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The safety of synthetic zeolites used in detergents

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Abstract Synthetic zeolites are replacing phosphates as builders in laundry detergents; workers and consumers may, therefore, increasingly be exposed to these materials and it is important to assess their safety. This article puts mechanistic, toxicological and exposure data into context for a safety assessment. Zeolites are hygroscopic compounds with ion-exchanging properties. They may partially decompose under acidic conditions such as in the stomach releasing sodium ions, silicic acid and aluminum salts. The intact molecule is not bioavailable after oral intake or exposure through the dermal and inhalational routes. Under current conditions of manufacture and use, no systemic toxicity is to be expected from neither the intact molecule nor the degradation products; a significant effect on the bioavailability of other compounds is not likely. Zeolites may cause local irritation. It is, therefore, important to minimise occupational exposure. The co-operation of detergent manufacturers with the manufacturers of washing machines is necessary to find the right balance between environmental aspects such as energy and water savings and the occurrence of detergent residues on textiles due to insufficient rinsing.

Keywords Synthetic zeolites · Laundry detergents · Builders · Safety · Exposure

Introduction

Zeolites (CAS register numbers 1318-02-1 and 1344-00-9; EINECS 215-283-8) are naturally occurring or synthetic crystalline aluminosilicates composed of $(SiO_4)^{4-}$ and $(AlO_4)^{5-}$ tetrahhedra, which share oxygen-bridging vertices and form cage-like structures in crystalline form. The ratio between oxygen, aluminum and silicon is O:(Al + Si) = 2:1. The frameworks acquire their negative charge by substitution of some Si by Al. The negative charge is neutralised by cations and the frameworks are sufficiently open to contain, under normal conditions, mobile water molecules (IUPAC 1979).

Applications of naturally occurring zeolites include use as materials for the construction industry, in paper, in agriculture and in other applications. Tailored synthetic zeolites with defined pore sizes have a wide variety of more specialized applications, such as in laundry detergents, as adsorbents, catalysts or molecular sieves and as catalysts in oil refineries (Budavari 1989; IARC 1997; Wenninger et al. 2000).

Due to their presence in laundry detergents, an evaluation of their safety is critical, the more so, as potential exposure of workers and consumers may be chronic and extensive.

Zeolites used in laundry detergents

This assessment focuses on synthetic zeolites used commercially in laundry detergents in Europe, i.e., zeolite A, zeolite P, zeolite X and zeolite Y. These zeolites belong to a class of crystalline, non-fibrous compounds defined by the generalised molecular formula $Na_x[(AlO_2)_x(SiO_2)_y]{\cdot}zH_2O$. The materials soften wash water by exchanging calcium ions and, to a lesser extent, magnesium ions for sodium ions, thereby preventing precipitation of surfactants. They are used as pure powders, which do not contain additives or clay binders.

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Zeolites were introduced in the mid 1970s as detergent builders and nowadays about 30% of EU detergent powders are zeolite based (Bajpai and Tyagi 2007). They are increasingly substituting phosphates in laundry detergents, which are considered a major source of eutrophication. In several European countries, only phosphate-free detergents are on the market, i.e, in Austria, Germany, Norway, Italy, the Netherlands and in Switzerland (CSTEE 2003).

Zeolite A, zeolite P, zeolite X and zeolite Y differ mainly in their aluminum content due to isomorphic exchange of Si versus Al. This influences the crystal structure and thereby the ion-exchange selectivity. The ion-exchange capacity and rate of dissolution increase with increasing Al-content, as does the Na-content. At pH-values below 4.0, zeolites may hydrolyse and their crystal structure is partly destroyed releasing sodium ions, silicic acid, and aluminum salts. Aqueous suspensions are alkaline (pH 10–10.5) (Cook et al. 1982).

Synthetic zeolites typically occur in crystal sizes of 1–10 µm, with the individual crystals belonging to a size distribution which differs from manufacturer to manufacturer.

Zeolite A (Fig. 1) is composed of sodalite cages connected by double 4-rings, and typically consists of 3–5 µm cuboidal-shaped crystals. The pores of the cages have a diameter of 0.41 nm admitting molecules with minimum cross sections of up to about 4.0 Å (hence the term zeolite 4 Å). Whilst calcium ions diffuse relatively easily into the interstices, the smaller magnesium ions are impeded by a hydrated shell, and are therefore incorporated more slowly.

Special type P zeolites (zeolite MAP, maximum aluminum P; Fig. 2) are zeolites of the gismondine family with a flexible, layered crystal structure and a high calcium exchange capacity that were developed for the use in detergents. The primary crystallites consist of platelets which agglomerate during synthesis to give 1 µm spheroidal and highly porous particles. Their interconnected channels have pore sizes of 0.31 × 0.44 and 0.28 × 0.49 nm (Carr et al. 1997; Newsam 1986).

Zeolite X and Y (Fig. 3) were introduced more recently into the detergent market. While the chemical composition of these zeolites is practically identical to that of zeolite A, they have a more spherical morphology with cubo-octahedron building blocks linked to a faujasite structure via hexagonal prisms. Due to their larger pore diameter of 0.74 nm (Newsam 1986) zeolites X and Y are capable of more readily including magnesium ions.

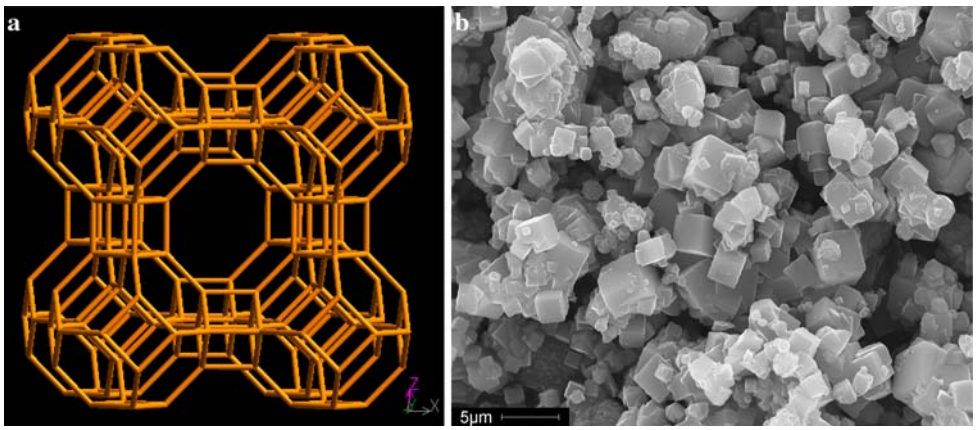

Fig. 1 Zeolite A framework type [taken from the IZA (International Zeolites Association) database of zeolite structures with kind permission of the IZA] and SEM picture [provided by EUZEPA (European Zeolites Producers Association)]

