HERA

Human & Environmental Risk Assessment on ingredients of European household cleaning products

Zeolite A

represented by CAS Number

1344-00-9 (Sodium Aluminium Silicate)

and by CAS Number

1318-02-1 (Zeolites)

Version 3.0

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"This updated version 3.0 of the HERA Risk Assessment takes account of recently generated data on terrestrial toxicity of Zeolite A, resulting in a revised risk characterisation for local soil compartment"

0 Contributors

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1 Executive Summary

Zeolite A (sodium aluminium silicate) is used as a builder in detergent powders and tablets for water softening in the washing process. Environmental risk assessments of Zeolite A were conducted with the default values of EUSES 1.0 and with the HERA detergent scenario as well. Based on the calculated PEC/PNEC ratios which are below 1 (RCR < 1) in both scenarios, no cause of concern was indicated for any of the environmental compartments, i.e. water, sediment, soil and and sewage treatment plant (STP). In contrast to the 1st version of the HERA Zeolite A risk assessment, a risk quotient < 1 has also been established for the local soil compartment due to recently generated plant toxicity data of a high reliability. The favourable outcome of the present environmental risk assessment and the knowledge about the long-term fate of zeolites which ultimately turn into natural constituents provide a sound basis for the conclusion that the use of zeolite A in detergent products does not pose a risk to the environment.

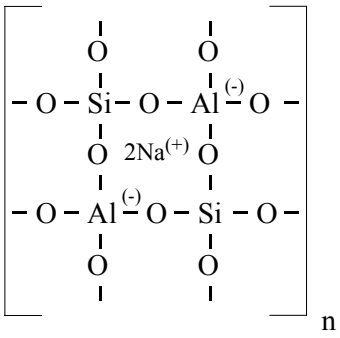
Scenarios relevant to the consumer exposure to Zeolite A (sodium aluminium silicate) have been identified and assessed using the margin of exposure or equivalent assessments. Due to the lack of irritant and sensitising effects the local effects of dermal exposure do not cause concerns. Developmental or carcinogenic effects were not observed in experimental studies. No studies have been identified that investigated the reproductive toxicity of sodium aluminium silicate. However, no indication of toxicity to reproductive organs have been observed in long term studies and no structure activity relationship is known that indicates a concern. Chronic oral studies demonstrate that sodium aluminium silicate causes adverse effects in the urogenital tract. The NOAEL for these effects in a two-year rat oral toxicity study is 60 mg/kg BW. The Margin of Exposure for the combined estimated systemic dose is 567. This Margin of Exposure is considered to provide sufficient protection of consumers exposed to sodium aluminium silicate. The same conclusion is reached in assessing the possible effects of inhaled sodium aluminium silicate dust. Accidental exposure scenarios such as ingestion or contact to eyes were also assessed. Due to the lack of acute toxic effects of sodium aluminium silicates, these scenarios also do not cause concern. In summary, the human risk assessment has demonstrated that the use of sodium aluminium silicate in household detergents does not cause concern with regard to consumer use.

2 Contents

3 Substance Characterisation

3.1 CAS No and Grouping Information

The zeolites used as builders in detergent formulations are synthetic sodium aluminium silicates with the general formula: $Na_x[(AlO_2)_x(SiO_2)_y]$ x zH_2O.



The Si/Al ratio in the detergent zeolites is approximately 1. While the chemical composition and the basic performance properties of the individual detergent zeolites (Zeolite A, Zeolite P, Zeolite X) are almost identical, the individual types have different crystalline structures resulting for instance, in a firmer binding of calcium ions by Zeolite P and a higher magnesium binding capacity of Zeolite X compared to Zeolite A (ZEODET, 2000 [1]). Although the more recently developed zeolite types P and X may have improved performance properties Zeolite A represents the most prominent type of zeolite used in detergents.
As presently no specific information is available about the ecological properties of these new zeolite types, this HERA risk assessment only addresses zeolite A. The itself-suggesting assumption that the environmental behaviour of zeolites P and X may be very similar to that of zeolite A is still to be substantiated by suitable bridging data until the HERA risk assessment can be extended to all zeolite types used in detergents.
Zeolite A is a synthetic sodium aluminium silicate with the formula $Na_{12}(AlO_2)_{12}(SiO_2)_{12}$ x $27H_20$. The cubic microcrystals have an optimised particle shape (rounded corners and edges) and an average particle diameter of 3.5 µm . They agglomerate partially during the spray-drying procedure to form bigger particles, which may disintegrate in water. The investigations into the ecological and toxicological behaviour of Zeolite A were conducted with the described particulate material. Zeolite A has a purity of $\geq$ 99%. Trace impurities may consist of Fe_2O_3 ($\leq$ 0,2%) and amorphous alumosilicates (IUCLID dataset).
The present HERA risk assessment of Zeolite A refers to data of the CAS-No. 1344-00-9 for "Silicic acid, aluminium sodium salt" (EINECS) and 1318-02-1 for "Zeolites" (EINECS) both of which are used to describe commercial Zeolite A.

3.2 Chemical Structure and Composition

CAS NO: 1344-00-9 **CAS NO: 1318-02-1**	**Protocol**	**Results / Remarks**	**Ref.**
Macro-molecular description (Physical State/Particle size)		Solid, crystalline structures	13
Molecular Weight	calculated	284 [g/mol] Na_2O x Al_2O_3 x 2 SiO_2 (Zeolite A 4 atro)	2
	calculated	2190 [g/mol] $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]$ x 27 H_2O	2
Melting Point	other *	1700 [°C]	2, 3
Boiling Point		not applicable	
Vapour Pressure		not applicable	4
Octanol-water Partition Coefficient (Log Pow)		not applicable (inorganic, poorly soluble)	
Water Solubility	other *	poorly soluble (< 10 [mg/l])	5
	other *	about 1.4 [mg/l] (Ca-Zeolite A in river water)	6
	other *	0.25 - 7.2 [mg/l] (depending on water composition)	7
	other *	< 1000 [mg/l]	13
Sorption coefficients		not applicable	
K_{OC}		not applicable	
Density	DIN/ISO 787 / IX	170 – 450 [kg/m^3]	13
Viscosity		not applicable	
pH-Value	other *	10.4 at 50 [g /l] and 20 [°C]	13
pK_a		not applicable	
Oxidation		not applicable	
Henry`s constant		not applicable	

* Method not contained in the IUCLID glossary of standard methods

3.3 Manufacturing Route and Production/Volume Statistics

The annual consumption of all zeolites used in the European detergent market has been relatively constant for a number of years. The figures for the years 1993 - 2000: were in the range 620,000 - 650,000 tons (ZEODET, 2000).
As there is presently no more detailed information available about the production/ consumption figures of the individual zeolite types, the total consumption figure of 650,000 tons/year will be used for the risk assessment of Zeolite A.
Synthetic Zeolites are manufactured from SiO_2- and Al_2O_3- containing substances, for instance silicic acid sodium salts, aluminium hydroxides, or aluminates, at temperatures greater than 50 °C and with alkalihydroxides (NaOH) as catalysts (Breck, Zeolite Molecular Sieves,1979) [8]. They occur as fine white powders or pastes as well as granulates.

3.4 Use Applications

Sodium aluminium silicates, especially Zeolite A, are used in household detergents to decrease the water hardness by exchanging the Ca-ions for Na-ions. The major part of phosphate-free household detergents is based on the use of Zeolite A as builder. Zeolites are also used as catalysts or molecular sieves.

4 Environmental Assessment

4.1 Environmental exposure assessment

4.1.1 Environmental Fate and Removal

CAS NO: 1344-00-9 **CAS NO: 1318-02-1**	**Protocol**	**Results**	**Ref.**
Photodegradation		Not relevant	
Stability in Water	other *	T1/2 = 60 days (hydrolytical decomposition of Zeolite A)	9
Monitoring Data		not applicable	
Transport and Distribution		Main entry to the environment via waste water, main distribution to sludge	
Biodegradation		not applicable (inorganic substance)	
Elimination in Sewage Treatment Plants	other *	90 % (conservative value derived from laboratory simulation and field tests) (Zeolite A)	10

* Method not contained in the IUCLID glossary of standard methods

4.1.2 Monitoring Data

No monitoring data are available due to the lack of substance specific analytical methods and the fact that alumosilicates (clays) like zeolites are commonly found in sediments and soils, thus representing an environmental ubiquitous formula (see 4.4)

4.1.3 Exposure assessment: EUSES Scenario description

Scenario A: Default values according to EUSES

- Fraction connected to sewer systems: 80% (regional release scenario acc. to TGD)
- Fraction of emission directed to waste water: 100 %
- 10 % of Zeolite A continental tonnage is going to region
- local tonnage increased by factor 4
- STP elimination 90%
- In-stream removal due to hydrolysis: 0.011 d^{-1} ($t_{1/2}$ = 60d)

Scenario B: Zeolite-specific scenario

Zeolite A is a high production volume detergent ingredient used in all countries where phosphate-reduced or -free detergents dominate the market. However, the use of such zeolite-containing detergents is not evenly distributed in Europe so that the prerequisites of the HERA exposure scenario (see HERA Methodology Document) may not apply totally. Hence, the zeolite-specific scenario (Scenario B) deviates from the HERA-scenario in terms of the regional release (see below). The local release of the HERA scenario remains unaltered as it is not concerned by the uneven European distribution of zeolite use in detergents.

The regional release scenario was modified according to the following facts:

- Italy is the country with the highest per capita use of detergents (cf. HERA Methodology Document) and with a 100 % use of phosphate-free (i.e., zeolite-containing) detergents (ZEODET 2000). Hence, Italy represents the worst case situation of the regional release of zeolites.

