SEPIOLITE

Sepiolite 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.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 18307-23-8

Chem. Abstr. Name: Sepiolite ($Mg_3H_2(SiO_3)_4 . xH_2O$)

Chem. Abstr. Serv. Reg. No.: 15501-74-3

Deleted CAS Reg. Nos: 1319-21-7; 69423-69-4

Chem. Abstr. Name: Sepiolite ($Mg_2H_2(SiO_3)_3 . H_2O$)

Chem. Abstr. Serv. Reg. No.: 63800-37-3

Deleted CAS Reg. Nos: 12639-43-9; 53664-61-2; 61045-54-3; 61180-58-3; 64418-10-6; 83271-15-2

Chem. Abstr. Name: Sepiolite ($Mg_2H_2(SiO_3)_3 . xH_2O$)

Synonyms: Ecume de mer; meerschaum

1.1.2 *Structure of typical mineral*

[Sepiolite in nature (without metallic substitutions) is approximately $Mg_4Si_6O_{15}(OH)_2 . 6H_2O$ (Anon., 1982), which does not correspond exactly to any of the formulas associated with CAS Registry Numbers.

The general structural formula for sepiolite is:

$(Mg_{8-y-z}R^{3+}_{y}\square_{z})_{oct}(Si_{12-x}R^{3+}_{x})_{tet}O_{30}(OH)_4(H_2O)_4R^{2+}_{(x-y+2z)/2} . 8H_2O$ (Bish & Guthrie, 1993)

where $R^{3+}_{y(oct)}$ is a trivalent cation, usually Mn, Fe, or Al, substituting for Mg^{2+} in the octahedral sheet and originating a vacancy (□). $R^{3+}_{x(tet)}$ is a trivalent cation, usually Al or Fe, substituting for silicon in the tetrahedral sheet and originating an excess of negative charge. R^{2+} represents the exchangeable cations, Ca^{2+}, Na^+ and K^+, which compensate the excess negative charge. The cation-exchange capacity of sepiolite ranges from 20 to 45 meq/100 g.]

In structure, sepiolite can be considered to be transitional between the chain-structured and layer-structured silicates (Alvarez, 1984; Harben & Bates, 1984). Individual crystals are composed of sheet silicate units, which consist of layers of SiO_4 tetrahedra orientated so that unshared oxygen atoms face each other. These are bonded together with magnesium atoms coordinated octahedrally between the individual unit chains. The units develop indefinitely along the c-axis of the crystal to produce a 'triple chain' of SiO_4 tetrahedra. In the b-axis of the crystal, the structural units are separated by a distance of one chain width; in the a-axis these layers are developed and offset with respect to the layer above and below (Alvarez, 1984; Bish & Guthrie, 1993). The structure formed is orthorhombic, with cell parameters of a = 1.35, b = 2.70 and c = 0.53 nm (Brindley, 1959). This structural arrangement results in long, very thin, lath-like crystals (Anon., 1978). Fibre lengths vary, depending in part on the location of the deposit from which the sepiolite was mined. Sepiolite laths or fibres are usually combined to form either dense or spongy masses; the latter are often very light and gave the mineral its original German name of *Meerschaum* (sea-foam) (Buie, 1983; Alvarez, 1984).

1.1.3 *Chemical and physical properties*

From Roberts *et al.* (1974) and Alvarez (1984), unless otherwise specified

(*a*) *Description*: Similar to palygorskite (see the monograph on palygorskite (attapulgite) in this volume) but with an additional SiO_4 tetrahedron at regular intervals on the chain so that the unit cell is about 50% larger than that of palygorskite (Harben & Bates, 1984); usually clay-like, nodular and fibrous; also compact massive (meerschaum) or leathery (mountain leather) (Roberts *et al.*, 1974; Alvarez, 1984; Renjun, 1984).

