ZEOLITES OTHER THAN ERIONITE

1. Exposure Data

Natural zeolites occur in over 40 countries and are mined in 11 of these at a rate of around 250 thousand tonnes per year. Discovery of the characteristic ion-exchange, dehydration and selective-adsorption properties of these zeolites, which are related to their unique honeycomb structure, stimulated the development of several processes for the manufacture of synthetic zeolites. These synthetic zeolites share and improve upon these properties of natural zeolites. So far, nearly 100 structural types of synthetic and natural zeolites have been reported (Meier *et al.*, 1996; Roland & Kleinschmit, 1996); within these types, a large number of chemically diverse synthetic zeolites and 40 natural zeolites are now known (Roskill Information Services Ltd, 1988).

Among the natural zeolites, erionite was previously evaluated as a human carcinogen (IARC, 1987) and is not included in this monograph.

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 1318-02-1

Deleted CAS Nos: 37305-72-9, 50809-51-3, 52349-29-8, 53025-48-2, 53060-43-8, 53569-61-2, 53789-62-1, 54693-40-2, 54824-24-7, 56747-83-2, 61710-45-0, 75216-11-4, 76774-74-8, 85117-23-3, 85117-24-4, 88813-85-8, 91082-97-2, 91082-98-3, 100215-47-2; 128280-69-3

Chem. Abstr. Name: Zeolites

Synonyms and trade names: Abscents 3000; Adsorbents, zeolites; Agrolithe 15/25; Aid Plus OCMA; Aluminosilicates, zeolites; Bactekiller BM 101A; Bactekiller BM 102A; Bactekiller BM 102B; Bactekiller BM 501A; Bactekiller BM 503; Bactekiller MB; Baylith AC 6184; Ca EH 4B; Calsit; Coratyl G; Crystal structure types, zeolitic; Crystals, zeolitic; CS 100; CS 100 (zeolite); CS 100S; EZA Zeolite A; Filtering materials, zeolites; Filters and Filtering materials, mol. sieves; GRZ 1; Harmony 70; HSD 640NAD; Ionsiv; JE 15P; KC-Perlkator D 10E; KKh 100; LM 104; LM 108; LM 204; LM 208; LM 208 (zeolite); LMS 9611; LP zeolites; Microzeokar 8; Mol. sieves, zeolites; Molecular sieves, zeolitic; MZ 3; NA 100; NC 300; Neounizeon SP 3000; Radiolite; SGK 1; Sieves, mol.; Silicates, alumino; Siliporite NK 10 Silton B 50; Silton B-MZ 260; Silton CPT 30; T 134 (zeolite); Wessalith NaP; Wessalith P; Zeolite 1014; Zeolite 1424; Zeolite 24P

For the natural zeolites, clinoptilolite, mordenite and phillipsite, the current assigned CAS names and registry numbers, synonyms and some selected properties are given in **Table 1**.

1.1.2 *Structure of typical mineral*

Zeolites may be obtained either from naturally occurring deposits or manufactured synthetically by one of several different processes.

Zeolites are a group of hydrated, crystalline alumino-silicates containing exchangeable cations of group IA and IIA elements such as sodium, potassium, magnesium and calcium. The zeolite framework consists of SiO_4 and AlO_4 tetrahedra joined by shared oxygen atoms. Metal cations (M) compensate the excess negative charge from the aluminium-containing tetrahedra. Zeolites can be represented by the empirical formula:

$$M_{2/n}O \,.\, Al_2O_3 \,.\, ySiO_2 \,.\, wH_2O$$

where n is the cation valence and w represents the water contained in the voids of the zeolite. Structurally, the minerals are complex inorganic 'polymers' based on an indefinitely extending framework of AlO_4 and SiO_4 tetrahedra. The channels or interconnecting voids of this framework, which may amount to as much as 50% of the zeolite by volume, normally contain the cations and water molecules. However, when a zeolite is reversibly dehydrated by heating, the cations become coordinated with the oxygen along the inner surfaces of the cavities, while the crystalline structure remains intact. This leaves a porous zeolite crystal permeated with cavities; the cavities are interconnected by channels of diameter 0.3–0.8 nm. Accessibility to the internal channels and cavities of zeolites is generally restricted to very small molecules (Breck & Anderson, 1981; Roskill Information Services Ltd, 1988).

The structural formula of a zeolite is based on a crystal unit cell which can be represented by:

$$M_{x/n}[(AlO_2)_x(SiO_2)_y] \,.\, wH_2O$$

where n is the valence of cation M, w is the number of water molecules per unit cell, and x and y are the total number of tetrahedra per unit cell. The ratio of y/x usually has values of 1–5, although zeolites have been prepared where y/x is 10 to 100 or higher; zeolites containing only silica have been prepared (Breck & Anderson, 1981; Roskill Information Services Ltd, 1988).

Nominal formulae for most common natural and synthetic zeolites are given in **Table 2**.

Natural zeolites that are fibrous include natrolite, tetranatrolite, paranatrolite, mesolite, scolecite, thomsonite, erionite and mordenite (Wright *et al.*, 1983; Gottardi & Galli, 1985).

Clinoptilolite in sedimentary rocks occurs as euhedral (idiomorphic) plates and laths, several micrometres in length and 1–2 µm thick. Most crystals display characteristic monoclinic symmetry and many are coffin-shaped (Mumpton & Ormsby, 1976).

Table 1. CAS names, registry numbers, synonyms and properties of some zeolites

Zeolite	CAS names and registry numbers	Synonyms and trade names	Window (O atoms in ring)	Pore size (nm)	SiO_2/Al_2O_3 ratio
Clinoptilolite	Clinoptilolite [12173-10-3] (Deleted CAS Nos: 12321-85-6; 67239-95-6) Clinoptilolite (Na($AlSi_5O_{12}$. xH_2O) [12271-42-0] Clinoptilolite ($AlNaH_{16}(SiO_4)$. $4H_2O$) [67240-23-7]	Klinosorb; 1010A	8 10 + 8	0.39 × 0.54 0.26 × 0.47 0.30 × 0.76 0.33 × 0.46	11.0
Mordenite	Mordenite [12173-98-7] Mordenite ($AlNaH_6(SiO_3)_5$) [12445-20-4] Mordenite ($Al_2CaH_{12}(SiO_3)_{10}$. H_2O) [66732-10-3] Mordenite ($Na(AlSi_5O_{12})$) [68652-75-5]	Prilolite; 2020A; Alite 150; Astonite; Jinyunite; Zeolon 100	12 8	0.65 × 0.70 0.26 × 0.57	9.0–35
Phillipsite	Phillipsite [12174-18-4] Phillipsite ($CaK[Al_3O(SiO_3)_5]$. $6H_2O$) [61027-84-7] Phillipsite ($AlNa(SiO_4)$. $6H_2O$) [66733-09-3]		8 8 8	0.42 × 0.44 0.28 × 0.48 0.33	4.0
Zeolite A[a]	[68989-22-0]		8	0.41	2.0–6.8
Zeolite L	NS		12	0.71	6.0–7.0
Zeolite X	[68989-23-1]		12	0.74	2.0–3.0
Zeolite Y	NS		12	0.74	3.0–6.0
ZSM-5	[79982-98-2]		10 10	0.53 × 0.56 0.51 × 0.55	25–∞

From Dyer (1988); Vaughan (1988); Holmes (1994); Meier *et al.* (1996); Roland & Kleinschmit (1996)

[a] Zeolites 3A, 4A and 5A are isostructural with zeolite A. The terms are derived from the pore openings which are changed by exchanging with different cations. Zeolite 3A is exchanged with K, zeolite 4A with Na and zeolite 5A with Ca.