- To obtain the zeolite consumption figure for Italy where concrete figures are deficient, the following calculations were made:

  - Zeolite use in (100 % phosphate-free) detergents in Germany: 139000 to/a (IKW, 2000 [11]) → 1.70 kg/cap · year
  - Per capita detergents use: Germany 7.73 kg/a , Italy 10.77 kg/a (AISE Code, 1996 [12]) → use of (phosphate-free) detergents in Italy is higher by a factor of 1.39
  - Zeolite use in Italy is calculated as follows: 1.70 (cf. Germany) x Factor 1.39 = 2.36 kg/cap · year

- Compared to the EU average (650000 to/a → 1.76 kg/cap · year) the zeolite use in Italy is higher by a factor of 1.34 while the HERA regional detergent exposure scenario is based on a consumption of 1.25 times the EU average. To maintain the conservative frame conditions of the zeolite-specific exposure scenario, a 7.4 % of the zeolite continental tonnage was assumed to go to region (instead of 7 % as assumed in the HERA standard exposure scenario).

As a consequence, the exposure calculations in Scenario B are based on the following frame conditions:

- Fraction connected to sewer systems: 80% (regional release scenario acc. to TGD)
- Fraction of emission directed to waste water: 100%
- 7.4 % of Zeolite A continental tonnage is going to region
- local tonnage increased by factor 1.5
- STP elimination: 90%
- In-stream removal due to hydrolysis: 0.011 d-1 ($t_{1/2}$ = 60d).

Data from laboratory simulation and field tests form a sound basis for the prognosis that Zeolite A concentrations are reduced by 90% in activated sludge plants. Thus, the remaining 10% is assumed to go into the water fraction resulting in the following PEC distributions (only the local PECs are reported, as these were used as the exposure endpoints for the risk characterisation):

4.1.4 Substance Data used for EUSES exposure calculations

		Range of available values	Literature cited
General name	Zeolite A		13
Description	e.g. $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]x\ 27H_2O$ e.g. Na_2O x Al_2O_3x $2SiO_2$		2, 13
CAS-Numbers	e.g. 1344-00-9, 1318-02-1	several CAS	13
EC-notification no.	-		
EINECS no.	215-684-8		13
Molecular weight [g/mol]	2190	284, 2190	2, 13
Melting point [°C]	1700	700, 1700	2, 3
Boiling point [°C]	n/a		
Vapour pressure at 25°C [Pa]	1E-6*		4
Octanol-water partition coefficient [log10]	-1**		4
Water solubility [mg/l]	1	0.25, < 1000	7, 13
Total tonnage in continent	650.000		1
Degradability	not applicable, inorganic		13
Hydrolysis (stability in water)	0.011 d^{-1} ($T_{1/2}$ = 60 days)		9
Fraction of emission directed to air	0		
Fraction of emission directed to water	0,1		10, 13
Fraction of emission directed to sludge	0,9	0.66, 0.98	10, 13
Fraction of the emission degraded	0		

* Zeolite A is not volatile. Therefore, the lowest standard input value for EUSES was used

** The solubility of Zeolite A in octanol is extremely low. Hence, it was assumed that the Kow is $\leq$ 0.1

4.1.5 PEC Calculations

The following table summarises the output of the exposure calculations based on the two scenarios: A) EUSES standard and B) modified HERA Scenario.

Zeolite distribution in local compartments	**Scenario A**	**Scenario B**
Concentration in dry sewage sludge [mg/kg]	4,06E5	1,13E5
PEC Water [mg/l]	2,76	1,24
PEC Agricultural Soil (total) 30d [mg/kg]	511	142
PEC Sediment [mg/kg]	2,17	0,98
PEC STP [mg/l]	17,8	4,94
Zeolite distribution in regional compartments		
PEC Water [mg/l]	0,98	0,75
PEC Agricultural Soil 30d [mg/kg]	1,5	1,11
PEC Sediment [mg/kg]	0,59	0,45

4.2 Environmental effects assessment

4.2.1 Toxicity

4.2.1.1 Ecotoxicity – Aquatic: Acute Test Results

	Species	Protocol	Result [mg/l]	Range [mg/l]	Reference
Algae EC50	Scenedesmus subspicatus	OECD 201	18		14
Invertebrate IC50	Daphnia magna	OECD 202	2808		15
Fish LC50	Leuciscus idus	OECD 203	1800		16

4.2.1.2 Ecotoxicity – Aquatic: Chronic Test Results

	Species	Protocol	Result [mg/l]	Range [mg/l]	Reference
Algae NOEC	Scenedesmus subspicatus	OECD 201	(4.9)	4.9, 100	17, 14 (see expert judgement 4.2.2.1)
Invertebrate NOEC	Daphnia magna	other *	37	10, 320	17, 18, 19 (see expert judgement 4.2.2.2)
Fish NOEC	Pimephales promelas	US-EPA	86.7		17
Other: Diptera NOEC	Paratanytarsus parthenogenica	other *	200		17

* Method not contained in the IUCLID glossary of standard methods

4.2.1.3 Terrestrial – Aquatic: Acute Test Results

	Species	Protocol	Result [mg/kg]	Range [mg/l]	Reference
Plants EC50	Avena sativa	OECD 208	15 000 (Na-form)		20
	Lepidium sativum		10 000 (Na-form)		20
	Raphanus sativus		4 000 (Na-form)		20
			> 240 000 (Ca-form)		21
Earthworms LC50			no data available		
Microorganisms LC50			no data available		
Other: Frog LC50	Xenopus laevis	other *	1800	1800, 3200	18

* Method not contained in the IUCLID glossary of standard methods

4.2.1.4 Terrestrial – Aquatic: Chronic Test Results

	Species	Protocol	Result [mg/kg]	Range [mg/l]	Reference
Plants EC10 **NOEC**	Raphanus sativus	OECD 208	900 (Na-form) 60 000 (Ca-form)		20 21
Earthworms NOEC			no data available		
Microorganisms NOEC			no data available		
Other: plant NOEC	Brassica rapa Avena sativa Lycopersicum esculatum	OECD 208	1000 * 1000 * 1000 *		7 7 7

* highest concentration tested

4.2.1.5 Microorganisms in Waste Water Treatment Plant (WWTP)

	Species	Protocol	Result [mg/l]	Range [mg/l]	Reference
Specific bacterial population EC50	Pseudomonas putida	DIN 38412, part 8	950		22
Specific bacterial population EC10	Pseudomonas putida	DIN 38412, part 8	330	330, 2000	7, 22

4.2.2 Evaluation of Chronic Toxicity Data used for PNEC Derivation

Long-term toxicity data (NOEC values) for all 3 aquatic toxicity endpoints, i.e. fish, daphnia and algae exist in literature. In addition, new supplementary data on the chronic terrestrial toxicity have been generated so that such long-term toxicity data could be used for the PNEC derivation in the aquatic and terrestrial compartment. In the tables 1-4 all existing chronic toxicity data are summarised and evaluated in terms of their reliability according to the criteria by Klimisch et al. (1997)[23]. The following subchapters 4.2.2.1 - 4.2.2.4 discuss in more detail the relevance and the applicability of the individual data for the environmental risk assessment of zeolite A as used in detergents.

Table 1: Chronic toxicity to aquatic invertebrates
Zeolite A (CAS 1344-00-9): Excerpt from IUCLID database, Chapter 4.5.2.

	Daphnia magna	**Daphnia magna**	**Daphnia magna**
Endpoint	Mortality & reproduction rate	reproduction rate	reproduction rate
Exposure period	21 days	21 days	21 days
NOEC (mg/l)	37	10	320
Test substance	Ca-exchanged Zeolite A	Zeolite Type 4A from Akzo-Chemie. Acc. to specification, this is not a zeolite typically used in detergents	Zeolite type NaA from Henkel. Typically used in detergents
Reference	17	18	18
Data reliability	Reliable with restr.	Reliable with restriction	Reliable with restriction

Table 2: Chronic toxicity to fish Zeolite A (CAS 1344-00-9): Excerpt from IUCLID database, Chapter 4.5.1.	
	Pimephales promelas
Endpoint	reproduction rate, survival of eggs, length and weight of young fish
Exposure period	30 days
NOEC (mg/l)	86.7
Test substance	Ca-exchanged Zeolite A
Reference	17
Data reliability	Reliable with restriction

Table 3: Toxicity to aquatic plants (e.g. Algae) Zeolite A (CAS 1344-00-9): Excerpt from IUCLID database, Chapter 4.3.				
	Scenedesmus subspicatus	**Microcystis aeruginosa**	**Selenastrum capricornutum**	**Navicula seminulum**
Endpoint	growth rate	growth	growth	growth
Exposure period	96 h	14 days	5 days	5 days
EC10 (mg/l)	4.9 (particle counting) 11 (fluorescence measurement)	NOEC = 50 mg/l	LOEC = 100 mg/l	LOEC = 50 mg/l
EC50 (mg/l)	18 (particle counting) 34 (fluorescence measurement)			
Reference	14	17	17	17
Remarks	GLP study, study conducted with Na-zeolite	Study conducted with Ca-zeolite	Study conducted with Ca-zeolite	Study conducted with Ca-zeolite
Data reliability	Reliable without restriction	Reliable with restriction	Reliable with restriction	Reliable with restriction

The IUCLID database does contain a number of further references on the effects of Zeolite A in algal growth inhibition tests.

In several of these tests based on the AAP-procedure (US-EPA, 1971) NOEC/LOEC values between 0.1 - 10 mg/l were measured.