(*b*) *Colour*: White with tints of grey-green or red; also light-yellow

(*c*) *Hardness*: 2–2.5 on Mohs' scale

(*d*) *Density*: ~2

Like palygorskite, sepiolite contains open channels in its structure that can trap molecules or ions of certain sizes and charge; surface areas in the range 75–400 m^2/g have been reported (Bish & Guthrie, 1993; Heivilin & Murray, 1994). This surface area comprises an inner surface within which small polar molecules (such as water or ammonia) interact and a large external area where non-polar organic molecules are adsorbed. Another important physical property is the elongate particle shape, which makes sepiolite useful as a viscosifier and suspending agent (Clarke, 1989; Roskill Information Services Ltd, 1991; Bish & Guthrie, 1993; Heivilin & Murray, 1994).

1.1.4 *Technical products and impurities*

The world's largest supplier of sepiolite sells granules of 75% and > 95% purity. These are available in many grades, the most important of which is the 6/30 mesh grade, which is used for absorbents. Finer grades, namely 30/60, 60/100, 120/400 and 400 mesh, are used as pesticide carriers, in animal feeds and in bleaching applications. The high-purity materials (> 95% pure) are normally marketed as catalysts or for rheological applications (Clarke, 1985). Sepiolite is also marketed and shipped as meerschaum in blocks (Buie, 1983; Ampian, 1984).

Trade names for sepiolite include: Aid Plus; Hexal; Milcon; ML 70DSA; Pangel; Pansil; Quincite; SP.

1.1.5 *Analysis*

Most sepiolite fibres have a diameter below the resolution limit of the light microscope (Alvarez, 1984). Thus, the analysis of clays, soils and dusts for the presence of sepiolite may require the use of both X-ray diffraction and electron microscopy. The crystallinity of sepiolite samples may vary considerably, but the strongest line at 1.21 nm in an X-ray powder diffraction pattern is best suited for its identification (Brindley, 1959; 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 for the characteristic magnesium : silicon ratio can confirm the identity of sepiolite particles (Brindley, 1959; Galan & Castillo, 1984; Rödelsperger *et al.*, 1985; Murray, 1986).

1.2 Production and use

1.2.1 *Production*

Sepiolite and sodium sepiolite (loughlinite) have been classed with palygorskite among the hormitic clays (Anon., 1978). Sepiolite may have been described geologically only in 1758, but it has been used in a nearly pure form for many hundreds of years in the Mediterranean basin for carving pipes and making pottery (Alvarez, 1984). In 1847 E.F. Glocker first used the name 'sepiolite' for the mineral called 'Meerschaum' by C.E. Werner in 1788 and 'ecume de mer' by R.J. Hauy in 1801 (Heivilin & Murray, 1994).

The material from which carved items are produced is known as meerschaum and, until recently, this was the term used to describe the commercially available, highly pure, compact form of sepiolite. As larger sepiolite deposits became known and other specific applications for sepiolite were developed, a dual nomenclature system arose. 'Sepiolite' came to be used for the industrial mineral, including both compact and earthy varieties, and 'Meerschaum' for the speciality mineral (compact variety) (Buie, 1983).

Commercial production of sepiolite began in Spain in 1945 (Galan & Castillo, 1984). Most production occurs in four countries — Spain, China, Turkey and the United States, with Spain accounting for over 90% of world production (Galan & Castillo, 1984; Clarke, 1985; Russell, 1991). Meerschaum has been mined on a very small scale and somewhat sporadically in France, India, Iran, Kenya, Somalia, Turkey and the United Republic of Tanzania (Buie, 1983). Sepiolite has been found rarely in the former USSR and probably was not mined in that country (Ovcharenko & Kukovsky, 1984).

Sepiolite is mined and marketed similarly to palygorskite, although less processing is required for the production of commercial grades. The large Spanish operation produces high-purity sepiolite and sepiolite–montmorillonite mixtures in various grades (Anon., 1979). Spanish production of sepiolite doubled from 1980 to 1990, from 250 to an estimated 500 thousand tonnes (British Geological Survey, 1985; Roskill Information Services Ltd, 1991).