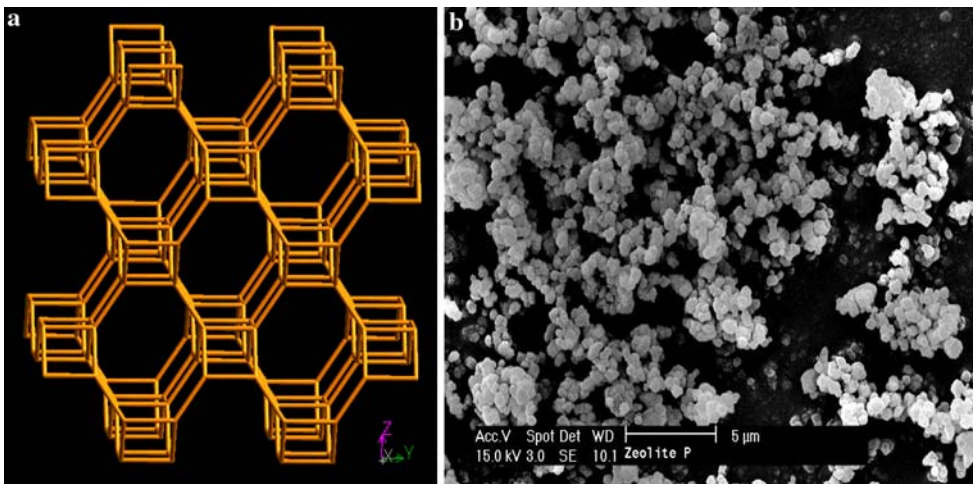

Fig. 2 Zeolite P framework type (taken from the IZA database of zeolite structures with kind permission of the IZA) and SEM picture (provided by EUZEPA)

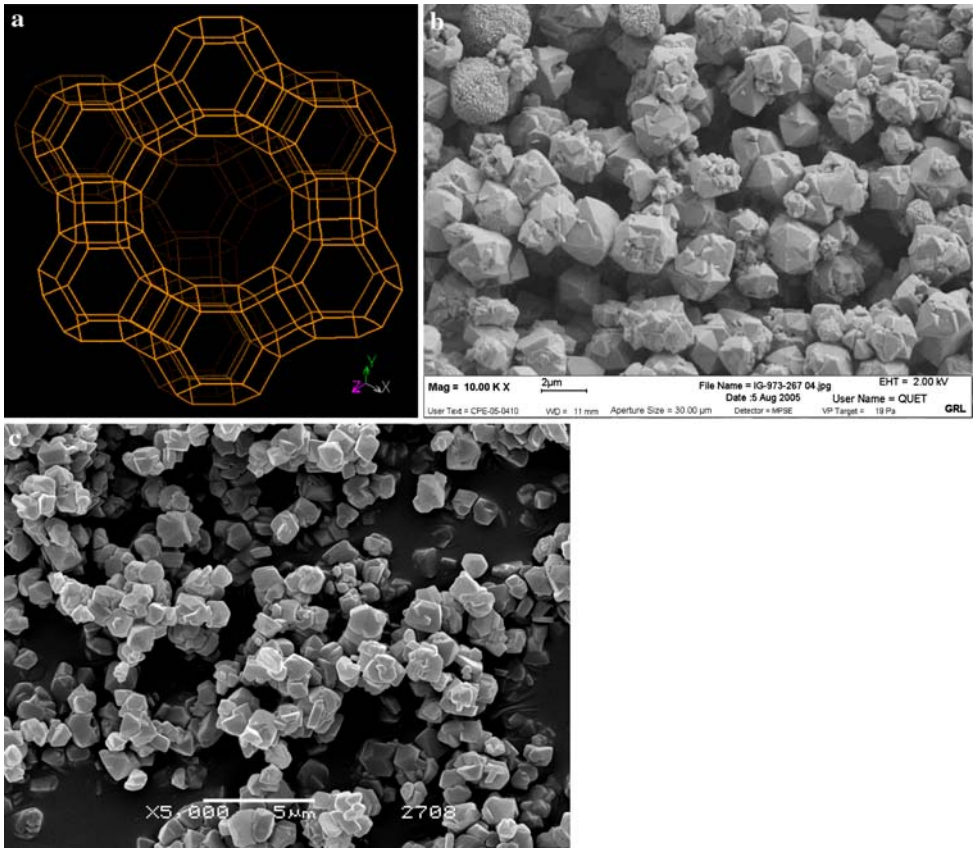

Fig. 3 **a** Zeolite X and zeolite Y framework type (taken from IZA database of zeolite structures with kind permission of the IZA). **b** Zeolite X, SEM picture (provided by EUZEPA). **c** Zeolite Y, SEM picture (provided by EUZEPA)

Main characteristics of the different zeolite types used in laundry applications are summarised in Table 1.

Mechanisms of action and biological activity

Zeolites are commercially used because of their adsorption, ion exchange, and/or catalytic characteristics. Catalytic applications are performed with special zeolite types, normally at high temperatures, and are therefore beyond the scope of this article.

Adsorption

The uptake of water or other molecules in zeolites is called adsorption. The main driving force for adsorption is the highly polar surface within the openings of the zeolite framework ("pores") enabling molecules smaller than the respective pore diameter to be adsorbed whilst larger molecules are excluded ("molecular sieve"). Because they are hygroscopic, it is often difficult to make precise measurements of key chemical characteristics for zeolites. The adsorption process is fully reversible and of purely physical nature. The structure of the zeolite remains intact during this process (Kerr 1989; Newsam 1986).

Ion-exchange

Another outstanding property of this class of compound is their ion exchanging capability. Synthetic zeolites are capable of exchanging their sodium ions with calcium and magnesium ions and with other cations, including heavy metals and trace elements (Kerr 1989; Newsam 1986). It is therefore possible, that the bioavailability of some elements, such as e.g. Mg, Zn, Cu might be influenced by zeolites.