However, it was pointed out in the remarks that these were test artefacts due to the binding of nutrients by the zeolite. Addition of minimal salts reverses the effects. Therefore, these data were not taken into account for the effects assessment of Zeolite A.

4.2.2.1 Algae

From Tables 1-3 it is evident that the lowest NOEC endpoint value is the algal EC10 = 4.9 mg/l from a study by Degussa/TNO (TNO report IMW-R 92/126, 1992) conducted with Na-Zeolite A. However, this algal toxicity value has to be considered with caution, since it is well known and supported by numerous investigations that the growth-inhibiting effects of complexing agents and ion-exchanging materials which are often observed in the nutrient-poor culture-media of ecotoxicological standard tests result from the depletion of trace heavy metals essential for algal growth. This nutrient-depleting effect of Zeolite A was specifically addressed in investigations by Maki and Macek (1978)[17] and Gode (1983) clearly underlining that nutrient exchange by zeolite was responsible for reduced algal growth. In nutrient-rich media no such effects were observed (Umweltbundesamt, 1979). Based on these observation it was concluded that the inhibitory effect of Zeolite A observed in nutrient-poor test media is without any practical relevance since Zeolite A as a detergent builder will never reach oligotrophic water bodies alone, but only in combination with other nutrients in treated and untreated effluents (UN-ECE, 1992 [24]).
With regard to the use of an appropriate algal NOEC it is important to note that detergent-based zeolite A entering the sewer system will be loaded with calcium ions as the result of its ion-exchange function in the washing process (Kurzendörfer et al., 1997). For that reason, algal NOEC data are to preferred being based on Ca-loaded zeolite A which exhibits a less pronounced ion-exchange of individual heavy metals. Hence, the algal NOEC = 50 mg/l (see table 3) was used for the risk assessment of zeolite A. It should be noted that this figure is far above the water solubility limit of zeolite A suggesting that the measured effects on algal growth at higher concentrations be linked to physical effects like turbidity-caused light attenuation.

4.2.2.2 Daphnia

Also the lowest Daphnia-NOEC value (10 mg/l) reported by Canton and Sloof, 1982 [18] (see table 1) requires a critical evaluation. This NOEC refers to a Zeolite Type 4 A from Akzo having a specification, which is different to the Zeolite Type A used in detergents. The authors mention that the 'sample tested was a precursor with sharp crystal structure' while the zeolite type relevant for detergent use is characterised by a rounded shape of the crystals in order to optimise fabric care (Jakobi and Löhr, 1987 [25]). Also the particle size distribution was different from the typical detergent Zeolite A (from Henkel KGaA) which was tested in the same study. As the obtained NOEC values differed considerably (see below) it was concluded that the Akzo zeolite NOEC should not be taken into account for the risk assessment of detergent-based zeolites. Instead, the next most sensitive NOEC value based on the 21-day Daphnia life-cycle test with a typical detergent Zeolite A (Maki and Maceck, 1978) was used in the context of the Zeolite A risk assessment. The FOEC was 130 mg/l and the NOEC = 37 mg/l. The authors' statement should be mentioned that the negative effects on survival and reproduction seen at higher concentrations (i.e. $\geq$ FOEC) were due to physical effects of the compound on feeding and mobility since these suspensions were extremely turbid. Hence, even this NOEC value must be considered as a very conservative assessment. The very low long-term Daphnia toxicity of Zeolite A was also confirmed by the NOEC values obtained in further studies: Canton & Slooff (1982) report on a NOEC = 320 mg/l of the Zeolite A type from Henkel KGaA (which was tested in parallel to the mentioned Akzo zeolite) and a NOEC = 500 mg/l was measured by Fischer & Gode (1977) when testing a typical detergent Zeolite A.

4.2.2.3 Fish

The long-term fish-study on Zeolite A originates from the work by Maki & Macek (1978)[17], too. Up to the highest tested concentration (87 mg/l) there was no adverse effect on hatchability of eggs and survival, mean total length and average weight of fry at a 30-day exposure of eggs and fry of fathead minnows (P. promelas) to Zeolite Type A. Thus, the conservatively evaluated NOEC is 87 mg/l.

4.2.2.4 Terrestrial plants

The first HERA environmental risk assessment of Zeolite A (March 2002) evaluated the terrestrial toxicity on the basis of the plant growth test data available in IUCLID (Table 4). The PNEC derived from this data was considered very conservative as it was derived from a NOEC which corresponds to the maximum concentration tested and, hence, may differ from a realistic view by one or more order(s) of magnitude.
For that reason, a new plant toxicity test was commissioned by ZEODET, the industry association of zeolites producers, aiming at testing Zeolite A at concentrations clearly above 1000 mg/kg. However, the results from testing the Na-form which corresponds to the material present in detergent products, exhibited a significant growth inhibition effect towards the most sensitive plant species, Raphanus sativus, at test concentrations higher than 900 mg/kg (Table 4). Acknowledging the considerably lower sensitivity of the two other test species and taking into account that the Ca-loaded form is the predominant species of Zeolite A in the environment, an additional test was conducted with Ca^{++}-Zeolite A and Raphanus sativus as test species. In fact, the Ca-form of Zeolite A turned out to be considerably less toxic with a NOEC = 60 000 mg/kg corresponding to a lower toxicity by a factor of 67 compared to the Na-form (Table 4). In line with similar observations in aquatic toxicity tests (cf. 4.2.2.1), it is obvious from these test results that the toxicity effected by the Na-form is due to the depletion of essential trace elements in the test system while the environmentally most relevant Ca-form is virtually non-toxic. For that reason, the NOEC = 60 000 mg/kg was used for the PNEC derivation in terrestrial risk assessment of Zeolite A.

Table 4: Toxicity to terrestrial plants
Zeolite A (CAS 1344-00-9, 1318-02-1, 68989-20-8)

Plant species	Exposure period (d)	Endpoint	Effect concentration (mg/kg) EC50	Effect concentration (mg/kg) NOEC / EC10	Remarks	Reliability	Reference
Avena sativa	21	growth		> 1 000*	Ca^{++} zeolite	2	7
Brassica rapa	21	growth		> 1 000*	Ca^{++} zeolite	2	7
Lycopersicum esculentum	21	growth		> 1 000*	Ca^{++} zeolite	2	7
Avena sativa	28	growth	150 000	n.d.	Na^{+} zeolite	1	20
Raphanus sativus	21	growth	4 000	900	Na^{+} zeolite	1	20
Lepidium sativum	21	growth	10 000	n.d.	Na^{+} zeolite	1	20
Raphanus sativus	21	seedling emergence	> 240 000	240 000	Ca^{++} zeolite	1	21
		shoot fresh weight	> 240 000	240 000			
		plant high	> 240 000	60 000			

* highest concentration tested

4.2.3 Derivation of PNEC

It should be noted that all the determined NOEC values are in a concentration range which is already above the solubility limit of Zeolite A. Therefore, it can be concluded that the effects measured above the NOEC may not be attributable to systemic toxic effects but may be due to physical effects of the undissolved material. Such effects will not be relevant in practice considering the expected environmental concentrations. Accordingly, the PNEC derived from the lowest NOEC is extremely conservative because it may not really address the aquatic toxicity of Zeolite A but reflects its physical effects measured at concentrations far above reality. Correspondingly, it can be concluded from the NOEC data that the soluble moiety of zeolite A present in the aquatic environment is not toxic to the biota.

	NOEC	**Assessment factor**	**PNEC**
Aquatic Organisms	37 mg/l	10	3,7 mg/l
Terrestrial Organisms	60 000 mg/kg	100	600 mg/kg
Microorganisms	330 mg/l	10	33 mg/l
Sediment Organisms	PNEC derived from aquatic NOEC		2.3 mg/kg

According to the facts and arguments discussed above (4.2.2), the most sensitive aquatic toxicity endpoint is the Daphnia NOEC = 37 mg/l. As NOEC data are available for fish, daphnia and algae, an assessment factor of 10 is to be applied for the PNEC derivation. Consequently, for the aquatic risk assessment of Zeolite A a PNEC = 3.7 mg/l is being used.

The terrestrial PNEC was derived from available NOEC data for the most sensitive of the 3 plant species tested (see 4.2.2.4) by using an application factor of 100. The PNEC for microorganisms in sewage treatment plants was derived from the EC10 of a test with a specific bacterial population (see 4.2.1.5) using (conservatively) an application factor of 10.

4.3 Environmental Risk Characterisation

Risk characterisation of EUSES Scenarios A and B (c.f. 4.1.5 Exposure Assessment)

		Scenario A	**Scenario B**
RCR Water	regional	0,26	0,20
	local	0,75	0,34
RCR Soil	regional	0,02	0,02
	local	0,84	0,23
RCR Sediment	regional	0,26	0,20
	local	0,95	0,43
RCR STP*	regional		
	local	0,54	0,15

* Sewage Treatment Plant (STP)

4.4 Additional environmental effects

Apart from the ecotoxicological effect evaluation, zeolites may also be discussed in terms of their possible impact to the balance of heavy metals in sewage treatment plants and surface waters. In addition, their influence on the sedimentation pattern of suspended solids and the possible consequences for benthic organisms may have to be taken into account. These additional topics not captured in the EUSES standard risk assessment approach are discussed below.