Production in the United States is controlled by one company, which has a capacity of 40 thousand tonnes per year but produces much less (Clarke, 1985, 1989). Turkish production of industrial sepiolite grades is probably minor, but 3–31 tonnes of crude or block meerschaum were produced annually in the 1970s (Buie, 1983) and about 6 tonnes in 1984 (Ampian, 1984). In 1990, two grades of sepiolite were mined in Turkey, one brown and one white, with a total annual output of approximately three thousand tonnes (Russell, 1991).

1.2.2 *Use*

One of the largest and most important uses of sepiolite is as a pet litter absorbent. Granular particles of sepiolite are an effective litter for absorbing animal waste and odours, particularly for domestic cats.

Another important use of sepiolite is in drilling fluids. Sepiolite is used in drilling fluids because the viscosity and gel strength of a sepiolite mud are not affected by variations in electrolytic content. Sepiolite drilling muds can be used in salt water or where formation of brines becomes a problem, and as sepiolite is the only known clay mineral that is stable at high temperatures, it is also used in drilling muds for geothermal wells.

Sepiolite is not easily flocculated because of its particle shape, and it is used as a suspending agent in paints, medicines, pharmaceuticals and cosmetics. Another use is as a floor sweep compound, for absorbing oil and grease spills in factories, service stations and other areas where oil and grease spills are a problem.

Sepiolite is also used extensively in agriculture as an absorbent and adsorbent for chemicals and pesticides. The active chemical is mixed with the granular sepiolite particle, and the treated particle can then be placed in the ground with the seed. The pesticide or fertilizer is then released slowly to provide the necessary protection or nutrient for the growing plant. Similarly, finely pulverized sepiolite that has been loaded with adsorbed chemicals can be dusted or sprayed onto plants or onto the surface of the ground (Murray, 1986; Clarke, 1989).

Other uses for sepiolite include the decolorization or bleaching of vegetable and mineral oils. Also, in animal feeds, sepiolite can act as a binder and as a carrier for nutrients and growth promoters (Alvarez, 1984).

Consumption of sepiolite in the United States is mainly as a suspending agent in fluid fertilizers and in liquid-feed supplements for animals (Russell, 1991). In 1984, 85% of high-purity Spanish sepiolite was used as absorbents; most of the remainder was used in animal feeds (7.5%) and as pesticide carriers (4%) (Clarke, 1985). In 1990, the pattern of use was reported to be similar (Russell, 1991).

The brown sepiolite from Turkey owes its coloration to a 3% carbon content. This sepiolite finds application in gels, as a suspension agent, and in fertilizer manufacture. The white grade from Turkey has a small dolomite content and is used for cat litter, drilling muds and absorbents (Russell, 1991). Meerschaum is almost exclusively carved into pipes and cigarette holders (Buie, 1983; Ampian, 1984).

Sepiolite is also used in anti-caking agents, cigarette filters, detergents, environmental deodorants, catalyst carriers, asphalt coatings, filter aids, plastisols, rubber, grease thickeners and carbonless copy paper (Alvarez, 1984; Clarke, 1989).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Sepiolite and meerschaum are found in sedimentary strata, in arid and semi-arid climates around the world (Callen, 1984). Significant deposits of sepiolite have been reported in China, France, Japan, Madagascar, the Republic of Korea, Spain, Turkey, the United Republic of Tanzania and the United States (Alvarez, 1984; Renjun, 1984; Clarke, 1985).

Sepiolite deposits that are exploited commercially occur in sedimentary formations that are believed to have formed under lacustrine conditions in fairly arid climates (Callen, 1984). Scattered, non-sedimentary (probably hydrothermal) deposits of sepiolite have been reported in Finland, China and other regions, and these are characterized by longer (> 20 μm), highly crystalline fibres (Lopez-Galindo & Sanchez Navas, 1989; Santarén & Alvarez, 1994).

Sepiolite in nature is often associated with other clays, such as palygorskite and montmorillonite (Anon., 1978), and non-clay minerals such as carbonates, quartz, feldspar and phosphates (Alvarez, 1984). The major mineral contaminant of sepiolite products from Spain is montmorillonite (Anon., 1978); the following minerals are minor contaminants: illite, palygorskite, calcite, smectite, dolomite, quartz, cristobalite and feldspar (Galan & Castillo, 1984). The composition of sepiolite from four deposits in Spain is presented in **Table 1**.