NS, not specified

Table 2. Formula of most common zeolites[a]

Zeolite	Typical formula
Natural	
Analcime	$Na_{16}[(AlO_2)_{16}(SiO_2)_{32}] . 16H_2O$
Chabazite	$Ca_2[(AlO_2)_4(SiO_2)_8] . 13H_2O$
Mordenite	$Na_8[AlO_2)_8(SiO_2)_{40}] . 24H_2O$
Ferrierite	$(Na,Mg)_2[(AlO_2)_6(SiO_2)_{30}] . 18H_2O$
Heulandite	$Ca_4[(AlO_2)_8(SiO_2)_{28} . 24H_2O$
Erionite	$(Ca,Mg,Na_2,K_2)_{4.5}[(AlO_2)_9SiO_2)_{27}] . 27H_2O$
Faujasite	$(Ca,Mg,Na_2,K_2)_{29.5}[(AlO_2)_{59}(SiO_2)_{133}] . 235H_2O$
Clinoptilolite	$Na_6[(AlO_2)_6(SiO_2)_{30}] . 24H_2O$
Phillipsite	$K_2(Ca,Na_2)_2[(AlO_2)_6(SiO_2)_{10}] . 12H_2O$
Laumontite	$Ca_4[(AlO_2)_8(SiO_2)_{16}] . 16H_2O$
Synthetic	
Zeolite A	$Na_{12}[AlO_2)_{12}(SiO_2)_{12}] . 27H_2O$
Zeolite X	$Na_{86}[(AlO_2)_{86}(SiO_2)_{106}] . 264H_2O$
Zeolite Y	$Na_{56}[AlO_2)_{56}(SiO_2)_{136}] . 250H_2O$
Zeolite L	$K_9[(AlO_2)_9(SiO_2)_{27}] . 22H_2O$
ZSM-5[b]	$(Na,TPA)_3[(AlO_2)_3(SiO_2)_{93}] . 16H_2O$

[a] Breck (1975); Griffith (1987); Roskill Information Services Ltd (1988); Holmes (1994); Hanson (1995); Meier *et al.* (1996); Roland & Kleinschmit (1996)

[b] TPA, tetrapropylammonium

Natural mordenite frequently contains thin, curved fibres, a few tenths of a micrometre in diameter. The fibres are extremely delicate; length : width ratios of 100 or more are common (Mumpton & Ormsby, 1976).

Phillipsite occurs as stout prisms and stubby laths, 3–30 μm in length and 0.3–3 μm thick, generally with pseudo-orthorhombic symmetry (Mumpton & Ormsby, 1976).

Commercial zeolites are generally prepared under conditions such that they are non-fibrous cage-like structures (Bergk *et al.*, 1991; van Hoof & Roelofsen, 1991; Jansen, 1991) Cation exchange capacities of synthetic zeolites vary considerably from around 2.3 to 5.5 meq/g.

1.1.3 *Technical products and impurities*

Specifications depend on the uses of the zeolite products and vary widely because of the broad range of natural and synthetic zeolite products, serving many markets. The American Society for Testing and Materials Committee No. D-32 sets general testing methods for zeolites in the United States. Specifications and standards in Europe and Japan are commonly set by the producing companies in a market-driven setting. Zeolite producers deal with specifications in the two following ways: on a custom basis to specifications negotiated with the buyer; or on a product-line basis, where each zeolite product has a name or number designation and specific physical and/or chemical characteristics.

In the United States, zeolite products are commonly sold under a trade name rather than as a mineral variety, e.g. clinoptilolite (Holmes, 1994).

Natural zeolites may contain benzo[*a*]pyrene. For example, zeolite dusts taken from five deposits in Russia and one deposit in Georgia were determined to contain 1.21–3.60 μg/kg benzo[*a*]pyrene (Pylev *et al.*, 1984; Valamina *et al.*, 1994).

1.1.4 *Analysis*

Natural zeolite minerals are identified primarily by their crystalline structure. Chemical analyses alone are not an effective method of identification, as many zeolites have similar chemical composition. Macroscopic zeolites, particularly those occurring in vesicles and fractures in basaltic rocks, may be identified by careful visual examination. However, virtually all natural zeolite occurrences of commercial value are of microscopic grain size. The positive identification and semi-quantitative determination of such fine-grained materials can be done only in the laboratory. The principal methods of identification are by X-ray diffraction and scanning electron microscopy; less often, optical microscopy and differential thermal analysis are used (van Hoof & Roelofsen, 1991; Holmes, 1994). In special circumstances, other analytical methods may be used. Such methods include infrared absorption spectrometry, Moessbauer spectroscopy, electron spin resonance spectroscopy, electron spin echo spectroscopy, solid state nuclear magnetic resonance, neutron diffraction and synchrotron X-ray diffraction (Holmes, 1994).

In characterizing zeolitic materials for commercial uses, specifications are generally tailored toward the desired application. The following physical and chemical properties and tests may be used to characterize a zeolite product: wet chemical analysis; cation exchange capacity; specific gravity and bulk density; brightness, whiteness, and colour; hydration/dehydration testing; gas adsorption; attrition in water; and internal and external surface area (Holmes, 1994).

1.2 Production and use

1.2.1 *Production*

Zeolites were first discovered in 1756 by Cronstedt, a Swedish mineralogist, who coined the name from two Greek words, zein (to boil) and lithos (stone), meaning 'boiling stones' (Roland & Kleinschmit, 1996). This name refers to the unusual frothing of zeolite minerals when heated in a blowpipe flame (Roskill Information Services, Ltd, 1988).

Reliable production statistics are not available for natural zeolite minerals. In 1979, world production was estimated at 280 thousand tonnes and this figure is now probably around 250 thousand tonnes. Japan is the largest producer with approximately 15 companies mining zeolites, although only two of these produce more than 10 thousand tonnes per year. In 1985, the United States Bureau of Mines estimated zeolite mineral production in the United States to be 13 thousand tonnes per year; in Hungary production was in the order of 40 thousand–50 thousand tonnes per year. Other countries that mine zeolite minerals include Bulgaria, Cuba, Italy and South Africa. Many countries such as Australia, Czechoslovakia, Greece and Turkey have large unexploited reserves of these minerals (Roskill Information Services Ltd, 1988).

Synthetic zeolites are produced in 13 countries by at least 39 companies (Roskill Information Services Ltd, 1988). World production in 1994 was about 1 million tonnes and production capacity was 1.5–2 million tonnes (Smart *et al.*, 1995).

Natural zeolites

Natural zeolite minerals are recovered from deposits by selective opencast or strip mining methods. The raw material is then processed by crushing, drying, powdering and screening. Some beneficiation processes for zeolites have been developed but these are not yet employed commercially. Natural zeolite minerals used for ion-exchange applications are usually sold as screened products in the –10 to +50 mesh (equivalent to 2 mm and 0.297 mm, respectively) size range. In Hungary, where zeolite ore is used for catalysts, ore containing about 70% clinoptilolite and mordenite is ground to the 0.1–1.6 mm size range and subsequently modified by ion exchange with ammonium ions and treated with hydrogen. For use in adsorption applications, natural zeolites such as chabazite or mordenite are ground to + 200 mesh (0.074 mm), mixed with a binder, extruded or pelletized and activated by heating for 1 h at a temperature of 427 °C. These activated products are then marketed in sealed drums (Roskill Information Services Ltd, 1988).

Synthetic zeolites

Since the late 1940s, when Union Carbide scientists carried out the first successful synthesis, more than 150 types of synthetic zeolites have been manufactured. Of these, many important types have no natural mineral counterpart (and conversely, the synthetic counterparts of many natural zeolites are not yet known). The conditions at synthesis have a direct impact on the type and composition of zeolite produced, both in nature and in commercial production (e.g. mordenite, faujasite, ZSM-5, etc.). However, neither composition nor crystal type is a good predictor of zeolite crystal morphology. Different zeolites of identical silicon, aluminium and oxygen contents can have very different shapes and sizes. Similarly it is possible to synthesize the same type of zeolite in markedly different sizes and shapes. Control over this morphology can have profound effects on the applicability of these materials for adsorption and for catalysis (Breck, 1974).