4.4.1 Impact on heavy metal distribution in waters

Numerous laboratory and field studies are reported in literature dealing with the influence of zeolite A on the heavy metal removal and remobilisation, respectively, in waste water treatment plants and surface waters (Kurzendörfer et al., 1997). Here, only the most relevant conclusions from these studies are summarised.
Ca-loaded zeolite A being the main zeolite species in spent washing liquors does not contribute significantly to the heavy metal removal from sewage in the course of the waste water treatment process. Accordingly, enrichment of heavy metals in Ca-loaded zeolite A at concentrations similar to those in rivers is only slight with the exception of the most selective heavy metal Pb. The minute heavy metal-loaded amounts of zeolite A present in rivers do not differ from sediment-forming natural heavy metal-loaded cation exchangers and contribute therefore to the stable deposition of heavy metals. In sum, the impact of detergent-based zeolite to the heavy metal balance in aquatic systems is low. There are no indications for a prevention of heavy metal removal or a remobilisation of heavy metals by zeolite A.

4.4.2 Impact on sedimentation pattern of suspended solids

There is limited information available in literature specifically addressing the possible impact of particulate zeolite to the sedimentation behaviour of suspended solids (SS) and, as a consequence, to the benthic community. However, investigations into the sedimentation behaviour of zeolites in waste water and further findings from previous studies into the environmental fate and effects of zeolite A (Umweltbundesamt, 1979) allow to draw some conclusions on this issue.
An investigation by Carrondo et al. (1981) [26] showed that the presence of zeolites (30 mg/L) does only minimally reduce the SS removal in sewage. Hence, zeolite has no significant effect on the removal of SS by sedimentation at environmentally relevant conditions.
Furthermore, it has to be considered that detergent-based zeolites represent, in contrast to most natural inorganic particles like loam, clay, gravel, sand etc., a monodisperse material with a narrow particle size distribution and a defined density. These properties lead to a relatively homogenous transportation and sedimentation behaviour allowing to define a zeolite particle size which guarantees that this material remains in suspension above a certain flow velocity. Accordingly, comprehensive laboratory experiments and field trials showed that only a very small fraction of zeolites is removed from the sewage by deposition, i.e. the zeolite-based depositions were minor and temporary even in horizontal sewage pipes of household and municipal sewerage systems (Kurzendörfer et al., 1997).
Taking the results from the mentioned lab and field measurements on the sedimentation behaviour of zeolites into account and considering the fact that only a small percentage of this material ($\leq$ 10%) will reach receiving waters it can be concluded that, for qualitative and quantitative reasons, the sedimentation of zeolites entering receiving waters may only have a very low effect on the sediment structure of water bodies. Given the less pronounced

sedimentation behaviour of zeolites compared to natural suspended solids, there is no reason to assume that this material has a significant impact to benthic organisms.

4.5 Discussion and Conclusions

Environmental risk assessments were conducted with the default values of EUSES 1.0 as well as with the HERA detergent scenario. Both scenarios do not indicate a risk for any of the environmental compartments, i.e. water, sediment, soil and and sewage treatment plant (STP) (RCR < 1). In contrast to the 1st version of the HERA Zeolite A risk assessment, a risk quotient < 1 has also been established for the local soil compartment due to recently generated plant toxicity data of a high reliability. The previously obtained RCR >1 was a consequence of the design of the applied standard test which did not examine test concentrations higher than 1000 mg/kg. Now, the new test data have provided a more realistic NOEC which is higher by a factor of 60.

Based on studies into the weathering of Zeolite A in natural waters by hydrolysis, forming natural alumosilicates (Cook et al., 1982 [27]) it can be anticipated that synthetic zeolites reaching the aquatic and terrestrial compartments will ultimately turn into natural constituents of waters, sediments and soils. These facts combined with the favourable outcome of the present environmental risk assessment provide a sound basis for the conclusion that the use of zeolite A in detergent products does not pose a risk to the environment.

5 Human Health Assessment

5.1 Consumer Exposure

5.1.1 Product Types

Zeolite A (sodium aluminium silicate) is widespread used in laundry detergents. In products it can be found in laundry regular and compact powder as well as in laundry tablets. Typical concentrations range between ca. 20% and ca. 34%. Sodium aluminium silicates are used in detergents to decrease the water hardness by exchanging Ca-ions for Na-ions.

5.1.2 Consumer Contact Scenarios

As relevant consumer contact scenarios the direct and indirect skin contact, inhalatory route, oral via drinking water and accidental uptake of sodium aluminium silicates were identified and assessed.

5.1.3 Consumer Exposure Estimates

There is a consolidated overview concerning habits and uses of detergents and surface cleaners in Western Europe issued by AISE [28]. This list reflects the consumer`s use of detergents in g/cup, tasks/week, duration of task and other uses of products and is relevant data for the calculation and reflection about consumer exposure in the following.

5.1.3.1 Direct skin contact via hand washed laundry

Sodium aluminium silicates under alkaline conditions are nearly insoluble (< 1 g/l). The contact time with sodium aluminium silicates in the course of handwashing is very short (approx. 15 min) and the percutaneous absorption of ionic substances has also been reported to be very low (SCHAEFER and REDELMEIER, 1996 [29]). Therefore, it can be assumed that the amount of sodium aluminium silicates systemically available via percutaneous absorption, if any, is quite low.
The following worst case should address this scenario:

- concentration of laundry detergent in handwashing is approx.1 % (10000 mg/l or 10 mg/ml).

- highest concentration of sodium aluminium silicates in laundry detergents amounts to 34.2%; 3420 mg/l or 3.4 mg/ml.

- highest amount of sodium aluminium silicates available for percutaneous absorption (worst case conditions): 1000 mg/l or 1 mg/ml of sodium aluminium silicates (taking into account the low solubility of sodium aluminium silicates)

- immersion of hands into solution would expose about 840 cm² (TGD, Part I, Annex VI [30]).

- assuming a film thickness of 100 µm (0.1 mm or 0.01 cm) (Lally, Ch., 2001 [31]) on the hands and a percutaneous absorption of 1 % for ionic substances in 24 hr exposure time, the following amount of sodium aluminium silicate absorbed via skin can be calculated:

840 cm² x 0,01 cm x 0.01 (fraction absorbed) x 1 mg/ml (cm³) =
0.084 mg sodium aluminium silicates absorbed in 24 hours

In 15 min contact time a smaller amount of absorbed substance can be expected, for the sake of simplicity and as it can be assumed that the rate of percutaneous absorption is not linear in 24 hours and is possibly maximal in the first hour, 0.084 mg is used in the assessment resulting in an estimated systemic dose of (60 kg BW assumed):

$Exp_{sys\ (direct\ skin\ contact)}$ < 1.4 µg/kg BW /day

5.1.3.2 Direct skin contact via laundry tablets

Contact time is low and area of contact with skin is so small that the amount absorbed percutaneously is considered insignificant.

5.1.3.3 Direct skin contact via pretreatment of clothes

Direct skin contact with Zeolite A is possible when clothing stains are being removed by spot-treatment with a detergent paste. As only the skin surface area of the hands is exposed and the treatment time only very short (< 1 min), it will not contribute significantly to the total exposure to sodium aluminium silicate.

5.1.3.4 Indirect skin contact via wearing clothes

Residues of components of laundry detergents may remain on textiles after washing and could come in contact with the skin via transfer from textile to skin. As explained above sodium aluminium silicate is nearly insoluble and the substance is deposited in solid form. Therefore, as a first rough estimation, the amount of sodium aluminium silicate percutaneously absorbed via this route should be insignificant.
That only minor amounts of sodium aluminium silicate could be percutaneously absorbed demonstrates the following calculation assuming a worst case scenario:

The HERA Guidance Document (08/2000) recommends an algorithm for the calculation of dermal contact to household cleaning products:

$$\mathbf{Exp_{sys} = F_1 \times C` \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW} \quad [mg/kg\ BW/day]$$

F_1 percentage (%) weight fraction of substance in product
C` product load in [mg/cm²]
S_{der} surface area of exposed skin in [cm²]
n product use frequency in number [events/day]
F_2 percentage (%) weight fraction transferred from medium to skin
F_3 percentage (%) weight fraction remaining on skin
F_4 percentage (%) weight fraction absorbed via skin
BW body weight in [kg]

Determination of C` ("Product applied to skin via fabric wash (hand, machine) and wear"):

$$\mathbf{C`} = M \times F` \times FD / w_l \ [mg/cm^2]$$

M amount of undiluted product used in [mg]
F` percentage (%) weight fraction of substances deposited on fabric
FD fabric density in [mg/cm²]
w_l total weight (of fabric) in [mg]

According to these algorithms cited above the following calculations were done:

1.) Determination of C`:
M 68400 [mg] (is equivalent to 34.2% [32] Zeolite in 200 g/cup maximum)
F` 5 [%] = 0.05 (worst case assumption !)
FD 10 [mg/cm²] [33]
w_l 1000000 [mg] (estimated)

C`= 0.0342 [mg/cm²]

Remark on the value chosen for F´: A publication on the relevance of detergents residues mentioned values for deposits of zeolites after washing (MATTHIES et al. –1990 [34]). These values were dependent on the washing machine used, the composition of the detergent, and type of textile. Values ranged from 0.1 % to 3.6 % zeolites per kg textile. However, the analytical methods used have not been described and a high variability has been observed. Therefore, the results of this publication are considered as not appropriate for this exposure assessment. To cover this exposure scenario, a worst case value of 5 % has been chosen. It has to be kept in mind that the real value is probably much lower than 5 %.