Table 1 Zeolites types used in laundry applications

Name	Formula	Synonyms	Framework type	Pore size (nm)
Zeolite A	$Na_{12}[(AlO_2)_{12}(SiO_2)_{12}] \cdot 27\ H_2O$	Zeolite 4A; Na 4A Zeolite; Linde type A;	LTA (Linde type A)	0.41
Zeolite P	$Na_6(AlO_2)_6(SiO_2)_6 \cdot 5\ H_2O$	Zeolite MAP; Na–P	GIS (gismondine)	ca. 0.3
Zeolite X	$Na_{86}[(AlO_2)_{86}(SiO_2)_{106}] \cdot 264\ H_2O$	Zeolite type X; Linde type X	FAU (faujasite)	0.74
Zeolite Y	$Na_{54}[(AlO_2)_{54}(SiO_2)_{138}] \cdot 245\ H_2O$	Zeolite type Y; Linde type Y	FAU (faujasite)	0.74

The cation exchange capacity (CEC) expressed in terms of milliequivalents per gram, is 5.48 mequiv. g/L for zeolite A. Based on this CEC, 1 g zeolite A could bind 0.126 g Na^+, 0.214 g K^+, 0.067 g Mg^{2+}, 0.11 g Ca^{2+}, 0.103 g NH_4^+ or 0.174 g Cu^{2+} (EFSA 2004).

Surface characteristics and cytotoxicity

Elevated rates of mesothelioma and lung cancer were found among residents in Turkish villages exposed to the naturally occurring fibrous zeolite erionite. Since then several studies have been undertaken on the mode of action of erionite carcinogenesis and on the influence of surface characteristics. A few of these studies have in parallel investigated zeolites of the non-fibrous types. These studies are summarised below.

Fach et al. (2002) investigated interactions of three different zeolite types (erionite, mordenite and zeolite Y) on NR8383 lung macrophage cells and the ability of the mineral surface to produce hydroxyl radicals from H_2O_2 (Fenton reaction). Cell viability was similar for all three particles types and dosages in this study. Using ammonium chloride as an endocytosis inhibitor, the authors concluded that the dose-dependent oxidative burst was mainly from phagocytised particles rather than due to particles attached to the membranes. The oxidative burst of the three materials was comparable and was correlated inversely with particle size (surface area). Iron on the surfaces of the three different zeolites produced different amounts of hydroxyl radicals and followed the order erionite > mordenite >> zeolite Y. Hydroxyl radical production by zeolite Y was little or insignificant, i.e., comparable to water-coordinated iron. The differences observed between the three zeolites were assumed to be arising from different coordination of the iron on the zeolite surface. The biological implication of these data is that the size (surface area) of the mineral rather than its structure is the determining factor for the oxidative burst upon phagocytosis, whereas the structure of the mineral plays a key role in determining the production of iron-mediated hydroxyl radicals via the Fenton reaction. The authors conclude that the considerable toxicity of erionite may be due to its fibrous nature and size, which ensures penetration into the lungs, and its surface chemistry, which promotes the formation of hydroxyl radicals. Mordenite, with comparable morphology, is also expected to be toxic because of its efficacy in the Fenton reaction.

These results confirm earlier observations by others (Fubini and Mollo 1995; Fubini et al. 1995; Prandi et al. 2001) who found that only a fraction of the iron species on the mineral surface of zeolite Y is in the right redox state and coordination environment to participate in the Fenton reaction.

The fibrous structure of erionite and mordenite is shown in Fig. 4 (erionite) and Fig. 5 (mordenite). The structural difference between these fibrous zeolites and the synthetic non-fibrous zeolites under review here is clearly visible (cf. Figs. 1–3 above).

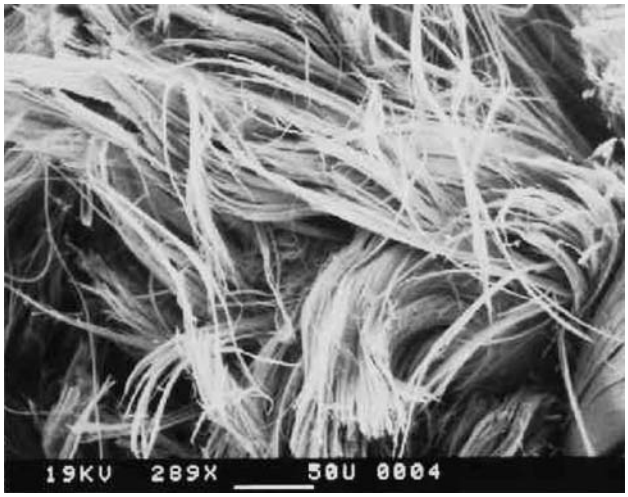

Fig. 4 Erionite, SEM picture

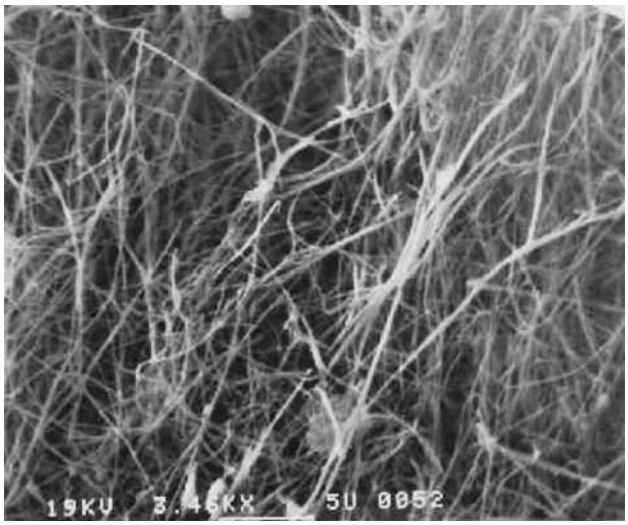

Fig. 5 Mordenite, SEM picture (SEM pictures provided by EUZEPA)

Exposure

Synthetic zeolites are used as builders in detergents, as binders, anticaking and coagulant agents in feed, and as odour absorbents in a wide variety of personal care products. The most common use of synthetic zeolites is in laundry detergents. Zeolites are used in concentrations of up to 40 % in laundry regular and compact powder formulations as well as in laundry tablets, and in concentrations of up to 60% in light duty laundry powders (CIR 2003; HERA 2004; Prud'homme de Lodder et al. 2006; RPA 2006; Wenninger et al. 2000).

Exposure to zeolites may occur through the oral, dermal and respiratory route of exposure.

Oral exposure may occur by accidental intake or by swallowing dust, particles too large to enter the deeper respiratory tract (see below). The public may also be exposed indirectly through drinking water.