Zeolite synthesis generally requires the following conditions: (i) reactive starting materials (e.g. freshly co-precipitated gels or amorphous solids); (ii) a relatively high pH (introduced in the form of an alkali metal hydroxide or other strong base, such as a tetra-alkylammonium hydroxide); (iii) a low-temperature hydrothermal state with concurrent low autogenous pressure at saturated water pressure; and (iv) a high degree of supersaturation of the gel components leading to the nucleation of a large number of crystals (Roskill Information Services Ltd, 1988).

Zeolites crystallize from gels in closed hydrothermal systems at temperatures varying from 20 °C to about 200 °C. The time required for this crystallization varies from only a few hours to several days. Some of the most significant parameters that influence the ultimate zeolite crystal morphology are temperature, degree of agitation, crystal growth inhibitor concentration, solution viscosity and the type of cation or directing agent that is used (Drzaj *et al.*, 1985; Vaughan, 1988). Temperature strongly influences the crystallization time of even the most reactive gels; for example, zeolite X crystallizes in 800 h at 25 °C and in 6 h at 100 °C (Roskill Information Services Ltd, 1988).

Typical gels are prepared from aqueous solutions of reactants such as sodium aluminate, sodium hydroxide and sodium silicate; other reactants include alumina trihydrate ($Al_2O_3 . 3H_2O$), colloidal silica and silicic acid. When the reaction mixtures are prepared from colloidal silica, sol or amorphous silica, additional zeolites may also form that do not readily crystallize from the homogeneous sodium silicate or alumino-silicate gels (Roskill Information Services Ltd, 1988).

Both mordenite and ZMS-5 are good examples of zeolites with multiple morphologies. Mordenite occurs naturally as a needle-like crystal. However, if high agitation rates and high viscosities are used in the synthesis, the crystal morphology changes from needle-like structures to individual crystals that resemble discs (Bodart *et al.*, 1984). If ZSM-5 is crystallized at low temperatures (e.g. 80 °C) or if a tetrapropylammonium cation is used as a directing agent, its morphology consists of discrete individual elongated prisms (Jansen, 1991). Under similar conditions, but with hexapropyl-1,6-hexanediammonium as the directing agent, the same composition ZSM-5 is produced (with the same X-ray diffraction pattern); however, the morphology is one of small intergrown crystallites, resembling a head of broccoli.

Some zeolites always have the same crystal shape, although the crystal size may be regulated by synthesis conditions (Barrer, 1985). An example of this is zeolite A which always has a cubic morphology (Anon., 1981).

See **Table 1** for selected properties of synthetic zeolites.

1.2.2 *Use*

Natural zeolites

Worldwide, the building and construction industry is thought to be the largest consumer of natural zeolites. Principal uses in this industry include lightweight aggregates, pozzolanas (component of strong, slow-hardening cements) and building stone. This industry, together with the paper industry in Japan, which uses white clinoptilolite as a paper filler and coating, and the agricultural industry, which uses zeolites as soil conditioners and animal feed supplements, accounts for around 80–90% of total natural zeolite production worldwide (around 200 thousand–225 thousand tonnes of an estimated total of 250 thousand tonnes per year) (Roskill Information Services Ltd, 1988).

The remaining 10–20% of natural zeolite output (25 thousand–50 thousand tonnes per year) is consumed in higher-value industrial applications that utilize the ion exchange, adsorption and catalytic properties of natural zeolites. It is in these applications that synthetic zeolites compete with these natural zeolites. Natural zeolites cannot match the homogeneous chemistry and increased cation exchange capacity of synthetic zeolites, although there may be specific markets, particularly in the area of water treatment, where they can be more cost effective. Other than in the limited treatment of radioactive waste, there is little overlap in the applications of synthetic and natural zeolites (Roskill Information Services Ltd, 1988).

Synthetic zeolites

The three principal uses of synthetic zeolites are in detergents, as catalysts and as adsorbents or desiccants. Approximately 80–90% of total synthetic zeolite consumption is in detergent builders, either as zeolite A powder or slurry. This application makes use of the ion-exchange properties of synthetic zeolite A to soften washing water and therefore increase the effectiveness of a detergent.

The widespread phasing out of tetraethyl lead in gasoline, together with increased world demand for motor fuel, has stimulated an increase in the use of synthetic zeolites as catalysts. The past few years have seen the development of over 30 new refining or chemical processes involving zeolite catalysts and this area is still in a rapid growth phase. The largest catalyst market for synthetic zeolites, fluid catalytic cracking (FCC), recently saw the replacement of rare earth zeolite Y by ultra-stable zeolite Y, to produce higher octane gasoline. The result is a higher zeolite content (up to 50%) in FCC catalysts due to the lower activity of the ultra-stable zeolite Y (Roskill Information Services Ltd, 1988).

Adsorbents and desiccants account for the third largest application of synthetic zeolites worldwide. Their major applications include the following: pressure swing adsorption gas separators; desiccants, either in combination or competition with silica gel and activated alumina, for the removal of water, hydrocarbons and other liquids; the removal of water and hydrocarbons in double glazing and brake systems; and the drying of industrial gases. These applications account for between 5 and 10% of total synthetic zeolite consumption (Roskill Information Services Ltd, 1988).

Limited consumption figures are available for western Europe, Japan and the United States. The demand in western Europe for detergent-grade synthetic zeolites in 1994 has been estimated at around 500 thousand tonnes. Catalyst applications and adsorbent and desiccant applications each consumed about 20 thousand tonnes. The demand for synthetic zeolite in Japan in 1994 was about 160 thousand tonnes; detergent builders account for 94% of total consumption, catalysts about 4% and desiccants and adsorbents about 3%. The United States represents a large proportion of the world catalyst market and therefore a higher proportion of their synthetic zeolite consumption is used in this application than in other countries. In 1994, of the total 320 thousand tonnes of synthetic zeolites consumed in the United States, about 70% was in detergents, 20% in catalysts and 10% in desiccants and adsorbents (Smart *et al.*, 1995).

1.3 Occurrence and exposure

1.3.1 *Natural occurrence*

Natural zeolites occur over much of the earth's surface including the sea bed. Until about 20 years ago, they were considered typically to occur in the cavities of basaltic and volcanic rocks. However, during the last 20–25 years, the use of X-ray diffraction for the examination of very fine-grained sedimentary rocks has led to the identification of several zeolite minerals that were formed by the natural alteration of volcanic ash in alkaline environments. More common types of natural zeolites include clinoptilolite, mordenite, chabazite and erionite (see **Table 2**) (Roskill Information Systems Ltd, 1988).

Of the 40 known types of natural zeolites, at least 20 have been reported from deposits in zeolitically altered rocks; however, only the following nine are known to occur in deposits large enough to mine: analcime, chabazite, clinoptilolite (most abundant; Mumpton & Ormsby, 1976), erionite, ferrierite, heulandite, laumontite, mordenite and phillipsite. These zeolites, which were formed by the natural alteration of volcanic alumino-silicate ash, occur in either closed-system or open-system deposits. Closed-system deposits tend to occur when volcanic ash is deposited underwater; over long periods of time, the alkaline constituents of the ash hydrolyse, the surrounding water becomes salty and alkaline and the ash crystallizes to form zeolites. Open-system deposits are created by the deposition of sediments on land in thick beds and the subsequent conversion of these sediments to zeolites by the downward percolation of surface water (Roskill Information Services Ltd, 1988).