2.) Calculation of systemic exposure:

F_1 1 (Zeolite fraction already calculated in 1.))
C` 0.0342 [mg/cm²]
S_{der} 19000 [cm²] (average value of literature data [35,36])
n 1 [event/day]
F_2 10 [%] = 0.1 (worst case assumption !)
F_3 100 [%] = 1 (worst case assumption !)
F_4 1 [% bioavailability] = 0.01
BW 60 [kg]

$Exp_{sys\ (indirect\ skin\ contact)}$ = 0.01083 [mg/kg BW/day] = **10.83 µg/kg BW/day**

5.1.3.5 Inhalation of detergent dust during washing processes

According to van de Plassche et al. (1998) [37] studies indicate an average exposure of about 0.27 µg dust per cup of product used for machine laundering, of which up to 34.2 % or 0.09 µg/use is sodium aluminium silicate. Even if the whole amount of dust is inhaled during machine loading the amount does not contribute significantly to the total exposure of sodium aluminium silicate.

5.1.3.6 Oral route via drinking water containing sodium aluminium silicates

No analytical method and, hence, no measured concentration data of sodium aluminium silicates is available. According to Roland (1979) [38] an elimination of > 90 % of sodium aluminium silicate during the process of preparation of drinking water was estimated. In the course of the HERA environmental risk assessment of sodium aluminium silicates a $PEC_{regional}$ of 1.18 mg/l was calculated resulting in a concentration of 118 µg sodium aluminium silicates/l in drinking water (90 % removal) under the (worst case) assumption that only surface water is used for processing.

Taking into account the uptake of 2 l drinking water per day and a bioavailability of 12 % (BENKE AND OSBORNE, 1979) for sodium aluminium silicates the following dose can be calculated:

$$\mathbf{Exp_{sys\ (oral\ route)}} = 118 \times 2 \times 0.12 \times 1/60 = \mathbf{0.472\ \mu g/kg\ BW\ and\ day}$$

This is a worst case scenario with the assumption that no ground water contributes to drinking water. In this assessment a value of 0.5 µg/kg BW/day is used.

5.1.3.7 Accidental or intentional overexposure

Accidental or intentional overexposure to sodium aluminium silicates may occur via laundry detergents. As this product may contain up to 34.2 % of sodium aluminium silicates this source of exposure has to be addressed.

No fatal cases arising from oral uptake of sodium aluminium silicate are known to us. The accidental or intentional overexposure to sodium aluminium silicate directly is not considered a likely occurrence for consumers, but it may occur via laundry detergents. The German Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV, 1999 [39]) published recently a report on products involved in poisoning cases. No fatal case of poisoning with detergents was reported in this report. Detergent products were not mentioned as dangerous products with a high incidence of poisoning.

Accidental spillage may cause eye contact of sodium aluminium silicate. Therefore, the eye irritation potential has to be considered in the context of accidental exposure.

5.2 Hazard Assessment

5.2.1 Summary of the available toxicological data

5.2.1.1 Acute Toxicity

5.2.1.1.1 Acute Oral Toxicity

The acute oral toxicity of sodium aluminium silicates was investigated in 9 studies with rats (DEGUSSA AG, 1978 [40], GLOXHUBER ET AL., 1983 , GAYNOR AND KLUSMAN, 1973 [41], THOMAS AND BALLANTYNE, 1992 [42], MOORE, 1974 [43], MOULTON, 1974 [44], DEGUSSA AG, 1988 A [45], LITTON BIONETICS INC., 1974 [46], J. M. HUBER CORP., 1973), one mouse study (HENKEL, TBD 780104 – 1978 [47]) and one study with dogs (STURM, 1973 [48]). The administered doses ranged from 5000 mg/kg BW up to 31800 mg/kg BW in the rat. No mortality was observed at any dose level. In the mouse study conducted at 10000 mg/kg BW and in the dog study with 1000 mg/kg BW mortality was also not observed.
Two rat studies have been performed according to GLP (DEGUSSA AG, 1990 A [49], DEGUSSA AG, 1990 D [50]) with a mixture of sodium and potassium aluminium silicates. In these studies 5110 mg/kg BW were administered. Mortality was not observed.
Dose finding studies for the in vivo evaluation of genotoxicity of sodium aluminium silicates were conducted in rats (LITTON BIONETICS INC., 1974 [39]). One study resulted in an LD50 value of > 5000 mg/kg, the other resulted in an LD50 value of 1050 mg/kg. The same test compound was used in both studies and the same laboratory has performed the studies. The authors have not discussed the conflicting results. Retrospectively, an explanation is not possible on the basis of the available information, especially since a subsequent 5-day administration of the test compound in rats was conducted with 5000 mg/kg/day. No signs of toxicity or abnormal behaviour were observed. Hence, the reported LD50 value of 1050 mg/kg is regarded as not reliable and will not be used in this risk assessment.

Conclusion

Due to the lack of acute toxicity it was not possible to determine an LD50-value in the studies conducted. The acute oral toxicity of sodium aluminium silicates is considered as very low.

5.2.1.1.2 Acute Inhalation Toxicity

The acute inhalation toxicity was investigated in two rat studies with whole body exposure. In one study the animals were exposed to aerosols of sodium aluminium silicates up to 205 mg/l for 1h (ULRICH, 747-132 – 1974 [51]). No adverse effects were noted. However, details about the method and air concentration monitoring are not available. In another study rats were exposed to up to 0.14 mg/l for 4 h (ULRICH, 747-147A – 1975 [52]). The results of this study with the selected very low concentrations do not contribute useful information for a hazard assessment.
The results of an acute toxicity study using intratracheal injection of up to 400 mg/kg BW in a constant volume of 1-ml tap water (Ulrich, 747-147B – 1975 [53]) are not regarded as useful information for this risk assessment due to the non-physiological application of the test compound.

Conclusion

The quality of the data available on the acute inhalation toxicity of sodium aluminium silicates is rated as not reliable. The results of the long-term inhalation studies discussed below provide more reliable data for assessment of inhalation risks.

5.2.1.1.3 Acute Dermal Toxicity

The acute dermal toxicity of sodium aluminium silicates was investigated in three rabbit studies (GLOXHUBER ET AL., 1983 [54], FRANK AND NIXON, A.6 – 1973 [55], J. M. HUBER CORP., 1978 A [56]). The doses applied ranged from 2000 to 5000 mg/kg BW. No mortality or other adverse effects have been observed.

Conclusion

The quality of the data has to be rated as reliable with restrictions. However, the data on acute dermal toxicity are in agreement with the results of the acute oral toxicity studies and show the absence of toxic effects in the dose range applied.

5.2.1.2 Skin Irritation

Eight skin irritation studies were conducted with rabbits (DEGUSSA AG, 1988 B [57], FRANCK AND NIXON, A.5 – 1973 , DEGUSSA AG, 1990 B [58], HENKEL, TBD 890429 – 1989 [54], HENKEL, TBD 890435 – 1989 [59], HENKEL, TBD 900328 – 1990 [56], J. M. HUBER CORP., 1973 [60], DEGUSSA AG, 1990 E [61]). The tests performed with undiluted substances according to the OECD Guideline 404 and according to GLP (DEGUSSA AG, 1990 B [50], DEGUSSA AG, 1990E [53]) using a mixture of sodium and potassium aluminium silicate as test compound did not show irritating effects. In another test according to OECD Guideline 404 but not according to GLP (DEGUSSA AG, 1988 B [49]) sodium aluminium silicate was also not irritating. Using other sodium aluminium silicates the same result was observed in studies conducted in 1973 (J. M. HUBER CORP., 1973 [52]), however only limited information about the methods are given.

Slightly irritating effects with 20 % sodium aluminium silicate were observed in another study conducted in 1973 using sodium aluminium silicate (FRANK AND NIXON, A.5 – 1973 [62]).

In contrast to these results, one study conducted with a undiluted moisturised “masterbatch” of sodium aluminium silicate according to OECD Guideline 404 and according to GLP (HENKEL, TBD 890429 – 1989 [63]) showed irritating effects. The authors explain the discrepancy to the results of the other studies with residues of sodium oxide in the test compound (HENKEL, TBD 900328 – 1990 [64]). Sodium oxide is probably converted to sodium hydroxide by the moisture present in the test compound.

In a poorly documented human patch test with 50 % sodium aluminium silicate in 8 volunteers no irritating effects were observed (WERTZ, 1978 [65]).

Conclusion

Reliable animal studies according to OECD with a mixture of sodium and potassium aluminium silicate as test compound did not show irritating effects. Less reliable studies using sodium aluminium silicates did show the same results. The only other study that reported irritation is not regarded as relevant for this risk assessment due to the contamination with sodium oxide. Sodium aluminium silicates are considered as not irritating to the skin.

5.2.1.3 Eye Irritation

Nine eye irritation studies were conducted with rabbits and one study with monkeys. Two studies were performed according to OECD Guideline 405 and according to GLP (DEGUSSA AG, 1990 F [66], DEGUSSA AG, 1990 C [67]) using a mixture of sodium and potassium aluminium silicate as test compound. These studies did not show an irritating potential of the test compound to rabbit eyes. Three less reliable other studies (THOMAS AND BALLANTYNE, 1992 [34], J. M. HUBER CORP., 1973 [52], J. M. HUBER CORP., 1978 B [68]) were conducted with rabbits using sodium aluminium silicates as 10%, 50% and 100% active substance, respectively. These studies did also not show an irritating potential.
Undiluted sodium aluminium silicate was used in another study according to OECD Guideline 405 but not according to GLP (DEGUSSA AG, 1988 C [69]). This study revealed a slight irritating potential of the test compound.
The same result was obtained in another less well documented study with undiluted test substance (BARNETT AND NIXON, 1973 [70]).
The only study reporting an irritation potential with 50% aqueous slurry of sodium aluminium silicates (J. M. HUBER CORP., 1973 [52]) is regarded as not reliable due to lack of documentation.
Instillation of 10 mg of sodium aluminium silicate powder into the rabbit eye caused a reaction due to the mechanical friction of the substance (GLOXHUBER ET AL., 1983 [47]).
Undiluted sodium aluminium silicate was used in a monkey study using 35 mg of test compound in 0.1 ml (SULLIVAN, 1974 [71]). The result of this study was slight irritation in the monkey eye.