Because of their poor solubility in water and the ionic character, zeolites are not expected to cross the intact skin barrier (IUPAC 2001). Hence, dermal uptake is assumed negligible as long as the skin is undamaged. In the case of damaged skin, uptake of zeolites may occur in very limited quantities as the poor solubility in aqueous systems and the ionic nature of the compounds prevents any significant uptake of the intact molecules by body fluids.

Zeolite particle size is normally between 1 and 10 µm; in air or detergent formulations the zeolite particles quickly aggregate to larger structures, which are trapped in the upper airways and swallowed. Only particles of intermediate size, i.e. <10 µm, may penetrate deep into the lungs and reach the alveoli. Small particles may stay in the alveoli for years, since alveolar membranes have no cilia to move the particles out of the lungs toward the pharynx (IUPAC 2001); they may also be taken up by macrophages.

Occupational exposure

Workers might be exposed to zeolites A, P, X or Y during manufacture of the substances or their processing. Exposure through the professional use of zeolite-containing laundry detergents is, however, limited because zeolites may affect the calendering process (A.I.S.E. 2000). The most likely routes of exposure are inhalation of zeolite-containing dust and dermal contact with laundry powder or granulate. Dust particles containing zeolites may be trapped in the upper respiratory tract and may be swallowed; if <10 µm, they may reach the lungs and alveoli.

Currently, there are no specific EU-wide occupational exposure limits for zeolites. Many countries, however, have regulated the maximum exposure to total dust and implemented limit values of 10 mg/m^3 for total dust and 3 or 5 mg/m^3 for respirable dust.

Consumer exposure

Product types that contain zeolites include laundry regular and compact powder formulations, laundry tablets, and laundry aids.

Consumers might be exposed to zeolites A, P, X or Y through dermal contact with detergents containing these substances. Dermal contact may occur with undiluted laundry products (laundry pre-treatment, filling laundry powder in washing machine) or with diluted detergent solution (hand wash). Exposure may also occur from the inhalation of detergent dust or aerosol particles during the filling of a washing machine or from detergent residues on the washed textiles.

Zeolites reaching the aquatic environment may be ingested by consumers with the drinking water. In aquatic environments, zeolites are converted to natural constituents of water (OECD 2006). Hence, this exposure is not considered to be of relevance.

Exposure during use of detergent

For Europe, the technical guidance documents give a frequency of washing with powder laundry products ranging from 1 to 21 times a week, with a typical frequency of 5 times per week (EC 2003). The amount of washing powder used per task is reported as 75 g (range 20–200 g) by A.I.S.E. (2002). Exposure time during filling the machine with laundry powder is short; the mean duration was measured as 11 (±3) s (Weegels 1997). Data reported by A.I.S.E (van de Plassche et al. 1998) show an average release of about 0.27 µg of total dust per cup of laundry powder used for a machine washing. For granules, it is assumed that a maximum of 10% is present in the form of powder. The inhalation exposure is, therefore, expected to be 10-fold lower than the exposure to a powder. For tablets, the inhalation and dermal exposure is considered negligible (Prud'homme de Lodder et al. 2006).

Modern detergent powders are designed to produce very low levels of dust and not to contain fine, respirable particles. Comparing particle size distributions of zeolite-containing with zeolite-free detergents showed essentially similar distributions with more than 99% of the particles being larger than 100 µm in size and hence not in the respirable range; about 50% of the particles were in the 400 µm range, and only 0.2 or 0.1% (w/w) of the particles were below 100 µm in the zeolite-free and zeolite-containing products, respectively. It is important to note that the proportion of smaller particles was not increased in the zeolite-containing product, and that the concentration of zeolite in the finer fractions was essentially the same as in the coarse fraction (Gloxhuber et al. 1983).

To assess consumer exposure to detergent dust, determinations were carried out by Gloxhuber et al. (1983) using a photoelectric particle counter and by gravimetric determination. In a model for testing pouring characteristics, the dust generation by a zeolite-containing detergent was compared with that of a reference substance (commercial detergent free of zeolite). Defined quantities of the detergents were poured out under standardised conditions and the particles present at a distance of 10 cm from the filling hole were counted. In two similar studies, dust generation was examined in ten households, i.e., in cellars where washing treated with detergents containing zeolite A were tumble-

dried. The estimations were performed both by means of the particle counter and by gravimetry. The comparison showed that the addition of zeolite A to the detergent did not alter the dust quality. Recently, Gudmundsson et al. (2007) identified particle emissions from textile handling in two Swedish households. The authors assumed that the dust originated from textiles containing detergent zeolite residues. The very limited data presented, however, do not allow any meaningful conclusion to be drawn from this experiment; furthermore, the authors' assumption is in contradiction with the earlier published results by Gloxhuber et al. (1983) that are cited above.

Exposure of hands to zeolite-containing detergent powders, either as such or in diluted solutions, may occur during the hand-wash of laundry or if laundry is pre-treated with laundry aids (pre-treatment bars or pastes, water conditioners) which may contain zeolites in concentrations greater than 30% (Prud'homme de Lodder et al. 2006). The exposure time during these operations is generally short, i.e., approximately 15 min when laundry is washed by hand, and less than 1 min if stains are removed by spot-treatment with a detergent paste (HERA 2004). Though, it is important to consider potential local effects such as irritation or sensitisation in these scenarios. The systemic zeolite exposure is considered not relevant based on the physico-chemical properties of zeolites that prevent them from readily passing the skin barrier.

A relevant consumer exposure to zeolites from the use of detergent formulations by the inhalational, oral or dermal routes of exposure is therefore not to be expected under normal conditions of use.

Exposure through residues on textiles

Quantitative data on the amount of detergent residues on textiles after laundering is scarce.

Under European washing conditions (German Miele washing machine, 18 L water volume, 60°C, overnight line drying), reported data on unsoiled polyester/cotton fabrics after 10 washes were for linear alkylbenzene sulphonate between 20 and 2,000 mg/kg, and from 20 to 13,400 mg/kg for fatty acid salts; for aluminum deposits the values ranged between 24 and 458 mg/kg and for silicon between 20 and 622 mg/kg (Rodriguez et al. 1994).

Results reported by Matthies et al. (1990) from experiments performed with four different household detergents, of which two contained zeolites (one with, one without phosphate binder) and two different household washing machines at 60°C showed that the amount of zeolite residues was dependent on the amount of water used by the machines, the type of washing powder and the type of fabric. After 25 washes, zeolite concentrations were between 1,050 ppm (=1,050 mg/kg; polyester fabric, washed with phosphate-containing detergent powder) and 36,765 ppm (cotton fabric, washed with phosphate-free detergent powder). An increase of 10% in water use reduced the amount of zeolite residues by a factor of 2–4. Zeolite residues on cotton baby shirts were determined after 1 and 25 washes at 95°C to be 2,900 and 8,300 ppm, respectively. The pH values of the textiles increased from 9.1 (cotton, unwashed) to 9.0 (after one washing), and 9.6–9.8 after 25 washes.

