carcinogenicity

Moderate persistent inflammation and focal fibrosis was observed in sheep after intratracheal instillation of palygorskite (attapulgite). [The Working Group noted that the mean fibre length of this sample was less than 1 μm.] Epithelial hyperplasia and fibrosis were also observed in rats after inhalation. On the basis of these animal studies, it cannot be ruled out that palygorskite (attapulgite) may induce persistent inflammation and fibrosis in human lungs. See also General Remarks on the Substances Considered.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Palygorskite is a hydrated magnesium aluminium silicate, which occurs as a fibrous chain-structure mineral in clay deposits in several areas of the world. There is a major deposit of commercial importance in the United States. Palygorskite fibre characteristics vary with the source, but fibre lengths in commercial samples are generally less than 5 μm. Palygorskite has been mined since the 1930s and is used mainly as an absorbent for pet wastes and oils and greases and as a component of drilling muds. Occupational exposure to palygorskite occurs during its mining, milling, production and use. General population exposures also may occur in its use as pet waste absorbent, in fertilizers and pesticides and by ingestion of antidiarrhoeal preparations.

5.2 Human carcinogenicity data

A single cohort study of palygorskite (attapulgite) miners and millers was available. It showed small excesses of mortality from lung cancer and stomach cancer, but no indications of any exposure–response for either cancer.

5.3 Animal carcinogenicity data

Samples of palygorskite from different regions vary considerably with regard to their fibre lengths. Results of studies in experimental animals suggest that carcinogenicity is dependent on the proportion of long fibres (> 5 μm) in the samples.

In one inhalation study in rats with palygorskite from Leicester, United Kingdom, in which about 20% of the fibres were longer than 6 μm, bronchoalveolar hyperplasia and a few benign and malignant alveolar tumours and mesotheliomas were observed. The same sample induced a high incidence of pleural mesotheliomas in rats after intrapleural administration. One sample from Torrejon, Spain, in which 0.5% of the fibres were longer than 6 μm, produced a significant increase in the incidence of pleural mesotheliomas after intrapleural injection.

In rats, intraperitoneal injection of a palygorskite sample (of unspecified origin and in which 30% of the fibres were longer than 5 μm) produced a high incidence of malignant abdominal tumours. A sample from Caceres, Spain, in which 3% of the fibres were

longer than 5 μm, induced malignant abdominal tumours in rats after intraperitoneal injection.

Several studies involving exposures of rats by inhalation, intrapleural or intraperitoneal injection using samples originating from Lebrija (Spain), Mormoiron (France) and Attapulgus (GA, United States) employed materials with relatively short fibres (≤ 0.5% were longer or equal to 5 μm). In these studies, no significant increase in the incidence of tumours was observed.

5.4 Other relevant data

Intratracheal instillation studies with palygorskite (attapulgite) fibres in sheep demonstrated significant and sustained inflammatory changes as measured in bronchoalveolar lavage fluids. These effects were mild compared to UICC chrysotile B but comparable to short chrysotile fibres. Intratracheal instillation studies in rats demonstrated that palygorskite (attapulgite) was less active than short chrysotile, UICC chrysotile B or aluminium silicate fibres but was more active than calcium silicate fibres. In-vitro studies have indicated that palygorskite can be toxic to mouse peritoneal and rat and rabbit alveolar macrophages.

In a single study, palygorskite did not show evidence for induction of sister chromatid exchange in rat pleural mesothelial cells.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of palygorskite (attapulgite).

There is *sufficient evidence* in experimental animals for the carcinogenicity of long palygorskite (attapulgite) fibres (> 5 μm).

There is *inadequate evidence* in experimental animals for the carcinogenicity of short palygorskite (attapulgite) fibres (< 5 μm).

Overall evaluation

Long palygorskite (attapulgite) fibres (> 5 μm) are *possibly carcinogenic to humans (Group 2B).*

Short palygorskite (attapulgite) fibres (< 5 μm) *cannot be classified as to their carcinogenicity to humans (Group 3).*

[1]For definition of the italicized terms, see Preamble, pp. 24–27

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