Conclusion

Sodium aluminium silicates are slightly irritating to non-irritating to eyes. The powder of the substance may cause reactions due to mechanical friction.

5.2.1.4 Sensitisation

One study according to the Magnusson-Kligman test protocol in guinea pigs using sodium aluminium silicate did not reveal a skin sensitising potential (GLOXHUBER ET AL., 1983). The same result was reported in a study conducted in guinea pigs according to the Bühler test protocol (YOUNG AND DOYLE, 1973 [72]). A human repeated patch test with 71 volunteers treated with a 5 % aqueous slurry 10 times over a period of three weeks and challenged after a rest period of 14 days also failed to show any signs of a sensitising potential (STOTTS, 1978 [73]).

Conclusion

The guinea pig studies conducted with regard to skin sensitisation were not performed according to standard OECD protocols or GLP. The results demonstrated the absence of a sensitising potential for sodium aluminium silicate. This is corroborated by the result of a human patch test. In summary, sodium aluminium silicate is considered as not sensitising by skin contact.
Test data with regard to sensitisation by inhalation are not available. There is no evidence from human experience, however, that sodium aluminium silicates can induce respiratory hypersensitivity (see section 5.2.1.11). The chemical structure of the compound does also not indicate any potential.

5.2.1.5 Repeated Dose Toxicity

5.2.1.5.1 Oral Administration

Sodium aluminium silicate (not further specified) was administered for 14 consecutive days to groups of male and female Fischer-344 rats (5 animals per group) in concentrations of 0, 0.625 %, 1.25 %, 2.5 %, 5 % and 10 % (w/w) in the diet (HENKEL , R 0100197 – 1979 [74]). Based on body weight, food consumption and gross necropsy findings no marked signs of toxicity were observed.
Sodium aluminium silicate (not further specified) was administered for 14 consecutive days to groups of male and female B6C3F1 mice (5 animals per group in concentrations of 0, 0.625%, 1.25 %, 2.5 %, 5 % and 10 % (w/w) in the diet (HENKEL, R 0100196 – 1979 [75]). Based on body weight, food consumption and gross necropsy findings no marked signs of toxicity were observed.
Sodium aluminium silicate (Zeolite A) was administered for 90 consecutive days to groups of male and female Wistar rats (20 animals in each group) in concentrations of 0, 1000 ppm, 5000 ppm, and 10000 ppm (w/w) in the diet (HENKEL, TBD 770012 – 1977 [76]). Only in the high dose group substance related effects were observed regarding function and histopathology of kidneys and bladder (urinary calculi in the bladder). The histological examination showed a hyperplastic reaction of the transitional epithelium in rats with calculi. In this study the influence of the oral ingestion of the test compound on the copper content in the livers was also investigated. No significant difference between control animals and high dose animals was reported. The cobalt content in livers, as well as the zinc, aluminium and silicate content in the kidneys was also investigated. In the kidneys of male high dose animals the silicate content was significantly different from control rats. The NOAEL was determined to be 5000 ppm, which can be estimated to equal approximately 250 to 300 mg/kg/day.
Sodium aluminium silicate (not further specified) was administered for 163-days to groups of male and female COX-SD rats (20 animals per group) in concentrations of 0, 0,5 %, 1,0 %, 2,0 % (w/w) in the diet (HENKEL, TBD EX 0143 – 1975 [77]). Interim sacrifices were performed at 28 and 91 days. The 28-day sacrifice did not reveal any indication of test

compound related toxicity. At the 91-day level three animals showed some form of urinary bladder difficulties, one had bladder stones; two others which died on day 84 and 85, respectively, showed evidence of bladder toxicity. During the extension of the study to 163 days, the bladder stones appeared at the intermediate and low dose (one animal at each dose) and more particularly at the high dose. A NOAEL can not be deduced from this study.
The potential urogenital toxic effect was examined in a follow-up study in three groups of 40 COX-SD rats each fed a diet with 0 %, 0.125 % or 2 % (corresponding to approx. 69 and 110 mg/kg BW, respectively) of a sodium aluminium silicate (Zeolite A-Type) for 160 or 200 days (HENKEL , TBD EX 0127 – 1976 [78]). In this study urinalysis did not reveal significant differences between treated and control groups. In the urine collections of treated rats white crystalline material was visible. A significant increase in the incidence of bladder and kidney stones was observed in the high dose group. Other than this there was no evidence of an alteration of urine parameters or kidney function. Pathological examination found histologic changes of the kidneys and urinary bladders in the 2 % dose group but not in the 0.125 % dose group. In the kidneys, the microscopic alterations were characterised by an increase in the severity of interstitial nephritis, regenerative epithelium and pelvic epithelial hyperplasia. Also, a non-staining crystalline material was frequently present in the pelvis of the kidneys of the high dose rats. In the urinary bladder, an increase in the incidence and severity of transitional epithelial hyperplasia was associated with the administration of the high dose. Compound related microscopic alterations were not observed in animals of the low dose groups. A NOAEL of 0.125 % (approx. 69 mg/kg BW/day) is deduced from this study.
In a 24-week oral toxicity study in Long-Evans rats (HENKEL , TBD EX 0129 – 1976 [79], TBD EX 0137 – 1976 [80]) groups of 10 animals per sex were fed a diet with 0, 0.125, 0.5 or 2.0 % of sodium aluminium silicate (Zeolite A-type). Evaluation of mortality, physical appearance, feed efficiency, body weights, organ weights and organ/body weight ratios did not reveal evidence of any toxic effects at any of the dose levels. In the male and female rats of the intermediate and high dose groups, pathology revealed compound related microscopic alterations in the kidneys. The low dose diet did not result in any compound-related microscopic changes. The NOAEL in this study can therefore considered to be 0.125 % in the diet (approx. 69 mg/kg BW/day).
In a oral chronic toxicity study (HENKEL, SAS 7900017 – 1979 [81], HENKEL, SAS 7900016 – 1979 [82]) male and female Wistar rats were fed 0, 10, 100 and 1000 ppm of sodium aluminium silicate of the Zeolite A-type (approx. equivalent to 0.6, 6.0 or 60 mg/kg/day) in the diet for 104 weeks (50 animals per dose group and sex). Mortality, feed consumption, body weights and water consumption were monitored. Ophthalmologic, blood, urinary and biochemical parameters were evaluated. After 104 weeks all animals were sacrificed. All organs were macroscopically as well as microscopically evaluated. No treatment-related signs of toxicity were observed and no indication of a chronic toxic response in any of the evaluated parameters was noted. No significant treatment-related effects were observed in any of the organs examined histopathologically. No treatment-related effect on the types or incidences of any neoplastic changes was observed. The NOEL determined was 60 mg/kg/BW/day in this well documented study.

Conclusion

Sodium aluminium silicates did not cause any gross signs of adverse systemic effects after oral ingestion. The only adverse effects related to the test compounds were observed with regard to the kidney and urinary bladder. These effects have been consistently reported in the repeated dose toxicity studies. One study was especially designed to investigate the effects of sodium aluminium silicates on the urogenital tract (HENKEL, TBD EX 0127 – 1976 [70]). The findings of this well documented study did indicate microscopic changes in kidney and

bladder associated with crystalline material in the kidney and excretion of crystalline material in the urine as the only functional difference in urinary parameters measured. These findings may be explained by absorption of small amounts of silicon-compounds from the gastrointestinal tract after dissociation of the sodium aluminium silicate to sodium, aluminium and SiO4 (see 5.3.1.10). The concentration of the SiO4 in the kidney, the subsequent formation of crystalline material and the excretion of this material via the urine may cause mechanical damage to the kidney and bladder associated with concurrent epithelial hyperplasia in these organs. The NOAEL for these effects was determined as 69 mg/kg BW/day in a 200-days study. A chronic study of 104-weeks duration did not show any toxic effects at the highest dose (60 mg/kg BW/day) and corroborated the NOAEL for rats observed in the 200-day study.
For risk assessment purposes, 60 mg/kg BW/day is considered as the relevant NOEL for chronic oral ingestion in the rat.