1.3.2 *Occupational exposures*

In a synthetic zeolite production facility in the United States, Greenberg *et al.* (1986) measured exposures to total respirable dust between 1980 and 1984 by means of personal samples. The results are summarized in **Table 3**. Of the 577 samples taken in the production areas, 87% were less than 1.0 mg/m^3 total respirable dust.

Table 3. Distribution of personal sampling measurements of total respirable dust in a United States zeolite production facility, 1980–84[a]

Work area	Number of samples	Percentage of readings in following categories (%)		
		< 0.2 mg/m^3	< 0.2–0.9 mg/m^3	≥ 1.0 mg/m^3
Total production	577	34.5	52.5	13.0
Catalysts	150	25.3	51.4	23.3
Adsorbents	263	34.2	54.4	11.4
Synthesis	164	43.3	50.6	6.1
Maintenance and distribution	42	61.9	35.7	2.4

[a] From Greenberg *et al.* (1986)

In a German detergent manufacturing facility using synthetic zeolite A, total dust exposures ranged from 0.2–5.2 mg/m^3 (34 samples). The mean exposure to zeolite A in the 'fine dust' was estimated at 0.09 mg/m^3 (Gloxhuber *et al.*, 1983).

In western Canada, Green *et al.* (1990) collected airborne dust samples generated during farming operations. These samples contained 1–17% quartz (by mass) but had no detectable fibrous zeolites.

Makhonko *et al.* (1994) measured the concentration of respirable zeolite dust [type not identified] in the working area [not specified] of the zeolite deposit in Pegass, Russia. Respirable zeolite dust was found to range from 31.2 to 127.7 mg/m^3.

1.3.3 *Environmental occurrence*

Although natural zeolites occur widely, no data were available to the Working Group on levels in ambient air or water.

It has been suggested that synthetic zeolite A does not persist in the environment. This zeolite hydrolyses rapidly in water at $\text{pH} \leq 8$, degrading to amorphous aluminates and sodium silicates (Anon., 1981).

1.4 Regulations and guidelines

Regulations and guidelines for exposures to zeolites other than erionite (Deutsche Forschungsgemeinschaft, 1996) have not been proposed.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Clinoptilolite

3.1 Intratracheal administration

Rat: Groups of 50 male (60 male controls) and 50 female Wistar rats (Wistar: Han: Lati, Gödöllö, Hungary), five weeks of age, were treated with a single intratracheal instillation of 0, 30 or 60 mg/animal respirable clinoptilolite particles (< 5 µm; total silica, 70%; cristobalite, 15–20%; Al_2O_3, 23%; Fe_2O_3, 1.38%; TiO_3, 0.07%; CaO, 1.42%; MgO, 0.69%; K_2O, 1.35%) suspended in 1 mL saline containing 40 000 IU crystalline penicillin. [The Working Group noted that it was not stated whether the cristobalite was present in free form or included within the clinoptilolite particles.] Controls were treated with 1 mL physiological saline only. Survivors (more than 50% of the test animals) were killed at the end of the study (104 weeks). All animals were examined macroscopically for the presence of gross lesions. Histological diagnosis and incidence of tumours were determined in each group of both sexes. Various types of tumours were observed in all treated groups and controls. None of the experimental groups showed a significant increase in the incidence of any specific tumours compared to the corresponding control value (Fisher's exact test), and no positive trend was noted in the occurrence of tumours (Cochran–Armitage linear trend test). The anatomical sites and histological characteristics of tumours were similar to those of spontaneous tumours, occurring in the strain of rats studied (Tátrai and Ungváry, 1993).

3.2 Intrapleural administration

Rat: A group of 44 male and 49 female random-bred rats [strain and age unspecified] was given three intrapleural injections of 20 mg/animal clinoptilolite suspended in 0.5 mL physiological saline at monthly intervals. The authors describe this zeolite as $(Na,K)_4Ca[Al_6Si_{30}O_{72}] \cdot 20H_2O$, with contamination of Cu, Pb, Zn, Ni, Co, Mo, Mn, Ti, Sr, Ba and Hg. Particle size measurements were as follows: < 3 μm, 6.3%; 5 μm, 5.9%; 10 μm, 5.9%; > 10–30 μm; 20.6%; > 30–100 μm, 35.1%; > 100–500 μm, 26.1%. Control animals (23 males and 22 females) were administered 0.5 mL physiological saline only, and 41 males and 45 females were left as untreated controls. Life span was recorded as 26 months and 11 days. Each animal was given a full histological examination. Pulmonary lymphosarcomas, pleural and abdominal lymphosarcomas and lymphatic leukaemias (described collectively as 'haemoblastosis') were observed in 5/45 vehicle controls, 7/86 untreated controls and in 47/93 treated animals. No mesothelioma or pulmonary tumour was observed in controls, but mesothelioma and bronchial carcinoma were detected in 2/93 and 1/93 of the treated animals, respectively (Pylev *et al.*, 1986). [The Working Group noted that a large proportion of the particles were larger than 10 μm. In addition, the authors reported that the incidence of 'haemoblastosis' was significantly higher ($p < 0.05$) in treated than in control animals, but did not enumerate the tumour types identified.]

Phillipsite

3.1 Intrapleural administration

Rat: A group of 50 male and 51 female random-bred rats [strain and age unspecified], weighing 100 g, received three intrapleural injections of 20 mg/animal mixed phillipsite dust in 0.5 mL saline at monthly intervals. The authors described this zeolite as $(Na_{1.38}, K_{0.53}, Ca_{0.87}, Mg_{0.25}) (Si_{11.93}, Al_{4.03}, O_{32}) \cdot 9H_2O$. Particle size measurements were as follows: < 5 μm, 14.5%; 10–30 μm, 32.8%; 50–70 μm, 16%; ≥ 100 μm, 36.7%. A control group of 25 males and 27 females was administered with 0.5 mL saline only. Average survival times were 17–18 months for controls and 13–15 months for treated animals. After death, each animal was given a full histological examination. In control rats, a total of 16 tumours were identified in 14/52 rats. Of these tumours, seven were pulmonary lymphosarcomas, pleural and abdominal lymphosarcomas and lymphocytic leukaemias (described by the authors as 'haemoblastosis'), four were mammary tumours and five were tumours at other sites [undetermined]. Of the rats exposed to phillipsite, 41/101 had a total of 50 tumours: one pleural mesothelioma, two pulmonary adenocarcinoma, 29 haemoblastosis, seven mammary tumours and 11 tumours in other sites [unspecified] (Pylev *et al.*, 1989). [The Working Group noted that a large proportion of particles were larger than 10 µm. In addition, the authors reported that the incidence of 'haemoblastosis' was significantly higher ($p < 0.05$) in treated than in control animals but did not enumerate the tumour types identified.]

Mordenite

3.1 Intraperitoneal administration

Mouse: In a preliminary experiment, two groups of 18 and five male Swiss albino mice, four to five weeks old, received a single intraperitoneal injection of 10 or 30 mg/animal mordenite, respectively, suspended in physiological saline. The dimensions of the mordenite were as follows: long axis of the granular component, 0.33–5.7 µm (98.6% < 5 µm), short axis, 0.27–1.67 µm (83.6% < 1 µm); fibrous component, 0.4–6 µm (average length, 1.5 µm), 98.2% < 5 µm) and 0.05–0.067 µm in width (average width 0.18 µm, 96.4% < 0.5 µm). A further group of 13 mice served as untreated controls. Ten months after exposure, no neoplastic changes were observed in the animals (Suzuki, 1982). [The Working Group noted the small numbers of animals, the short duration, the lack of information on survival and that the proportion of fibres in the material was not specified.]