Sainio (1996) washed standardized 100% cotton textile strips soiled with blood, red wine, cocoa and soot at 60°C using three different detergents: one containing phosphate, and two containing zeolites (a concentrated detergent and an "ecological detergent"). The residues present in highest concentration were anionic tensides (110–490 mg/kg). Electron microscopy showed that phosphate-free detergents left approximately 50% more particles on textiles than traditional detergents (no quantitative data provided). Additional rinses reduced the amounts of residues.

The ConsExpo model assumes 6,000 mg detergent residues per kg fabric, based on 150 g of washing powder used per 5 kg of laundry, and a deposition of 20% (Prud'homme de Lodder et al. 2006), while HERA (2004) assumes 5% deposition as a "worst-case scenario" in the case of zeolites.

Recently, Gudmundsson et al. (2007) identified particle emissions from textile handling in two Swedish households. The authors assumed that the dust originated from textiles containing detergent zeolite residues. The very limited data presented, however, do not allow any meaningful conclusion to be drawn from this experiment.

In conclusion, the amount of detergent residues deposited on textiles is dependent on the composition of the detergents, the conditions of washing and rinsing, and the type of fabric. Values reported for zeolites range from less than 100 mg zeolite/kg fabric to up to 37,000 mg/kg fabric. Daily exposure through residues of laundry detergents on textiles was calculated to be in the range of micrograms per kilogram bodyweight (HERA 2004). As zeolites are not expected to be systemically available through dermal uptake, the systemic exposure through this route can be considered negligible.

Toxicology/safety

Zeolites for laundry applications have undergone extensive investigation for their safety and toxicological properties in animal studies, occupational surveillance and human volunteer tests. The toxicological data on zeolites have recently been summarised in peer-reviewed documents (OECD 2006) and by industry (HERA 2004; Smulders et al. 2003). Methodological aspects of many of the key studies are described in detail in the OECD document and are therefore not reiterated here.

Absorption, distribution, metabolism and excretion

At pH-values below 4.0, such as in the stomach, zeolites may partly hydrolyse and their crystal structure is partly destroyed releasing sodium ions, silicic acid and aluminum salts which could be taken up by the gastrointestinal tract.

In dogs, no appreciable gastro-intestinal absorption of aluminum was found from orally administered zeolite A (30 mg/kg bw), sodium aluminosilicate (16 mg/kg bw) or aluminum hydroxide (675 mg/kg bw). About 2–3% of the silicon in the administered zeolite A was taken up by the gastrointestinal tract (Cefali et al. 1995, 1996).

Rats dosed with up to 1,000 mg/kg bw of various silicon-containing chemicals (zeolite A, sodium aluminosilicate, sodium silicate or magnesium trisilicate) excreted urinary silicon in excess of background levels. The urine of animals dosed with zeolite A did not show any detectable increase in aluminum (Benke and Osborn 1979).

After oral administration of 1,000 mg/kg bw of zeolite A to rats, about 1% of the administered silicon was absorbed and eliminated via the kidneys and in the urine. Absorption of aluminum could not be traced in the urine. The major part of the administered dose was excreted unchanged in the faeces (Gloxhuber et al. 1983). Urinary excretion of both silicon and aluminum was slightly increased in rats treated for 104 weeks with 1,000 ppm of zeolite A in their diet (Gloxhuber et al. 1983).

Inhalation of zeolite A by rats (20 mg/m^3, 5 h/day, for 13 days) resulted in the deposition of the substance in the lung parenchyma. The total weight of silicon in the lungs of treated animals was significantly higher (0.0822 ± 0.0294 mg) than that found in control lungs (0.0493 ± 0.0123 mg) (Gloxhuber et al. 1983).

Because of their physico-chemical properties, zeolites are not expected to be absorbed through the intact skin.

Acute toxicity

Oral administration of synthetic zeolite particles (zeolites A, Y, and X) produced a very little or no acute toxicity in a variety of animal species. Clinical signs were non-specific (sedation, dyspnoea, lateral posture, piloerection, hypoactivity) and were only observed at extremely high exposures (Gloxhuber et al. 1983; OECD 2006). It can be concluded that these zeolites were non-toxic after acute oral exposure.

No abnormal clinical signs were observed after acute dermal exposure to high dose levels of zeolites A and Y (OECD 2006). It can be concluded that these zeolites were non-toxic after acute dermal exposure.

Inhalation studies in rats and hamsters of synthetic zeolite A produced no significant pulmonary inflammation or interstitial fibrosis. No clinical effects were observed after acute exposure to zeolites A, Y and X, with 1-h inhalation LC_{50} values in rats of >18,300 mg/m^3, and >2,300 mg/m^3 for zeolites A and Y, respectively (Gloxhuber et al. 1983; OECD 2006).

Local tolerance

Zeolite A, Y and X were slightly or moderately irritating to the eyes of rabbits (OECD 2006). Instillation of 10 mg zeolite A in the rabbit eye caused a foreign-body reaction for up to 48 h after the administration (Gloxhuber et al. 1983), possibly explained by mechanical irritation or pH change in the aqueous environment.

Zeolite A, Y and X were not or very slightly irritating to the skin of rabbits (OECD 2006). Repeated administration for 21 days of an ointment containing 10% zeolite A to rabbit skin did not elicit any skin reactions nor did bathing of hairless mice with a 2.5% zeolite A suspension. Human skin tolerated without reaction a 24-h exposure to a 1% suspension of zeolite A in a patch test (Gloxhuber et al. 1983).

Forty volunteers with seborrhoic or sebostatic skin were patch tested with textile probes containing zeolite residues in concentrations between 1,050 and 36,765 ppm (Matthies et al. 1990). The patches were applied under occlusive conditions for 48 h. A second series of textiles containing 2,900 or 8,300 ppm zeolite residues were provided to 30 children (7 months to 6 years of age); the textiles were worn between 1 and 11 days. In neither group, any skin reactions were found.

Skin and respiratory sensitisation

Zeolite A was not a skin sensitiser in limited animal tests; there is no evidence from human experience that synthetic zeolites may induce respiratory sensitisation (OECD 2006). There was no evidence of skin sensitisation in a guinea-pig maximisation test (Gloxhuber et al. 1983).