5.2.1.5.2 Inhalation

Male adult Wistar rats inhaled sodium aluminium silicate dust (HENKEL, TBD 770048 – 1977 [83]) at 0 or 20 mg/m³ on Monday, Wednesday and Friday for 5 hours per day for a total of 13 inhalation applications (24 animals per dose group). No signs of toxicity or macroscopic changes in organs were observed. Histopathologic examinations were not performed. Analysis of silicon content in the lungs revealed a small but significant increase of silica in the 20 mg/m³ group compared to the control group (222 ppm vs. 142 ppm).
Thirty male rats and five guinea pigs were exposed for 5 hrs/day on 5 days/wk over a period of 11 weeks to a mean sodium aluminium silicate dust concentration of 2000 mg/m³ (GLOXHUBER ET AL., 1983 [47]). The number of control animals is not reported. The dust concentration was checked three times a day and a range of 1000 – 3000 mg/m³ was determined. All groups were affected by a respiratory infection and showed signs of pneumonitis. The study is regarded as not reliable due to poor documentation and reported illness of the experimental animals.
Male and female Wistar rats were exposed to 0 and 20 mg/m³ sodium aluminium silicate dust (HENKEL, TBD 780088 – 1978 [84], HENKEL, TBD 790062 – 1979 [85], HENKEL, TBD 790133 – 1979 [85]) for three days a week (Monday, Wednesday, Friday) 5 hrs/day over a period of 22 months (30 animals per dose group and sex). After one year, 25 animals per dose and sex were added to the groups. 80 % of the particle size distribution was reported to be 1-6 µm in diameter. The study was aborted after 22 months since the rats of all groups displayed chronic respiratory disease. The examination of the animals after termination of the study did not indicate any specific reaction of the animals to the test substance in the respiratory tract. 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 seen also in the mediastinal lymph nodes. No connective tissue reaction or other reactions were observed around these deposits. No indication of degeneration or tumorigenic response other than observed in historical controls was seen. The study is regarded as valid with restrictions due to the chronic respiratory tract disease of the test animals. However, the lack of an increase in tumour incidences and the lack of a silicogen or fibrinogen reaction after long-term inhalation have to be noted.
Male and female Syrian hamsters were exposed to 0 and 20 mg/m³ sodium aluminium silicate dust (HENKEL, R 9500444 – 1978 [86], HENKEL, TBD 770056 – 1977 [84], HENKEL, TBD EX 0107 – 1977 [87]) for three days a week (Monday, Wednesday, Friday) 5 hrs/day over a period of 12 months (30 animals per dose group and sex). 80 % of the particle size distribution was reported to be 1- 6 µm in diameter. The hamster study was terminated after 12 months following a considerable incidence of deaths due to a specific infection. In the

treated hamsters, macrophages containing accumulations of foreign material were found, mainly in the alveoli, but no signs of inflammation or connective tissue reaction were seen in the interstitial or alveolar region. The study is regarded as valid with restrictions due to the chronic respiratory tract disease of the test animals. However, the lack of an increase in tumour incidence as well as the lack of silicone or fibrinogen reaction after long-term inhalation has to be noted.

In a well documented study with cynomolgus monkeys (Macaca fascicularis), groups of 3 females and 3 males each were exposed to 0, 1, 6 and 50 mg/m³ sodium aluminium silicate dust (Zeolite A-type) for 6 hours per day, 5 days a week for a period of 6, 12 or 24 months (HENKEL, TBD EX 0113 – 1979 [86], HENKEL, TBD EX 0130 – 1977 [87], HENKEL, TBD EX 0142 – 1976 [88]). As a positive control quartz dust was used in an exposure concentration of 50 mg/m³. The exposure of the animals of the positive control and of the high exposure group was discontinued after 55 weeks. Chamber atmospheres were sampled daily during exposures to determine gravimetric dust concentrations and particle size distributions were obtained at regular intervals throughout the study. The mean measured concentrations were 1.17, 6.14 and 44.37 mg/m³ for the 6-months study, 1.25, 6.28, and 53.29 mg/m³ for the 12-months study, and 1.29, 6.04 and 48.95 mg/m³ for the 24-months study, respectively. Group mean values for mass median diameter were 2.79, 3.39, and 3.44 µm with ranges of geometric standard deviations of 1.43 – 3.27, 1.40 – 1.76, 1.34 – 1.91, respectively.

The compound in any of the exposure groups did not affect pulmonary function, body weight, haematology, serum chemistry, urinalysis, ophthalmic parameters, or organ/body weight ratios. There were no compound-induced histomorphological changes seen neither in the upper airways nor in any non-respiratory tract organs examined.

The exposure to sodium aluminium silicate did not produce evidence of progressive pulmonary fibrosis at the concentrations tested. In contrast, exposure to quartz dust, the positive control, produced a progressive diffuse granulomatous inflammation with progressive pulmonary fibrosis after 29 and 55 weeks of exposure.

Exposure to the target concentration of 50 mg/m³ sodium aluminium silicate dust produced some focal nonsuppurative inflammatory reactions of the lungs after 29 and 55 weeks of exposure which were not completely resolved in individual monkeys after a 90-day recovery period (sporadic inflammatory changes in one monkey after 29-weeks of exposure and little change other than macrophage accumulation after the last exposure at 55 week; however, three months after exposure one of three monkeys had multifocal to diffuse nonsuppurative bronchiolitis and alveolitis; the other two monkeys exposed to 55 weeks and held three months did not have any compound-related inflammatory response to the macrophage accumulations).

Exposure to the target concentration of 6 mg/m³ sodium aluminium silicate dust produced free alveolar and septal wall macrophages after 26 weeks. Similar macrophage accumulations were present after 52 and 104 weeks. They were accompanied by sporadic nonsuppurative bronchiolitis and alveolitis in the lungs of three of the six monkeys exposed for 52 weeks and the one monkey exposed for 104 weeks. Primarily in lobes of the lungs there was residual damage from the lung parasite Pneumonyssus sp. (lung mites) or from kaolin (a component of a therapeutic compound utilised to control diarrhoea). These changes had not completely reversed after a 90-day recovery period in two of four monkeys. However, no compound-related inflammatory reaction was observed after the 90-day recovery period in the two other monkeys.

Exposure to the target concentration of 1mg/m³ sodium aluminium silicate dust produced free alveolar and septal wall macrophage accumulations after 26, 52 and 104 weeks. Sporadic areas of nonsuppurative bronchiolitis and alveolitis were present in the lungs of three of the four monkeys. Following the recovery period of 90 days, primarily macrophage

accumulations without any inflammatory response were observed. The sporadic non-suppurative inflammatory reactions, which occurred in individual monkeys after 104 weeks were not evident after the 90-day recovery period.

Conclusion

Long-term inhalation studies with sodium aluminium silicate dust have been performed in the rat, the guinea pig, the hamster and the monkey. The available information on the mean diameter of the dust particles indicates that a large fraction of the generated dust has reached the lungs in these studies. Despite a number of deficiencies in the quality, the studies failed to produce any evidence of systemic toxicity, fibrosis or an increase in the incidence of neoplastic changes.
The monkey study is the best-documented inhalation study, which is also most relevant to the human risk assessment. With regard to local effects in the respiratory tract, the upper airways were not affected by the inhalation exposure. The histopathological effects observed in the lungs were macrophage accumulations accompanied by sporadic nonsuppurative bronchiolitis and alveolitis. No evidence of progressive pulmonary fibrosis was observed. Hence, sodium aluminium silicate dust is regarded as a poorly soluble non-fibrogenic dust with regard to human inhalation risk. Dose-related nonsuppurative inflammatory reactions were observed in animals of all dose groups. These reaction had diminished in severity but had not fully disappeared in the mid and high dose group. In the 1 mg/m³ dose group, these effects were not evident after the 90-day recovery period. The LOAEL for inhalation is 1 mg/m³.

5.2.1.5.3 Dermal Administration

No studies were identified describing the results of repeated dermal administration of sodium aluminium silicates.

5.2.1.6 Genetic Toxicity

5.2.1.6.1 In Vitro

Two Ames tests were performed with sodium aluminium silicate in various Salmonella typhimurium strains (TA 98, TA 100, 1535, TA 1537, TA 1538) with and without metabolic activation. The test compound was not mutagenic in these studies. One test was conducted according to OECD Guidelines (ZEIGER ET AL., 1987 [88]) but is poorly documented. The second negative study is well-documented (PRIVAL ET AL., 1991 [82], SIMMON AND ECKFORD, 1989 [89]). Another study used Salmonella typhimurium strains 1530 and G 46 as in vitro controls to a host mediated assay (LITTON BIONETICS INC., 1974 [39]). The poorly documented study did not report any mutagenic potential.
A reverse mutation assay was conducted in Escherichia coli WP2 with sodium aluminium silicate with and without metabolic activation (PRIVAL ET AL., 1991 [90], SIMMON AND ECKFORD, 1989 [81]). No mutagenic potential was detected in this well documented study.
One study used Saccharomyces cerevisiae as in vitro control to a host mediated assay (LITTON BIONETICS INC., 1974 [39]). The poorly documented study did not report a mutagenic potential.
A cytogenetic assay used human embryonic lung cell cultures (W 38), which were cultivated in the presence and absence of different concentrations of sodium aluminium silicate (LITTON BIONETICS INC., 1974 [39]). No clastogenic potential was observed in this poorly documented study.

The result of a DNA-repair assay was reported to be negative in an abstract (FASEB, 1977[91]).

Conclusion

Although the in vitro assays were not performed according to current Guidelines and were partly poorly documented there is no indication of genetic toxicity for sodium aluminium silicates in in vitro test systems.