A group of 50 male BALB/c mice, five to six weeks of age, was given a single intraperitoneal injection of 10 mg/animal mordenite suspended in 1 mL physiological saline. This sample of mordenite had the following dimensions: length of particles, 94% < 3 µm and 4% > 3.8 µm; diameter of particles, 89% < 1 µm and 6.25% > 1.4 µm. A similar group of 129 controls were treated with saline alone. In these controls, no peritoneal tumours were observed (0/118). In the mice exposed to mordenite, no peritoneal tumours were seen (0/44) 7–23 months after injection, and nor were there any tumours in other organs. Mild peritoneal fibrosis was however observed in treated mice (Suzuki & Kohyama, 1984). [The Working Group noted the lack of information on survival.]

Non-fibrous Japanese zeolite

3.1 Intrapleural administration

Rat: Two groups of 20 male and 20 female Fischer 344 rats, about 60 days of age, received a single intrapleural injection of 20 mg/animal non-fibrous respirable Japanese zeolite [size unspecified] suspended in 1 mL saline or 1 mL saline alone (controls). Mean survival time was 715 days in the zeolite-treated group and 720 days in controls. One pleural and one peritoneal mesothelioma were observed in the non-fibrous zeolite-treated group, whereas one pleural mesothelioma was found in the saline-treated control group (Wagner *et al.*, 1985).

Synthetic zeolite

3.1 Oral administration

Rat: Groups of 50 male and 50 female Wistar rats, 5–6 weeks old, were fed via the diet 0, 10, or 1000 mg/kg of diet (ppm) synthetic zeolite A ($Na_{12}(AlO_2)_{12}(SiO_2)_{12} . 27H_2O$) for up to 104 weeks. The authors recorded clinical signs and mortality and characterized gross and microscopic pathology for the presence of neoplastic and non-neoplastic lesions. Based on feed intake, the synthetic zeolite A intake for the 10-, 100- and 1000-ppm groups was 0.62, 6.1 and 58.5 mg/kg bw per day for males and 0.65, 6.53 and 62.2 mg/kg bw per day for females. No differences in body weight gain or clinical parameters were observed between controls and experimental animals. No significant treatment-related effects were observed in any of the organs examined histologically, and there was no treatment-related effect on the types or incidence of any neoplastic changes seen (Gloxhuber *et al.*, 1983).

3.2 Inhalation

Rat: Groups of 20 male and 20 female Fischer 344 rats, about 57 days of age, were exposed by inhalation in chambers to a mean respirable dust concentration of 0 or 10 mg/m^3 (10.4×10^3 particles > 0.5 μm/mL) of a synthetic non-fibrous zeolite (of chemical composition identical to that of erionite). Exposures were for 7 h per day on five days a week for 12 months, followed by observation for life span. In addition, similar groups of rats were exposed to 10 mg/m^3 erionite from Oregon or UICC crocidolite. Three males and three females per group were killed at three, six, 12 and 24 months after the start of exposure. Mean survival times were 797 days for the rats exposed to the synthetic zeolite, 504 days for those exposed to erionite from Oregon, 718 days for those exposed to UICC crocidolite and 738 days for the untreated groups. The investigators diagnosed one pleural mesothelioma and one pulmonary adenocarcinoma in rats exposed to the synthetic zeolite; no tumours were found in the untreated controls. In the positive controls, 27 mesotheliomas were found in 28 rats exposed to erionite from Oregon and one squamous-cell carcinoma of the lung was observed in 28 rats exposed to UICC crocidolite (Wagner *et al.*, 1985).

A group of 15 male and 15 female Wistar rats was exposed for 5 h per day, three times a week to 20 mg/m^3 synthetic zeolite A ($Na_{12}(Al)_2)_{12}(SiO_2)_{12} . 27H_2O$) for 22 months. A group of 30 untreated male rats served as controls. The particle size distribution for the airborne synthetic zeolite A particles was as follows: 0.5–1 μm, 15.7%; 1–2 μm, 14.8%; 2–5 μm, 62% and 5–10 μm, 7.3%. The authors performed histopathological examinations of the trachea and lung of 10 treated (5 males, 5 females) and five control (1 male, 4 females) rats. Rats in the treated and control groups showed moderate to extensive respiratory disease. No treatment-related tumours were observed (Gloxhuber *et al.*, 1983). [The Working Group noted the small number of animals.]

3.3 Intraperitoneal administration

3.3.1 *Mouse*

Groups of 50 male BALB/c mice, five to six weeks of age, received a single intraperitoneal injection of 10 mg/animal synthetic zeolite 4A (average particle length, 2.4 μm; average diameter, 2.24 μm) suspended in 1 mL saline or 1 mL saline only. No mesothelioma was observed 7–23 months after injection (Suzuki & Kohyama, 1984). [The Working Group noted the lack of details on survival.]

3.3.2 *Rat*

Groups of 20 male and 20 female Sprague-Dawley rats, eight weeks of age, received a single intraperitoneal injection of 25 mg/animal of the synthetic zeolite MS4A (sodium aluminium silicate) or MS5A (calcium aluminium silicate) in 1 mL water or 1 mL water only (controls). All animals were observed for their life span, and full post-mortem and histology were performed. At 141 weeks after treatment, the authors found one peritoneal mesothelioma in a male treated with zeolite MS4A (Maltoni & Minardi, 1988). [The Working Group noted the lack of information on either survival or the size of the test material.]

3.4 Intrapleural administration

Rat: Groups of 20 male and 20 female Sprague-Dawley rats, eight weeks of age, received a single intrapleural injection of 25 mg/animal of the synthetic zeolites MS4A or MS5A suspended in 1 mL water or a single intraperitoneal injection of 1 mL water only. The authors found no difference in the incidence of tumours between control and treated animals (Maltoni & Minardi, 1988). [The Working Group noted the lack of information on survival and on the size of the test material.]

3.5 Subcutaneous administration

Rat: Groups of 20 male and 20 female Sprague-Dawley rats, eight weeks of age, received a single subcutaneous injection of 25 mg/animal of the synthetic zeolites MS4A or MS5A suspended in 1 mL water or a single intraperitoneal injection of 1 mL water only. The authors found no noticeable difference in tumour incidence between treated and control animals (Maltoni & Minardi, 1988). [The Working Group noted the lack of information on survival and on the size of the test material.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Kinetics

Several studies have attempted to investigate whether the ion-exchange capabilities of zeolites influence microbial and animal metabolism through the preferential trapping and release of cations.

In a 148-day feed-lot experiment, 48 cross-bred steers were fed a 70% sorghum diet with clinoptilolite substituted at 0, 1.25 and 2.5% of the diet dry matter. No differences were found among treatments in average daily weight gain, feed intake or feed efficiency (McCollum & Galyean, 1983).

To test the efficacy of clinoptilolite as a feed additive, a total of 120 16-week-old hens (of three strains) were fed a diet that contained clinoptilolite for 28 days. Sterile river sand replaced clinoptilolite in control diets. No significant effects of clinoptilolite were found between treatments with respect to body weight, age at first egg, egg weight, Haugh scores or food intake per hen. Significant effects in favour of clinoptilolite were noted with regard to the number of eggs laid per hen, shell thickness, efficiency of food utilization, droppings moisture content and mortality (Olver, 1989).

Weanling Landrace × Yorkshire pigs were fed a basal diet containing 3% clinoptilolite with or without 150 ppm cadmium chloride or 3% sodium zeolite A with or without 150 ppm cadmium chloride for 31 days. Pigs fed cadmium in the absence of zeolites had depressed levels of haematocrit and haemoglobin; pigs fed cadmium in the presence of zeolites did not. Liver cadmium concentration was increased dramatically by the addition of cadmium to the diet but this effect was significantly reduced in animals also fed with clinoptilolite. Liver iron and zinc were decreased by dietary cadmium; liver iron was not affected significantly by clinoptilolite or sodium zeolite A, but liver zinc was increased by sodium zeolite A (Pond & Yen, 1983a).