Genotoxicity

In vitro

Ames tests performed with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA 1538 and *E. coli* WP2 (uvrA) both in the absence and the presence of metabolic activation at concentrations up to 10,000 µg/plate showed no evidence of mutagenic activity of zeolite A (Prival et al. 1991; Zeiger et al. 1987).

In vivo

Sodium aluminum silicate was evaluated for its cytogenetic effects in male rats by the US Food and Drug Administration in oral single dose and repeated dose experiments

(NTIS 1979). The test material did not induce chromosomal aberrations in bone marrow cells nor dominant lethal mutations at the investigated dose levels of up to 5,000 mg/kg bw.

Repeated dose toxicity and carcinogenicity

Key elements of repeated dose toxicity studies are summarised in Table 2.

Oral route

No adverse effects were observed in Wistar rats that were fed zeolite Y for a week at dose levels of 0, 800, 2,000 or 5,000 mg/kg bw/day. Body weights as well as liver and kidney weights were not different from controls (Union Carbide Corporation 1977 as cited in OECD 2006).

In a 90-day feeding study with Wistar rats, the NOAEL of zeolite A was determined to be 5,000 ppm or approximately 250–300 mg/kg bw/day (OECD 2006; Gloxhuber et al. 1983). At 10,000 ppm effects regarding the function and histopathology of kidneys and bladder were found (i.e., diminished urine secretion, hematuria, and ketone bodies in the urine, 12/20 male animals revealed urinary calculi mainly composed of Si). The histological examination showed a hyperplastic reaction of the transitional bladder epithelium in rats with calculi. At 10,000 ppm, silicon concentrations of kidneys were significantly higher than in controls. No significant differences were found with regard to the concentrations of iron in blood, copper and cobalt in the liver, and zinc, aluminum, and copper in the kidneys.

In COX-SD rats fed zeolite A for 160–200 days, the NOAEL was 75 mg/kg bw/day (Procter & Gamble 1975, 1976 as cited in OECD 2006). At 1,000–2,000 mg/kg bw/day (LOAEL) a significant increase in the incidence of bladder and kidney stones was observed. Other than this, there was no evidence of an alteration of urine parameters or kidney function.

In an oral chronic toxicity and carcinogenicity study (Gloxhuber et al. 1983; OECD 2006) groups of 50 male and 50 female rats were fed 0, 10, 100 and 1,000 ppm of zeolite A (corresponding to about 0.6, 6.0 or 60 mg/kg bw/day) in the diet for 104 weeks. Satellite groups of 15 males and 15 females were used for initial and interim investigations. Body weights and mortality rates of the treated groups were not significantly different from the control group. Excretion of both silicon and aluminum in the urine was slightly higher in the 1,000 ppm group, but was not significantly different from controls. In animals that had died during the study or were sacrificed because of their poor condition, the main causes of death or ill health were basophilic adenoma and adenocarcinoma of the pituitary gland, adenoma and fibroadenoma of the mammary glands, subcutaneous fibroma and some tumours of the genital tract. No significant incidence of a particular type of tumour or of spontaneous mortality was evident in any group. No treatment-related findings were seen in any of the organs examined histologically, and there was no indication of any treatment-related induction of neoplasms.

If a cow is brought into a state of negative calcium balance, the calcium homeostatic mechanisms are activated, thereby preparing the animal for the sudden draw on calcium around calving and preventing milk fever. In order to bind calcium in the intestinal tract and thereby decrease feed calcium availability, zeolite A may be added as feed supplement. Treatment for 2 weeks with 500 g/day of zeolite A was shown to significantly reduce milk fever incidence in dairy cows. This treatment also reduced feed intake and induced transient hypophosphataemia; it may reduce serum magnesium levels. Serum levels of copper and zinc were unaffected (EFSA 2007; Thilsing-Hansen and Jørgensen 2001).

Dermal route

There were no data available.

Inhalation route

Unpublished industry studies by the respiratory exposure route are summarised in the OECD SIDS document (OECD 2006). Further to this information, the Procter & Gamble Company performed a study in the mid-1970s at Hazleton Laboratories Inc. using groups of 3 female and 3 male Cynomolgus monkeys. These animals were exposed to 0, 1, 6 and 50 mg/m^3 zeolite A dust for 6 h/day, 5 days a week for a period of 6, 12 or 24 months. Group mean values for mass median diameters were between 2.8 and 3.8 µm, indicating that a fraction of the generated dust has reached the alveolar region of the lungs in these studies. A positive control group received quartz dust at 50 mg/m^3. The exposure of the positive control group and of the high exposure group was discontinued after 55 weeks. There were no clinical signs reported except for episodes of diarrhea that had to be treated medically. Compound-induced histomorphological changes were seen neither in the upper airways nor in any of the non-respiratory tract organs examined. The histopathological effects observed in the lungs of animals of all groups in a dose-dependent manner were macrophage accumulations accompanied by sporadic bronchiolitis and alveolitis. No evidence of progressive pulmonary fibrosis was observed. After a 90-day recovery period, these reactions had diminished in severity but had not fully disappeared in the mid and high dose group. In the 1 mg/m^3 dose group, these effects were not evident after the 90-day recovery period. No increase in the incidence of neoplastic

Table 2 Repeated dose animal toxicity data for zeolites

Compound	Type of study	Species	Doses/results	Reference
Oral route				
Zeolite A	14 days	Cow	500 g/day in feed: reduced calcium bioavailability, hypophosphataemia (transient), reduced feed intake	EFSA (2007); Thilsing-Hansen and Jørgensen (2001)
Zeolite A	90 days	Rat	NOAEL: 5,000 ppm in diet (ca. 250–300 mg/kg bw/day) LOAEL: 10,000 ppm in diet (ca. 500–600 mg/kg bw/day; effects on kidney, urinary bladder)	Gloxhuber et al. (1983); OECD (2006);
Zeolite A	160–200 days	Rat	NOAEL: 1,250 ppm in diet (ca. 75 mg/kg bw/day) LOAEL: 20,000 ppm in diet (1,000–1,200 mg/kg bw/day; effects on kidney urinary bladder)	Procter & Gamble 1975, 1976, in: OECD (2006)
Zeolite A	2 years	Rat	NOAEL: 1,000 ppm in diet (ca. 60 mg/kg bw/day; highest tested dose)	Gloxhuber et al. (1983); OECD (2006)
Zeolite Y	7 days	Rat	NOAEL: 5,000 mg/kg bw/day (no histopathology performed; highest tested dose)	Union Carbide Corporation 1977, in; OECD (2006)
Dermal				
No studies available				
Inhalation				
Zeolite A	6, 12, 24 months	Monkey	LOAEL 1 mg/m^3 (sporadic inflammatory reactions in lungs; reversible)	Procter & Gamble 1976, 1977, in: OECD (2006)
Zeolite A	22 months	Rat	LOAEL 20 mg/m^3 (greyish-white deposits; respiratory disease, also in controls)	Gloxhuber et al. (1983)
Other routes				
Zeolite A	Intraperitoneal, 1–50 mg	Rat	Inflammation, deposits of injected material; not fibrogenic, not silicogenic	Gloxhuber et al. (1983)
Zeolite MS 4A, MS 5A	Intrapleural, intraperitoneal, subcutaneous, 25 mg	Rat	No tumours after intrapleural or subcutaneous injection; 1/40 with mesotheliom after intraperitoneal injection of MS4A	Maltoni and Minardi (1988)