Table 1. Theoretical and actual composition (%) of sepiolite

Component	Theoretical composition[a]	Actual composition from four deposits in Spain[b]
SiO_2	60.7	59–63
Al_2O_3	–	1–4
Fe_2O_3	–	0.3–0.9
MgO	27.2	21–24
CaO	–	0.4–0.5
$Na_2O + K_2O$	–	0.3–2
H_2O	12.1	11–13

[a] For $Mg_2H_2(SiO_3)_3 . H_2O$
[b] From Galan & Castillo (1984)

1.3.2 *Occupational exposure*

McConnochie *et al.* (1993) reported a cross-sectional study of the total workforce of the largest sepiolite production plant in the world, which is located near Madrid, Spain. The dust exposure of workers at the plant was assessed by measuring the airborne dust concentrations in the various departments (see **Table 2**). Size-selective personal samplers were used for periods exceeding 6 h, and respirable dust samples obtained in the breathing zones of workers were evaluated gravimetrically. Samples of total dust obtained over short periods were analysed by optical and electron microscopy to determine fibre concentrations numerically. Highest concentrations were found in the bagging department and in the classifier shed. Employees did not work continuously in the classifier shed and respirators were usually worn, but workers in the bag filling operation were exposed continuously. Fibres, that is particles having length : diameter ratios equal to or greater than 3, formed a proportion of the dust, but > 95% were shorter than 5 μm (**Table 3**). The longer sepiolite fibres were formed from elongated aggregates of interdigitated short fibres.

Table 2. Concentrations of respirable dust, total dust particles and fibres in a large sepiolite production plant near Madrid, Spain

Location of workers	Type of job[a]	Respirable dust (mg/m^3)	Total dust particles/mL (length > 1.0 μm)	Fibres/mL	
				Total	Length ≥ 7 μm
Bagging shed	P, M				
20-kg bags		9.5	158	15	2
5-kg bags		11.4	260	105	2
Special products	P, M	2.3	3.5	6	NR
Bagging, classifying	P, M	18.5	159	43	NR
Primary crusher	O, M	NR[b]	35	2	NR
Transport area	O, M	NR	15	0.1	NR

From McConnochie *et al.* (1993)
[a] P, packaging; M, maintenance; O, other plant worker
[b] NR, not reported

1.4 Regulations and guidelines

For occupational exposures, sepiolite is regulated by the United States Occupational Safety and Health Administration (1995) 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). 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 sepiolite (fibrous dust). However, sepiolite is classified in Germany as belonging to category IIIB, that is a substance suspected of having carcinogenic potential (Deutsche Forschungsgemeinschaft, 1996).

Table 3. Size distribution of airborne sepiolite fibres in a large sepiolite production plant near Madrid, Spain

Fibre length		Fibre diameter	
Range (µm)	Proportion of sepiolite fibres within range (%)	Range (µm)	Proportion of sepiolite fibres within range (%)
< 1.0	6.5	< 0.1	2.8
1.0–1.9	55.1	0.1–0.19	60.8
2.0–2.9	26.2	0.2–0.29	25.2
3.0–3.9	8.4	0.3–0.39	5.6
4.0–4.9	1.0	0.4–0.49	3.7
5.0–6.9	0.9	0.5–0.59	–
7.0–9.9	–	0.6–0.69	–
≥ 10.0	1.9	≥ 0.7	1.9

From McConnochie *et al.* (1993)