Pond *et al.* (1981) carried out experiments to determine the effects of clinoptilolite on portal blood ammonia concentrations following oral administration of 45 or 90 g/kg bw ammonium carbonate to Sprague-Dawley rats. The clinoptilolite was administered by gastric intubation to the rats at 315, 472.5, 630 or 945 g/kg bw and was found to reduce the portal vein blood ammonia concentrations of the rats. The authors considered that clinoptilolite had the capacity to bind free ammonia in the gastrointestinal tract and that the degree of binding was predictable from its known ion-exchange capacity. This ammonia binding may be related to the improved efficiency of feed utilization reported in some animals fed diets containing clinoptilolite.

Pond *et al.* (1989) carried out a study to test the hypothesis that tissue storage of major and trace elements is altered by the addition of clinoptilolite to diets differing in concentrations of iron and calcium. Thirty-two castrated growing male pigs were fed various diets containing calcium, iron or clinoptilolite. On day 84, all of the pigs were killed and analysed. Dietary concentrations of calcium, iron and clinoptilolite had no effect on daily weight gain, daily feed intake or the ratio of weight gain : feed intake of growing pigs.

One of two groups of five sheep was given a diet containing 0.15 g/kg bw of zeolite for three months. At the end of the study, no difference in health effects was found between the two groups; health effects included general behaviour, total and actual acidity, content of volatile fatty acids in rumen contents, blood picture, content of microelements, transaminase activity and acid–base homeostasis in the blood (Bartko *et al.*, 1983).

Chung *et al.* (1990) conducted three experiments to evaluate the effects of hydrated sodium calcium alumino-silicates on zinc, manganese, vitamin A and riboflavin utilization in young broiler chicks. The results suggested that 0.5% or 1.0% dietary calcium alumino-silicate did not impair manganese, vitamin A, or riboflavin utilization, but that zinc utilization was reduced.

Frost *et al.* (1992) conducted three experiments to determine possible mechanisms involved in the improvement of eggshell quality with dietary supplementation of sodium zeolite A and cholecalciferol (vitamin D_3). It was concluded that sodium zeolite A did not influence the synthesis of 1,25-dihydroxycholecalciferol or plasma levels of 1,25-dihydroxycholecalciferol, ionic calcium, total calcium, pH or phosphorus.

Watkins and Southern (1993) designed two experiments to study the effect of sodium zeolite A on zinc utilization in chicks 5–15 days old. Irrespective of whether chicks were fed inadequate, adequate or toxic levels of zinc, the addition of sodium zeolite A to the diet resulted in an increased tissue zinc concentration.

Rabon *et al.* (1995) conducted two experiments to determine whether serum silicon and aluminium are increased in hens intubated with sodium zeolite A and whether dietary cholecalciferol (vitamin D_3) influences the absorption of silicon or aluminium by hens fed sodium zeolite A. It was concluded that silicon and aluminium from sodium zeolite A are absorbed by commercial Leghorn hens, and that a possible involvement of silicon or aluminium should be considered in the mechanism of action of sodium zeolite A associated with improved eggshell quality and bone development.

Roland *et al.* (1993) considered that the mechanisms by which zeolite affects eggshell quality could be related either to its ion-exchange properties or to individual zeolite A elements (aluminium or silicon). To determine whether any zeolite A passes through the digestive system in its original form and whether any aluminium and silicon absorption occurs, the authors intubated unfed hens at oviposition with either 0 or 5 g zeolite A and intubated fed and unfed hens at oviposition with 0, 1 or 2 g zeolite A. Some zeolite A was found to pass through the digestive system with its crystalline structure unchanged — a result that could not rule out a possible ion-exchange mechanism of zeolite A. However, most of the zeolite A was solubilized and at least some of the silicon and aluminium was absorbed. Therefore, a mechanism whereby silicon or aluminium are utilized could also not be ruled out.

Shurson *et al.* (1984) evaluated growth, nutrient balance, plasma ammonia levels and urinary *para*-cresol excretion in growing pigs fed diets containing various levels of zeolite A or clinoptilolite. In a six-week growth trial, cross-bred pigs were fed diets containing no zeolite, 0.3% zeolite A or 0.5% clinoptilolite. Average daily weight gain, average daily feed intake and feed : weight gain ratio were unaffected by supplementation of either zeolite in the diet; metabolizable energy utilization was improved by feeding diets containing either zeolite.

The administration of the zeolite group of minerals has been suggested as a means of both decreasing the uptake of radioactive caesium by humans and domestic animals and accelerating the excretion of radioactive caesium that has already been absorbed. Artificial mordenite, one of the zeolites being considered for this purpose, was dispersed in liquid paraffin and the mixture was administered to goats and lambs fed radioactive caesium-contaminated hay. The animals' faeces and urine were analysed separately by gamma spectrometry on each day of the experimental period. At a dose of 10 g per day mordenite, the amount of radioactive caesium excreted was more than double the amount ingested with the fodder, due to extraction of the radioactive caesium stored in the body. Initially, the effect : dose ratio was even higher. It was shown conclusively that mordenite can reduce the uptake of radioactive caesium by goats and lambs, and also, without changing the fodder, reduce their body burden (Forberg *et al.*, 1989).

The phyllosilicate clay, hydrated sodium calcium alumino-silicate (HSCAS), has been shown to prevent aflatoxicosis in farm animals by reducing the bioavailability of aflatoxin. Sarr *et al.* (1995) determined the effects of HSCAS on the metabolism of aflatoxin B_1 in an aflatoxin-sensitive species. Male Fischer 344 rats were administered orally 0.125, 0.25, 0.5 or 1 mg/kg bw aflatoxin B_1 alone or in combination with 0.5% HSCAS; urine samples were collected after 6, 24, 36 and 48 h. The metabolites aflatoxin M_1 and aflatoxin P_1 were detected in most urine samples, with or without HSCAS; aflatoxin M_1 was the major metabolite. Metabolite concentrations were significantly decreased in the presence of HSCAS, and no additional metabolites were detected.

Cefali *et al.* (1995) compared the oral bioavailability of silicon and aluminium from zeolite A, sodium alumino-silicate, magnesium trisilicate and aluminium hydroxide in dogs. Twelve female dogs received each compound as a single oral dose separated by one week in a randomized four-way crossover design. Plasma samples, drawn at time 0 and 24 h after dosing, were analysed for silicon and aluminium concentrations by graphite furnace atomic absorption. The authors found that, after administration of the silicon-containing compounds, the mean silicon area under the curve (AUC) and C_{max} values were elevated when compared to a baseline; only the AUC from zeolite A was significantly elevated ($p = 0.041$). There was no statistically significant absorption of aluminium from the other aluminium-containing compounds.

Cefali *et al.* (1996) carried out a study in beagle dogs to estimate the bioavailability of silicon and aluminium from zeolite A administered as either a capsule, an oral suspension or an oral solution relative to an intravenous bolus infusion administered over a 1–1.5-min period. Twelve dogs were given single doses of zeolite A after a one-week control period in a randomized five-way crossover design. Plasma samples, drawn at time 0 and 36 h after dosing, were analysed for silicon and aluminium concentrations by graphite furnace atomic absorption. The results showed that the extent of absorption of aluminium from the oral dosage forms was less than 0.1%, relative to the intravenous infusion. The plasma aluminium AUC values from the oral capsule and suspension showed no statistical difference from those during the control period, but the aluminium

AUC of the oral solution was statistically greater than the AUC of the corresponding control period.