NOAEL no observed adverse effect level

LOAEL lowesr observed adverse effect level

changes was reported. A limitation of this study are the potential side effects caused by the medical treatment of the animals, and the associated uncertainty in deriving the no-observed-adverse effect-level (NOAEL).

A group of 15 male and 15 female Wistar rats were exposed to 20 mg/m^3 of zeolite A for 5 h/day, three times a week for 22 months. The test material consisted of particles ranging from 0.5 to 10 µm, with most being less than 5 µm in diameter. Moderate to extensive signs of respiratory disease were seen in treated and control groups. Greyish-white deposits were seen in the phagocytes of the alveoli or the peribronchiolar or perivascular areas as well as in 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. No tumours of the respiratory tract were diagnosed (OECD 2006; Gloxhuber et al. 1983).

Groups of 20 male and 20 female Fischer 344 rats were exposed in inhalation chambers to a mean respirable dust concentration of 0 or 10 mg/m^3 of a synthetic non-fibrous zeolite (chemical composition identical to erionite). Exposures were for 7 h/day, 5 days/week for 12 months. All animals were observed for their life span. Three males and three females per group were killed at 3, 6, 12, and 24 months after exposure. Oregon fibrous erionite and crocidolite were used as positive controls. The mean survival time for animals exposed to the synthetic non-fibrous erionite was 797 days, 504 days for animals exposed to Oregon erionite, 718 days for animals exposed to crocidolite, and 738 days for untreated animals. One pleural mesothelioma and one pulmonary adenocarcinoma were seen in the non-fibrous erionite-exposed rats. No neoplasms were found in controls; 27 mesotheliomas were found in Oregon erionite-treated rats and 1 squamous-cell carcinoma of the lungs was found in crocidolite-treated rats (Wagner et al. 1985).

No adverse health implications of long-term worker exposure to synthetic zeolites have been reported (OECD 2006).

Other routes

Long-term carcinogenicity bioassays with zeolite types MS 4A (sodium aluminum silicate) and MS 5A (calcium aluminum silicate), administered by intraperitoneal, intrapleural, and subcutaneous injection in Sprague-Dawley rats, were undertaken by Maltoni and Minardi (1988). In these studies, groups of 20 male and 20 female Sprague-Dawley rats each were administered 25 mg of the test material in 1 ml of water or the solvent alone by single intraperitonel, intrapleural or subcutaneous injection. All animals were kept until spontaneous death. Full necropsy and histopathologic examinations were performed in each animal on the tissue at the site of injection, brain and cerebellum, thymus, lungs, liver, kidneys, adrenals, spleen, pancreas, stomach, uterus, gonads, subcutaneous, mediastinal and mesenteric lymph nodes, and any other organs with pathologic lesions.

At the site of injection, only one tumour was found: a peritoneal mesothelioma, which was observed at necropsy in a male rat treated by intraperitoneal injection with MS 4A, 141 weeks after treatment. No other differences were found between the treated and control groups. According to the study authors, the spontaneous onset of peritoneal mesotheliomas in the breed of rats used at the institute is infrequent, but not exceptional (3 cases in 1,179 rats). The responsiveness of the model used to the mesotheliomatogenic effects of particles is high. Under the same experimental conditions, the intraperitoneal injection of 25 mg crocidolite caused the onset of peritoneal mesotheliomas in 97.5% of animals, and the intrapleural injection of 25 mg erionite produced pleural mesotheliomas in 87.5% of animals.

Gloxhuber et al. (1983) studied the silicogenic activity of zeolite A (pure and formulated material) in several animal studies. Doses between 1 and 50 mg of zeolite A, suspended in 0.5 mL Tyrode's solution were administered by single injection intraperitoneally into Wistar rats.

Injections of quartz DQ12 served as positive controls; animals were sacrificed after 3, 6 or 11 months and examined histologically. Zeolite application led to an inflammation of abdominal organs and to deposits of the administered material in the regional lymph nodes, the abdominal cavity and the mediastinum without fibrogenic or silicogenic effects. At study end deposition seemed in many rats to be reversible with exception of the highest dose level. Administration of zeolite A induced deposits on the capsule of the liver, spleen and kidney. The administration of quartz led to the formation of quartz typical lesions within the abdomen.

Reproductive and developmental toxicity

No signs of toxicity to reproductive organs by synthetic zeolites were reported in the unpublished studies reviewed by OECD (2006), or in the studies reported by Wagner et al. (1985) and Gloxhuber et al. (1983).

Type A Zeolite ("Arogen 2000", JM Huber Corp.) containing 15.8% sodium 19.0% silicon, and 20.1% aluminum was tested for its teratogenic potential (Nolen and Dierkman 1983). Studies were performed using the standard FDA Segment II protocol using Sprague-Dawley rats and New Zealand rabbits. Zeolite A in distilled water was given to rats by gavage at concentrations of 74 or 1,600 mg/kg of body weight on days 6–15. Rabbits were given doses of 74, 345, and 1,600 mg/kg of Zeolite A by oral gavage on days 6–18. Vehicle controls were included but no details were provided. Type A zeolite produced no adverse effects on the

dam, the embryo, or the fetus in either the rats or rabbits at any of the doses tested.

Food grade aluminosilicate with a Na:Al:Si ratio of 1:1:13 has been tested for teratogenic potential by the US Food and Drug Administration and was found to have no effects in rats, mice, rabbits and hamsters (NTIS 1973).