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

Rat: A group of 20 male and 20 female Fischer 344 rats, six weeks of age, was exposed to 10 mg/m^3 sepiolite dust in chambers for 6 h a day on five days a week for 12 months. The sepiolite was a commercial product from Vicálvaro-Vallecas (Madrid, Spain) (Santarén & Alvarez, 1994) and the dust was respirable [it was not stated explicitly whether this was respirable to rats or to humans]. This respirable dust contained 115 × 10^6 fibres/µg; the dimensions of all fibres were < 6 µm in length and < 0.5 µm in diameter. After three, six, 12 and 24 months, two animals of each sex were killed and their lungs were removed to assess the severity of fibrosis. The remaining animals were allowed to live out their normal life span [exact survival times not stated]. A full necropsy was performed on all animals; lungs, liver, spleen, kidneys and other relevant organs were examined histologically. The score of fibrosis in animals killed up to 24 months was grade 3 — early interstitial reaction. Bronchoalveolar hyperplasia was observed in 1/40 rats; 1/40 rats had a squamous carcinoma; and 1/40 rats had both lesions. In a positive control group treated with 10 mg/m^3 UICC crocidolite, broncho-alveolar hyperplasia was observed in 3/40 rats; one rat had a lung adenocarcinoma. In an unexposed control group, no tumours or hyperplasia were 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 on inhaled sepiolite. In addition, as 12 animals per group were removed for serial killings, the effective group size would have been reduced to 28 rats.]

3.2 Intrapleural administration

Rat: 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 sepiolite suspended in 0.4 mL saline. Three samples of sepiolite from Vicálvaro-Vallecas (see Section 3.1) were used. Two samples were a direct product of the initial milling of a crude sample (with and without being dispersed ultrasonically). The third sample was from a commercial product and was also used for the inhalation test (see Section 3.1). Of this latter respirable sepiolite sample, all the fibres were < 6 μm in length and < 0.2 μm in diameter. The animals were allowed to live out their natural life span but were killed if moribund. For each animal, a full necropsy and a histological examination were performed on both lungs, any pleural nodules, the liver and the spleen. Pleural mesotheliomas were observed in 1/40 rats treated with the crude ultrasonicated sample and in 1/40 rats treated with the commercial sample. No pleural mesothelioma was found in animals treated with the crude non-ultrasonicated sample. The incidences of pleural mesotheliomas were 1/40 in a saline control group and 19/39 in rats exposed to 20 mg/animal UICC chrysotile B (Wagner *et al.*, 1987). [The Working Group noted the short fibre length of the samples used and the absence of data on survival.]

Two groups of 44 male Fischer 344 rats [age unspecified] were injected intrapleurally with 15 mg/animal sepiolite. One group of rats received a sample of 'long' sepiolite from China (length, 1–100 μm; diameter, 0.05–0.1 μm) and the other a sample of 'short' sepiolite from Turkey (length, 3–5 μm; diameter, 0.01 μm). Animals were killed when moribund or at 100–110 weeks. No tumour (0/26) was observed in the group treated with the sepiolite from Turkey. In the group exposed to the sepiolite from China, 3/29 rats had hyperplasia of the pleural mesothelium and 5/29 rats had pleural mesotheliomas. Survival of the mesothelioma-bearing animals was between 531 and 740 days. In an unexposed control group, no tumour was detected in 27 rats. In a positive control group treated with 20 mg UICC chrysotile B, 7/25 rats developed pleural mesotheliomas within 612–751 days (Fukuda *et al.*, 1988).

3.3 Intraperitoneal administration

3.3.1 *Mouse*

Four groups of 10 female ICR mice, eight weeks old, were injected intraperitoneally with 5 mg or 15 mg/animal of one of two samples of sepiolite. The characteristics of these two samples, one from China and the other from Turkey, are described in Section 3.2. In all four groups, half of the mice were killed after 12 months and the remainder after 18 months. Peritoneal mesotheliomas were observed in 2/10 mice treated with 5 mg of the sepiolite from China and 2/10 mice treated with 15 mg of the sepiolite from China. In the group that received 15 mg of the sepiolite from China, 1/10 mice had peritoneal mesothelial hyperplasia. No tumours were observed in 10 mice treated with 15 mg of the sepiolite from Turkey or in 17 mice in an untreated control group. In contrast, 2/17 mice in a positive control group injected with 15 mg UICC chrysotile B developed peritoneal mesotheliomas (Fukuda *et al.*, 1988). [The Working Group noted the small number of animals.]