4.2 Toxic effects

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

(*a*) *Inhalation studies*

Gloxhuber *et al.* (1983) carried out a number of safety assessments and toxicology tests using zeolite A, a sodium aluminium silicate developed as a substitute for phosphates in detergents. The test programme included oral studies (acute, subchronic and long-term carcinogenicity tests), and dermal, ocular and inhalation studies on the silicate alone and on appropriate detergent formulations. For the acute oral, dermal and eye studies, rats tolerated a single oral dose of 10 g zeolite A without any overt reaction; the acute LD_{50} (50% toxicity) values exceeded 5 g/kg. In addition, the cytotoxicity of zeolite A was compared to that of DQ 12 quartz. With concentrations of 0.25, 1.0 and 3.0 mg/mL zeolite A, haemolysis following an incubation period of 60 min was negligible when compared with the cytotoxicity of DQ 12 quartz. Release of lactate dehydrogenase by alveolar macrophages was significantly less following exposure to zeolite A relative to DQ 12 quartz (test concentration, 150 µg/mL). Finally, a chronic inhalation study was carried out in which groups of 15 male and 15 female hamsters and 15 male and 15 female rats were exposed to zeolite A batch F 325 dust for 5-h periods, three times a week. The rats were exposed for 22 months and the hamsters were exposed for 12 months. Groups of 30 male rats and 15 male and 15 female Syrian hamsters exposed to untreated air under similar conditions served as controls. The trachea and lungs from each animal were examined microscopically. The hamster study was terminated after 12 months following a considerable incidence of deaths due to a specific infection. Histological examination of trachea and lung was limited to 10 treated hamsters (four males and six females) and eight controls (four males and four females) and to 10 treated rats (five males and five females) and five controls (one males and four females). Both species showed moderate to extensive signs of respiratory disease in the treated animals and controls. In the treated hamsters, macrophages containing accumulations of foreign material were found, mainly in the alveoli, but no signs of inflammation or connective tissue reactions were seen. In the rat lungs, greyish-white deposits were seen in the phagocytes of the alveoli or the peribronchiolar lymph nodes near the hilus. Isolated deposits were also seen in the mediastinal lymph nodes. No connective tissue reactions or other reactions were seen around these deposits.

(*b*) *Intratracheal instillation*

To determine pulmonary pathological reactions, mordenite (60 mg respirable sample; no data given on dimensions) was instilled intratracheally into the lungs of male CFY rats. Groups of 10 rats were killed one week, one month, three months, six months and 12 months after exposure. At one week after exposure, non-specific confluent bronchopneumonia was observed, followed by sequestration in macrophages after one month. At later time points a mild fibrosis was observed, and, at the end of 12 months, transmission electron microscopy and microanalysis verified that the aluminium : silicon ratio in macrophages was similar to the ratios found in natural zeolites (Tátrai *et al.*, 1991). Tátrai *et al.* (1992) examined the lung cervical and hilar lymph nodes of these same animals at 1, 3, 6 and 12 months after exposure, using routine histology, histochemistry and electron microscopy. Dust-storing macrophage foci developed in the interstitium, showing minimal fibrotic tendency by the end of the first year. At this time point, 3/10 of the treated rats had atypical hyperplasia. Electron microscopic examinations showed that the dust was stored in macrophages without structural changes. However, energy dispersive X-ray microanalysis indicated that, in intracellularly stored dust, the ratio of the two main elements, aluminium and silicon, changed in favour of aluminium as compared to the original mordenite sample.

Kruglikov *et al.* (1992) studied the phagocytosis of clinoptilolite in lungs of white random-bred male rats (120–150 g bw), after a single intratracheal injection of 50 mg clinoptilolite in saline to each rat; on days 1, 3–5 and 18 after injection, lungs were examined histopathologically. On the first day, the smallest clinoptilolite particles were phagocytized by neutrophils in addition to the more general particle size range phagocytized by macrophages. Only 25% of macrophages had phagocytized more than six dust particles per cell; less than 2% of macrophages were degenerated. On days 3–5 after injection, the pattern of phagocytosis had changed. There were no more particles observed in neutrophil cells and the number of these cells had decreased. However, the proportion of macrophages with more than six dust particles in the cytoplasm had increased to 90%; 7% of the macrophages had degenerated. Electron microscopy study of the phagocytized particles showed that they were mostly oval form. On day 18, the pattern of phagocytosis was similar to that on days 3–5, but the proportion of degenerated macrophages had decreased to 4%.

Time-dependent increases in the phagocytosis of zeolite dust were observed in white random-bred male rats (120–150 g bw), following a single intratracheal administration of 50 mg/animal natural zeolite dust, at one and three days and one and three months after injection. Morphological changes in lungs after the exposure to zeolite dust was described as exogenous fibrous alveolitis (Kruglikov *et al.*, 1990).

(*c*) *Other routes*

Kosarev and Tkachev (1994) examined the toxicity of 15 natural zeolites from nine deposits in Russia using 610 random-bred white rats and 20 rabbits. No acute toxic effects of zeolite dust were observed in rats after oral administration of 10 g/kg bw or after 4 h inhalation at concentrations ranging from 374 to 416 mg/m^3. After a single intraperitoneal injection of zeolite dust in saline, the LD$_{50}$ for the zeolite dusts was found to range from 2290 mg/kg bw to 10 270 mg/kg bw. After daily intraperitoneal injections of zeolite dusts at a dose of 1% of the LD$_{50}$ with a 1.5 × increase in the dose after every four injections, reduced body movement and feed consumption, lethargy, swelling of the belly and diarrhoea were observed. A significant decrease in red blood cells and haemoglobin was found. Animals started to die from day 11 of injections. After three months inhalation of the zeolite dusts by rats at concentrations of 13.9, 1.83 and 0.21 mg/m^3, toxic effects such as decreased body weight, coagulation of blood and cholinesterase in blood, liver and brain and increased total lipids in lungs and phospholipids in blood were observed.

(*d*) *In-vitro studies*

Treatment of normal human osteoblast-like cells for 48 h with zeolite A at concentrations of 0.1–100 μg/mL induced a dose-dependent increase in DNA synthesis and in the proportion of cells in mitosis. The mitogenic action of zeolite A was dependent on cell seeding density. Alkaline phosphatase activity and osteocalcin release were also increased but did not significantly affect collagen production per individual cell. Zeolite A treatment increased the steady-state mRNA levels of transforming growth factor β (Keeting *et al.*, 1992).

Total degradation of peritoneal macrophages of random-bred white male rats was observed during 15 min incubation with natural clinoptilolite dust (particles < 5 μm) at a concentration of 1 mg/mL, and during 30 min at a concentration of 0.5 mg/mL. At a concentration of 0.25 mg/mL, 38% of the macrophages were killed within the first 30 min and 55.7% of red cells were also degraded (spontaneous degradation, 8.9%). When the peritoneal macrophages were mixed with the clinoptilolite dust in the presence of luminol, dose-dependent chemiluminescence was observed in the first 10–20 s of incubation. The cytotoxic effects of clinoptilolite dust were found to be decreased significantly (30–50%) by catalase; ethanol, sodium azide or mannitol had no effect (Korkina *et al.*, 1984).

Syrian hamster and rat alveolar macrophages were exposed *in vitro* to non-toxic concentrations of mordenite and other fibrous particulates. By measuring the reduction of cytochrome c in the presence and absence of superoxide dismutase, the amount of O_2^- released by cells in response to the various dusts was determined. Mordenite particles were less active than fibres at comparable concentrations (Hansen & Mossman, 1987).