Discussion

Synthetic and naturally occurring zeolites are used in a variety of applications, including the use as desiccants, adsorbants, catalysts and molecular sieves. The synthetic zeolites A, P, X and Y are increasingly used in laundry detergents to substitute phosphates as builders. Workers and consumers may, therefore, repeatedly be exposed to these materials. This article puts mechanistic, toxicological and exposure data into context for a safety assessment.

Exposure to zeolites may occur through the oral, dermal and respiratory route. Oral exposure may occur by swallowing airborne zeolite dust particles that were trapped in the upper respiratory tract because of their size, or through zeolite-containing drinking water. Oral exposure may also occur by accidental intake of zeolite-containing detergents. The acute and repeated dose toxicity of laundry zeolites after oral exposure has been investigated in several animal studies and was shown to be extremely low, most probably because of their low systemic bioavailability. Most of the ingested amount remains undissolved in the gastrointestinal tract and is excreted unchanged in the faeces; part of the zeolites decomposes under the acidic conditions of the stomach to release silicon and aluminum species which could be absorbed by the gastrointestinal tract.

No observed adverse effect levels (NOAELs) in animal studies were around 60 mg/kg bw/day with higher doses (around 200–300 mg/kg bw/day) inducing effects on the kidney and urinary bladder after long-term ingestion. No other signs of systemic toxicity were observed; in particular, there was no influence on electrolytes and trace element concentration of plasma and organs. Effects on kidney and urinary bladder were due to long-term silicon uptake from decomposed zeolites by the gastro-intestinal tract followed by increased silicon concentrations in kidney and urine with the formation of silicon containing calculi in the urinary tract and mechanical irritation of the bladder epithelium by these concrements. Whilst an increase in silicon levels could be shown in animal studies after oral zeolite exposure to high doses, no increase was found in the aluminum levels of tissues, urine or blood plasma. Nevertheless, the uptake of aluminum released from zeolites in the gastrointestinal tract could be seen as a potential safety concern because of the recognised effects of aluminum on reproduction and the developing nervous system. These effects led to the replacement of the previous provisional tolerable weekly intake level of aluminum of 7 mg/kg bw by a new proposed value of 1 mg/kg by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2006). Aluminum was also considered as potentially neurotoxic. As the absorption of free aluminum by the gastrointestinal tract is however minimal, i.e. less than 0.1%, the contribution to the body burden from orally ingested laundry zeolites is negligible. Furthermore, humans are frequently exposed to aluminum through their diet, drinking water, and utensils used during food preparations and efficient excretion mechanisms exist in the human body to maintain homeostasis.

Under the current conditions of manufacture and use, no significant effects of synthetic zeolites on the bioavailability of other compounds, including trace elements, are to be expected.

Synthetic zeolites released into the aquatic environment were shown to be converted into natural occurring alumosilicate species and natural constituents of waters, sediment and soils (Cook et al. 1982). A direct exposure to zeolites through the drinking water is therefore not expected.

Serious effects after accidental oral ingestion of detergent formulations and cleaning agents have been reported (e.g. BfR 2005). These effects are generally attributed to the corrosivity and severe irritation of mucosal membranes that may be caused by ingredients other than zeolites if swallowed in large quantities. In view of the ion exchange properties, however, zeolites may be expected to alter the ionic composition, pH and buffering capacity of the gastrointestinal tract under conditions of overexposure. Except for episodes of diarrhoea in monkeys exposed to high doses of zeolite A dust by inhalation (and probably having swallowed most of the particles) no adverse gastrointestinal effects have however been reported from animal studies performed with high zeolite exposures.

Dermal exposure to zeolites may occur in occupational settings or in households when detergents are handled either as such or in solutions. Because of their physicochemical properties zeolites are however not expected to be taken up through the intact skin. Systemic exposure is, therefore, not expected to be relevant. Zeolites in aqueous environment form alkaline suspensions (pH 10–10.5) which may cause skin or mucous irritation. It is, therefore, recommended that personal protection equipment is worn by workers. Dermal exposure to zeolites by consumers is however very limited as the contact time when unpacking laundry powder or tablets is short, and the solutions used for the hand-wash of laundry are diluted.

Since the poorly soluble zeolite particles are small enough (1–10 μm) to enter the lungs, short-term inhalation of these materials could overload lung clearance mechanisms, causing temporary irritation. Formation of NaOH

may add to the irritant action of zeolites in the airways. As zeolites are hygroscopic and quickly agglomerate to larger particles, most of the material will however be retained in the upper airways or be swallowed. Particles that reached the lung are deposited there and may cause histopathological effects such as macrophage accumulations accompanied by inflammatory effects such as bronchiolitis and alveolitis. From animal studies and medical surveillance there is no evidence that inhalation of these types of zeolite can cause silicosis or tumours.

Zeolites A and X induced no gene mutations in vitro. In vivo clastogenesis studies showed no evidence of induction of chromosomal aberrations. It is important to note that erionite—a naturally occurring fibrous zeolite—has been shown to be genotoxic and to induce mesothelioma in humans and animals. Though the mechanism of action is not fully understood yet, it is believed that the fibrous shape and surface properties of erionite play a significant role in the carcinogenic process. A comparative study of the biological response and chemical reactivity of several zeolites (erionite, mordenite, zeolite Y) concluded that the toxicity of zeolite Y would be very low.

Depending on the conditions of washing and rinsing, detergent residues may remain after the wash on textiles. For zeolites, residue concentrations of up to 37,000 mg/kg fabric have been measured. Although it is not expected that zeolites penetrate the intact skin barrier and thereby become bioavailable, these deposits of crystalline material might possibly cause effects on sensitive skin by mechanical irritation ("intolerance reactions"). Co-operation of detergents manufacturers with manufacturers of washing machines is, therefore, important to find the right balance between environmental aspects such as energy and water savings and the risk of detergent residues on textiles due to insufficient rinsing.

Conclusion

Based on available mechanistic and toxicological data and taking into account exposure information, it is concluded that the synthetic zeolites A, P, X and Y as currently used in detergent formulations are safe for consumers under the conditions of the recommended use. This is in accordance with earlier opinions on the safety of zeolites (BfR 2007; CSTEE 2003; OECD 2006). Due to irritant effects of the undiluted materials on mucous membranes and the respiratory tract, the exposure of workers should be controlled. The co-operation of detergent manufacturers with the manufacturers of washing machines is necessary to find the right balance between environmental aspects such as energy and water savings and the occurrence of zeolite residues on textiles due to insufficient rinsing.

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