3.3.2 *Rat*

A group of 32 female Wistar rats [age unspecified] was injected with 80 mg/animal sepiolite from Vicálvaro-Vallecas intraperitoneally [single or multiple treatment not specified]. The median fibre length was 1.2 μm and the median fibre diameter was 0.05 μm; the aspect ratio of the fibre was 25. The sample contained 180×10^6 fibres/mg ≥ 5 μm in length [0.9%], which corresponded to a total dose for each animal of 14×10^9 fibres ≥ 5 μm in length (Rödelsperger *et al.*, 1987). Surviving animals were sacrificed about 2.5 years after treatment (median survival of treated rats, 112 weeks) and parts of tumours or organs with suspected tumour tissue were investigated histopathologically. Abdominal tumours (sarcomas or mesotheliomas) were observed in 2/32 rats. Another group of 36 female Wistar rats was injected intraperitoneally with 10 mg of a sepiolite from Finland. The median fibre length of this sample was 2.9 μm and the median fibre diameter was 0.05 μm; the length to diameter ratio of the fibre was 64. The sample contained 55×10^8 fibres/mg ≥ 5 μg in length — considerably more than in the Spanish sample described above. The total dose of fibres ≥ 5 μm in length given to each animal was 55×10^9. The median survival time was 62 weeks. Abdominal tumours (sarcomas or mesotheliomas, excluding tumours of the uterus) were observed in 24/36 rats. However, Rödelsperger *et al.* (1987) noted that this sepiolite sample contained amphibole contaminants, which they identified as anthophyllite. In a control group treated with an intraperitoneal injection of saline, 4/204 rats had abdominal tumours. In a positive control group injected intraperitoneally with 1 mg/animal UICC chrysotile B from Canada, abdominal tumours were observed in 30/36 rats (Pott *et al.*, 1990). [The Working Group noted the presence of amphibole fibres in this Finnish sample of sepiolite.]

Two groups of 36 female Wistar rats, weighing about 160 g [age unspecified], were injected intraperitoneally with 50 mg or 250 mg/animal sepiolite from Vicálvaro-Vallecas (Spain) (five weekly injections each of 50 mg). The median fibre length of this sample was 1.0 μm and the median fibre diameter 0.06 μm. The 50 mg dose corresponded to 7.56×10^9 fibres [0.9%] with a length > 5 μm, a diameter < 2 μm and an aspect ratio > 5; the 250 mg dose corresponded to 37.8×10^9 fibres of the above dimensions. The number of rats per group was reduced by an infectious disease of the lung in months 12 and 13; 13 rats died in the group treated with a single injection of 50 mg sepiolite, and 15 died in the group treated with five injections of 50 mg. [The Working Group noted that this did not severely compromise the results of the study.] The median survival of the remaining rats was 105 weeks for the first group and 126 for the second group. In the histopathological evaluation, animals with tumours of the uterus only were excluded, but rats with mesothelioma or sarcoma and a simultaneous tumour of the uterus were included. In the group dosed with 50 mg sepiolite, no abdominal tumour was found (0/23). In the high-dose group (250 mg), 2/21 abdominal tumours (mesothelioma/sarcoma) were observed. In a control group treated intraperitoneally with saline, the tumour incidence was 2/50. In a further group dosed with 25 mg silicon carbide fibres, abdominal tumours were reported in 36/37 rats (Pott *et al.*, 1991).

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*

Baris *et al.* (1980) encountered clinical and radiological evidence of pulmonary fibrosis (small irregular opacities) in 10/63 sepiolite trimmers in Eskisehir, Turkey. These ten workers were smokers and came from dusty rural regions where tremolite and zeolites are present. Radiological examination of inhabitants of four villages near Eskisehir, where sepiolite has been mined and processed for more than 100 years, showed no evidence of pleural disease.