Palekar *et al.* (1988) compared the cytotoxicity to Chinese hamster lung V79 cells of non-fibrous erionite (mordenite), two preparations of fibrous erionite from Rome, Oregon, United States, erionite with a mean length of 2.2 μm, and erionite c prepared by ball milling and with a mean length of 1.4 μm; UICC crocidolite, with a mean length of 1.3 μm; and UICC chrysotile, with a mean length of 2.4 μm. For a comparative measurement of cytotoxicity as a function of mass dose, the minerals that achieved at least 50% toxicity within the dose range from 10 to 100 μg/mL were considered toxic. The dose in numbers of fibres was determined by multiplying the fibre concentrations by mass of dose. Mordenite was non-toxic while the tumorigenic minerals were toxic — they showed more than 50% toxicity for at least one dose between 10 and 100 μg/mL.

Chinese hamster V79-4 and A579 cells were incubated with concentrations of dusts in the range 5–100 μg/mL. The concentrations inhibiting plating for non-fibrous Japanese zeolite, erionite from Oregon, erionite from New Zealand, and as a positive control, UICC crocidolite were estimated using the LD_{50}. The non-fibrous Japanese zeolite had a substantially higher LD_{50} value (that is, a lower toxicity) relative to the two fibrous erionite samples and crocidolite. Also, this sample of non-fibrous Japanese zeolite was not toxic in the A549 cell assay (Brown *et al.*, 1980).

4.3 Reproductive and developmental effects

Pond and Yen (1983b) examined the effects of long-term ingestion of clinoptilolite on reproduction in female rats and on the postnatal development of the progeny of these rats; concurrently, the authors investigated whether or not clinoptilolite offers protection against the toxic effect of long-term cadmium ingestion. Four groups of female Sprague-Dawley rats were fed the following diets: (i) control; (ii) control plus clinoptilolite; (iii) control plus cadmium; and (iv) control plus cadmium and clinoptilolite; at about 13 weeks, a young adult male rat was placed in each cage until mating. Subsequent results showed that reproductive performance of the female rats had been unaffected by the various diets. Dietary cadmium level had no effect on body weight gain during growth, gestation or lactation. Although the supplemental level of clinoptilolite resulted in reduced body weight during gestation, body weight at parturition and postpartum was similar for rats in all diet groups.

Nolen and Dierckman (1983) tested synthetic zeolite A (Arogen 2000) containing 15.8% sodium, 19.0% silicon and 20.1% aluminium for its teratogenic potential in Sprague-Dawley rats and New Zealand rabbits. The zeolite was givben in distilled water by gavage to the test animals. The rats received doses of 74 or 1600 mg/kg bw on days 6–15 of gestation and the rabbits doses of 74, 345 or 1600 mg/kg bw on days 6–18 of gestation. Vehicle controls were included in each study. The synthetic zeolite A produced no adverse effects on the dam, the embryo or the foetus in either species at any of the doses tested.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group on the genetic effects of natural or synthetic zeolites in exposed humans.

4.4.2 *Experimental systems* (see also **Table 4** and Appendices 1, 2 and 3)

Durnev *et al.* (1993) tested the clastogenic potential of zeolite particles < 10 μm in length obtained from Chonguruu, Russia, in peripheral blood lymphocytes prepared from healthy human volunteers. Chrysotile fibres < 10 μm long from Bazhenov, Russia, were used as a positive control. Both fibre types produced statistically significant increases in the percentage of aberrant metaphases, mostly resulting from chromatid breaks. Superoxide dismutase (50 μg/mL) protected against induction of aberrant metaphases by chrysotile asbestos, but not by zeolite. Catalase (20 μg/mL) protected against induction of aberrant metaphases by zeolite, but not by chrysotile asbestos.

Table 4. Genetic and related effects of natural zeolites

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CHL, Chromosomal aberrations, human whole blood cultures	+	NT	50	Durnev *et al.* (1993)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	(+)		50 ip × 1	Durnev *et al.* (1993)
CLA, Chromosomal aberrations, mouse leukocytes (peritoneal lavage) *in vivo*	+		50 ip × 1	Durnev *et al.* (1993)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; NG, not given

Durnev *et al.* (1993) also studied chromosomal aberrations in cells of C57Bl/6 mice. The cells, collected by peritoneal lavage and from the bone marrow of mice weighing 20–22 g, were sampled at one, two, seven and 28 days after intraperitoneal injection of either 50 mg/kg (approximately 100 μg/mouse) natural zeolite particles from Chonguruu, Russia, or chrysotile asbestos from Bazhenov, Russia. The peritoneal lavage sample contained 20% lymphocytes, 20–30% macrophages and 50–60% polymorphonuclear leukocytes. Aberrant metaphases were scored in 50 cells collected by peritoneal lavage or 100 bone marrow cells from each mouse. Intraperitoneal injection of zeolite induced a statistically significant increase in aberrant metaphases after seven and 28 days in peritoneal lavage cells. Chrysotile asbestos induced a statistically significant increase in aberrant metaphases at all time points in both peritoneal lavage and bone marrow cells. [The Working Group noted the unconventional design of this in-vivo genotoxicity assay.]

No data were available to the Working Group on the genetic and related effects of synthetic zeolites in experimental systems.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Zeolites are crystalline alumino-silicate minerals with cage-like crystal structures. Zeolites have been used extensively since the late 1940s in a variety of applications. Naturally occurring zeolites, some of which are fibrous, occur worldwide and many are used in materials for the construction industry, in paper, in agriculture and in other applications. A large number of zeolites have been synthesized for use in detergents, as catalysts and as adsorbents and desiccants. Exposures may occur during the mining, production and use of zeolites.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Clinoptilolite with a particle size in the respirable range was tested for carcinogenicity in rats by intratracheal instillation. No significant increase in the incidence of tumours was found.

No adequate study was available to the Working Group on *phillipsite.*

Mordenite was studied for carcinogenicity in one experiment in mice by intraperitoneal injection. No peritoneal tumours were found.

Non-fibrous Japanese zeolite was tested for carcinogenicity in one experiment in rats by single intrapleural injection. No increase in pulmonary tumours was found.

Synthetic zeolite A was tested for carcinogenicity in one experiment in rats by oral administration in the diet. No increase in tumour incidence was found.

Synthetic non-fibrous zeolite was tested for carcinogenicity in rats by inhalation exposure. No increase in pulmonary tumours was found.

Synthetic zeolite 4A was tested for carcinogenicity in mice by single intraperitoneal injection. No abdominal tumour was observed.

Synthetic zeolites MS4A and MS5A were tested for carcinogenicity in rats by intraperitoneal, intrapleural and subcutaneous injection. No increase in the incidence of tumours was found.

5.4 Other relevant data

Oral administration of natural and synthetic zeolite particles produced little toxicity in a variety of species. Intratracheal instillation of mordenite in rats produced mild fibrosis and hyperplasia.

Inhalation studies in rats and hamsters of synthetic zeolite A produced no significant pulmonary inflammation or interstitial fibrosis

Mordenite exhibited low cytotoxicity *in vitro.* A sample of natural zeolite particles from Chonguruu, Russia, induced aberrant metaphases in human whole blood cultures *in vitro.* This zeolite sample also induced aberrant metaphases in cells collected by peritoneal lavage of mice after intraperitoneal injection.

No data were available to the Working Group on the genetic and related effects of synthetic zeolite.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of zeolites other than erionite[2].

There is *inadequate evidence* in experimental animals for the carcinogenicity of clinoptilolite, phillipsite, mordenite, non-fibrous Japanese zeolite and synthetic zeolites.

Overall evaluation

Clinoptilolite, phillipsite, mordenite, non-fibrous Japanese zeolite and synthetic zeolites *cannot be evaluated as to their carcinogenicity to humans (Group 3).*

6. References

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

[2] Erionite was evaluated previously as being carcinogenic to humans (Group 1); see IARC (1987).

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