McConnochie *et al.* (1993) studied 218 workers (210 men and eight women) in a cross-sectional study of the total workforce of the largest sepiolite production plant in the world (located near Madrid, Spain). In the study area, the size distributions of airborne sepiolite fibres were as follows: < 1 μm (6.5%), 1–1.9 μm (55.1%), 2–2.9 μm (26.2%), 3–3.9 μm (8.4%) and ≥ 4 μm (3.8%). For each subject various parameters were recorded, including height, age and smoking history and the results of chest radiographs, pulmonary function tests and personal samplers. Analysis of the results indicated that (when smoking habits were controlled for) workers exposed to dry dust had significantly reduced FEV_1 (forced expiratory volume in one second) and FVC (forced vital capacity) with age compared with workers who had had little exposure to dry dust. Chest radiographs were scored according to a modified ILO system (scores 0–1) and this score was found to increase with age; no clear patterns were detected with other variables. Nevertheless, a greater deterioration in lung function was found in those subjects who had had greater exposures to dust.

4.2.2 *Experimental systems*

Wagner *et al.* (1987) exposed 20 male and 20 female Fischer 344 rats to sepiolite from Spain by inhalation at 10 mg/m^3 for six months. Concurrently, groups of rats were exposed to similar concentrations of UICC crocidolite, chrysotile B and kaolin. At sequential time periods, animals were killed and evaluated. Sepiolite produced an early interstitial reaction and bronchoalveolar hyperplasia.

Sepiolite fibres at concentrations > 10 mg/mL have been shown to cause the haemolysis of sheep red blood cells (Schnitzer & Pundsack, 1970; Wright *et al.*, 1980). Chamberlain *et al.* (1982) showed that although short sepiolite fibres (90% < 2 μm in length) at a concentration of 150 μg/mL were not toxic to Swiss mouse peritoneal macrophages, longer fibres (90% > 4 μm in length) at the same concentration induced the release of lactate dehydrogenase (LDH) following treatment for 18 h.

Olmo *et al.* (1988) studied the growth, morphology and collagen biosynthesis of human fibroblasts obtained and cultured on sepiolite–collagen complexes. This non-standard culture substrate appeared to have no effect on any of these attributes.

Lizarbe *et al.* (1987a) studied the adhesion, spreading and attachment of human fibroblasts on sepiolite–collagen complexes. The fibroblasts were grown out from skin explants obtained via human skin biopsies. Measurements of cell attachment characteristics indicated that sepiolite–collagen complexes are adhesive for cells.

Lizarbe *et al.* (1987b) designed a further series of experiments to characterize the response of connective tissue cells to sepiolite–collagen complexes. Cell migration from skin explants to these complexes (both normal and glutaraldehyde-treated) was similar in both experimental and control conditions.

Governa *et al.* (1995) tested *in vitro* the ability of one commercial sample of sepiolite and two samples of commercial vermiculite (clay materials) to (i) activate complement to lyse red blood cells, and (ii) elicit the production of reactive oxygen species (ROS) with human polymorphonuclear leukocytes or bovine alveolar macrophages. These investigators used UICC chrysotile B as a reference standard, as well as kaolinite and illite, members of the clay mineral family. The sepiolite and the two samples of vermiculite were found to cause minimal activation of complement, unlike chrysotile which caused a marked activation of the alternate pathway of complement. In consequence, the haemolytic effects of sepiolite and the two samples of vermiculite were lower than that of chrysotile. Luminol-amplified chemiluminescence was used as a measure of the generation of ROS. In both cell types used, this chemiluminescence was low for sepiolite.

Hansen and Mossman (1987) tested a series of fibrous and non-fibrous particles *in vitro* for the ability to stimulate the generation of the superoxide anion (O_2^-) in hamster and rat alveolar macrophages. The substances tested were as follows: (fibrous) — sepiolite (mean length, 1 μm), crocidolite, erionite and Code 100 fibreglass; and (non-fibrous) — riebeckite, mordenite and glass. The amount of superoxide anion released by cells in response to these dusts was determined by measuring the reduction of cytochrome c in the presence and absence of superoxide dismutase. All fibrous dusts, including sepiolite, caused a significant increase in the release of superoxide anion from rat macrophages and zymosan-triggered superoxide anion from hamster macrophages. Non-fibrous particles were less active than fibres at comparable concentrations.

Koshi *et al.* (1991) examined the toxic and haemolytic activities of various kinds of asbestos and asbestos substitutes with reference to their mineralogical and physicochemical characteristics. Among the 35 fibrous and non-fibrous samples tested, all four types of sepiolite were strongly haemolytic. Sepiolite-induced cytotoxicity was correlated with crystallinity and fibre length.

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 sepiolite in exposed humans.

4.4.2 *Experimental systems*

Denizeau *et al.* (1985) tested a sample of natural sepiolite from the Institut de Recherche et de Développement sur l'Amiante, Sherbrooke, Canada (average fibre length of 86% of the fibres, 2.04 μm; diameter of 96% of the fibres, 0.01–0.1 μm) for the induction of unscheduled DNA synthesis as measured by liquid scintillation counting [this technique is no longer considered valid]. To do so, rat primary hepatocyte cultures were exposed for 20 h at doses of 1 or 10 mg/mL sepiolite either alone or in combination with 2-acetylaminofluorene (0.05 or 0.25 μg/mL). Sepiolite neither induced unscheduled DNA synthesis nor enhanced the positive effect of 2-acetylaminofluorene.

In testing four samples of sepiolite (from China, Japan, Spain and Turkey), Koshi *et al.* (1991) found that each type induced polyploidy in Chinese hamster lung cells after incubation for 48 h at doses of 10–300 μg/mL. The sepiolite from China (fibre length, 1–10 μm; diameter, 0.05–0.1 μm) was most potent, and this sample had the highest order of crystallinity as determined by X-ray diffraction analysis. The other sepiolite samples were equally effective in the induction of polyploidy but far less potent than the sample from China. The dimensions of the other sepiolite samples were as follows: sepiolite from Japan, 3–7 μm long and 0.01–0.07 μm in diameter; and sepiolite from Spain and Turkey, 3–5 μm long and 0.01 μm in diameter. None of these samples induced chromosomal aberrations.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Sepiolite is a hydrated magnesium silicate that occurs as a fibrous chain-structure mineral in clays in several areas of the world. The major commercial deposits of sepiolite are in Spain. Sepiolite fibre characteristics vary with the source, but fibre lengths in commercial samples are generally less than 5 μm. Sepiolite has been mined since the 1940s, finding its greatest use as an absorbent, particularly for pet waste, and oils and greases. It is also used as a drilling mud and as a carrier for fertilizers and pesticides. Meerschaum, a compact form of sepiolite, has been used for centuries for the production of smokers' pipes. Occupational exposure occurs during the mining, milling, production and use of sepiolite.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In one inhalation study in rats using sepiolite from Vicálvaro-Vallecas, Spain, in which all fibres were shorter than 6 μm, no significant increase in tumour incidence was found.

In one study by intrapleural injection to rats, sepiolite from China (fibre length, 1–100 μm) induced pleural mesotheliomas. In similar studies by intrapleural injection using samples from Turkey and Vicálvaro-Vallecas (all fibres shorter than 6 μm), no increases in tumour incidence were observed.

In two studies in rats by intraperitoneal injection using samples (0.9% of fibres > 5 μm) from Vicálvaro-Vallecas, no significant increases in the incidences of abdominal tumours were found.

In one study in mice by intraperitoneal injection, sepiolite from China (fibres, 1–100 μm in length) produced a small increase in the incidence of peritoneal mesotheliomas but sepiolite from Turkey (fibre length, 3–5 μm) did not.

5.4 Other relevant data

One study in sepiolite-exposed workers demonstrated clinical evidence of pulmonary function deficits. The results of one in-vitro study indicated that sepiolite was relatively potent in inducing superoxide anion release from both hamster and rat alveolar macrophages. Sepiolite is strongly haemolytic in some in-vitro assays.

In a single study, samples of sepiolite from China, Japan, Spain and Turkey induced polyploidy, but not chromosomal aberrations, in cultured Chinese hamster lung cells.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of sepiolite.

There is *limited evidence* in experimental animals for the carcinogenicity of long sepiolite fibres (> 5 μm).

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

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

Overall evaluation

Sepiolite *cannot be classified as to its carcinogenicity to humans (Group 3).*

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