5.2.1.6.2 In Vivo

Male Albino rats (10 – 12 weeks old, 15 animals per group) were used in two set of experiments with differing dosages for the evaluation of cytogenic effects of sodium aluminium silicate in vivo. In both sets, a single dosing as well as repeated dosing (5 consecutive days) was employed (LITTON BIONETICS INC., 1974 [39]). Triethylene melamine was used as positive control and saline was used as negative control. In the first set 4.25, 42.5 and 425 mg/kg BW were administered orally by intubation. In the second set 5000 mg/kg BW was administered. Observation time points were 6, 24 and 48 hrs after dosing. Metaphase chromosomes spreads were prepared from the bone marrow and scored for chromosomal aberrations. Neither the variety nor the number of chromosomal aberrations in bone marrow from dosed animals differed significantly from the negative controls. A positive response was observed in bone marrow from animals treated with triethylene melamine. The test compound was considered as non-mutagenic as measured by this assay.
Male albino rats (10 – 12 weeks old, 10 animals per group) were used in two sets of experiments with differing dosages of sodium aluminium silicate in order to evaluate chromosomal aberrations of germ cells in the dominant lethal assay. In both sets, a single dosing as well as repeated dosing (5 consecutive days) was employed (LITTON BIONETICS INC., 1974 [39]). Triethylene melamine was used as positive control and saline was used as negative control. In the first set 4.25, 42.5 and 425 mg/kg BW were administered orally by intubation. In the second set 5000 mg/kg BW was administered. Following treatment, the

males sequentially were mated to two females per week for eight weeks (seven weeks in the subacute study). Pregnant females were sacrificed at 14 days after separation from the male. At necropsy, the uterus was examined for early deaths, late foetal deaths and total implantations.
In the acute study of the first set, a significant not dose-dependent decrease in average corpora lutea and preimplantation losses were seen in the experimental groups from mating weeks 4 and 5 when compared to the negative controls, but not when compared to the historical controls. Average resorptions showed significant but not dose dependent increases in the experimental group from mating week 3 in all dose groups when compared to the negative control (zero value), but not when compared to historical controls. In the acute study using 5000 mg/kg BW, no significant differences between the negative control and the dosed animals were observed.
In the subacute study of the first set, significant dose-related increases (intermediate and high dose) in average implantations and corpora lutea were seen in the experimental groups from mating week 4 when compared to the negative control. When compared to the historical controls, the negative as well as the intermediate dose group were significantly different. Significant dose-related increases in average resorptions were seen in the intermediate and high dose groups from mating week 6 when compared to the negative controls. However, no differences were observed when these groups were compared with the historical controls. In the subacute study using 5000 mg/kg BW, a significant increase in preimplantation loss was observed in animals from mating week 1 and 3. This increase was attributed by the authors to a high number of corpora lutea unmatched by implantations in some females and was not regarded as compound related.
The positive control caused significant preimplantation loss and embryo resorption in animals from the first 5 mating weeks.
The authors concluded that the test compound does not induce dominant lethal mutations as measured by this study. They based their conclusion on the fact, that no dose response or time trend patterns were revealed in the assay.
Male ICR mice (10 animals per group) were used in two sets of experiments with differing dosages of sodium aluminium silicate for the evaluation of gene mutations in the host mediated assay using ip injections of Salmonella typhimurium TA 1530 and G 46 as well as Saccharomyces cerevisiae (LITTON BIONETICS INC., 1974 [39]). In both sets, a single dosing as well as repeated dosing (5 consecutive days) was employed. The positive control was run by the acute system only using dimethyl nitrosamine for Salmonella and ethyl methane sulfonate for yeast, respectively. In the first set 4.25, 42.5 and 425 mg/kg BW were administered orally by intubation. In the second set 5000 mg/kg BW was administered. Three hours after administration of the test compound and indicator organism each animal was sacrificed. The indicator organisms were collected from the peritoneal cavity and the number of mutant was counted after plating on minimal agar. The test compound caused no significant increases in mutant or recombinant frequencies in both set of experiments and in all doses used. No indication of genetic activity of the test compound was detected in the host-mediated assay.

Conclusion

The results of the in vivo test systems corroborated the results from the in vitro assays. Sodium aluminium silicate was tested in a cytogenetic assay in rats, a dominant lethal assay in rats, and a host mediated assay in mice. Doses ranged from 4.25 to 5000 mg/kg BW and an acute and subacute dosing regime was employed. All of these tests did not indicate a genetic toxicity of the test compound in vivo.

5.2.1.7 Carcinogenicity

In an oral chronic toxicity study (HENKEL, SAS 7900017 – 1979 , HENKEL, SAS 7900016 – 1979 [74], see section 5.2.1.5.1 for more details) male and female Wistar rats were fed 0, 10, 100 and 1000 ppm of sodium aluminium silicate of the Zeolite A-type (approx. equivalent to 0.6, 6.0 or 60 mg/kg/day) in the diet for 104 weeks (50 animals per dose group and sex). No treatment-related effect on the types or incidences of any neoplastic changes was observed in this study.

Male and female Syrian hamsters were exposed to 0 and 20 mg/m³ sodium aluminium silicate dust (HENKEL, R 9500444 – 1978 [78], HENKEL, TBD 770056 – 1977 [92], HENKEL, TBD EX 0107 – 1977 [79], see section 5.2.1.5.2) for three days a week (Monday, Wednesday, Friday) 5 hrs/day over a period of 12 months (30 animals per dose group and sex). The study is regarded as valid with restrictions due to a chronic respiratory tract disease of the test animals. The study was not designed as carcinogenicity assay according to current guidelines. However, the lack of an increase in tumour incidence after long term inhalation has to be noted.

Male and female Wistar rats were exposed to 0 and 20 mg/m³ sodium aluminium silicate dust (HENKEL, TBD 780088 – 1978 [76], HENKEL, TBD 790062 – 1979 [93], HENKEL, TBD 790133 – 1979 [77], see section 5.2.1.5.2) for three days a week (Monday, Wednesday, Friday) 5 hrs/day over a period of 22 months (30 animals per dose group and sex). The study is regarded as valid with restrictions due to a chronic respiratory tract disease of the test animals. The study was not designed as a carcinogenicity assay according to current guidelines. However, the lack of an increase in tumour incidences after long term inhalation has to be noted.

Cynomolgus monkeys (Macaca fascicularis) were exposed to 0, 1, 6 and 50 mg/m³ sodium aluminium silicate dust (Zeolite A-type) for 6 hours per day, 5 days a week for a period of 6, 12 or 24 months (HENKEL, TBD EX 0113 – 1979 [94], HENKEL, TBD EX 0130 – 1977 [95], HENKEL, TBD EX 0142 – 1976 [96]; see section 5.2.1.5.2). The available information on the mean diameter of the dust particles indicates that a fraction of the generated dust has reached the alveolar region of the lungs in these studies. Although the study was not designed as a carcinogenicity assay no indication of an increase in the incidence of neoplastic changes was observed.

In order to evaluate the silicogenic activity after single adminstration of sodium aluminium silicate (Zeolite A), four studies in experimental animals have been conducted (GLOXHUBER ET AL., 1983).

A single ip administration of 0,5 ml Tyrode' s solution, or 50 mg sodium aluminium silicate dust (mean diameter 9,3 µm) in 0,5 ml Tyrode's solution or 50 mg quartz DQ 12 dust in 0,5 Tyrode's solution was conducted in 40, 70 or 40 male Wistar rats, respectively. The animals were sacrificed after 6, 13 or 18 months and the relevant organs were examined histologically.

A single ip administration of Tyrode' s solution or sodium aluminium silicate dust (mean diameter 9,3 µm) in Tyrode's solution or quartz DQ 12 dust in Tyrode's solution (1, 2.5, 5, 10 and 50 mg/kg BW) was conducted in male Wistar rats. The animals were sacrificed after 3, 6 or 11 months and the relevant organs were examined histologically.

In male mice, 10 mg sodium aluminium silicate and Quartz DQ 12 suspended in 0,2 ml Tyrode's solution were administered ip to groups of 70 and 30 animals, respectively. Control animals received Tyrode's solution only. The animals were sacrificed after 3, 6 or 18 months.

In the fourth study, intratracheal adminstration to 25 male and 25 female Wistar rats of 50 mg sodium aluminium silicate and Quartz DQ 12 in Tyrode's solution was performed after dissection of the of the trachea in anaesthetised animals. The animals were sacrificed after 3, 6, 18 and 24 months and the relevant organs examined microscopically.

In summary, sodium aluminium silicate did not induce silicotic reactions in these tests. A recent IARC evaluation of other studies of similar types, which addressed the potential of mesothelioma induction in experimental animals, corroborates the result described above (IARC, 1997 [97]).

Conclusion

The long-term studies were not performed to current guidelines for carcinogenicity bioassays, but they are assessed as of sufficient quality to demonstrate absence of carcinogenicity. The oral and inhalation long term studies performed did not indicate any potential of sodium aluminium silicate to induce neoplastic lesions. The tests conducted to evaluate the silicogenic activity in experimental animals did also not reveal a potential of sodium aluminium silicate to induce silicotic reactions. This is in line with the cubic structure of the synthetic Zeolite A. A recent IARC evaluation of synthetic Zeolites came to the overall conclusion "cannot be evaluated as to their carcinogenicity in humans" (IARC, 1997 [89]).

5.2.1.8 Toxic to Reproduction

No studies have been identified that investigated the reproductive toxicity of sodium aluminium silicate. However, no indication of toxicity to reproductive organs have been observed in long term studies and no structure activity relationship is known that indicates a concern.

5.2.1.9 Developmental Toxicity / Teratogenicity

Pregnant Charles River rats were treated daily with sodium aluminium silicate (HENKEL, R 0100168 – 1978 [98]) with 0, 74, or 1600 mg/kg BW on gestation days 6 – 15 per gavage (20 animals per dose). The dams were sacrificed on gestation day 20. Conception rates were high and no maternal, embryo or foetal toxicity was noted. No significant differences were observed in the incidence of soft tissue malformations or of skeletal defects in the treated animals relative to the controls. These data show that the test compound was not teratogenic in rats at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity in this well documented study.
Pregnant Wistar rats were treated daily with sodium aluminium silicate (FDRL, 1973 [99]) with 0, 16, 74, 345 or 1600 mg/kg BW on gestation days 6 –15 per gavage. The dams were sacrificed on gestation day 20. The administration of the test compound had no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities seen in either soft or skeletal tissues in the test groups did not differ from the number occurring spontaneously in the control group. These data show that the test compound was not teratogenic in rats at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity. The study is valid with restrictions.
Pregnant CD-1 mice were treated daily with sodium aluminium silicate (FDRL, 1973 [91]) with 0, 16, 74, 345 or 1600 mg/kg BW on gestation days 6 –15 per gavage. The dams were sacrificed on gestation day 17. The administration of the test compound had no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities seen in either soft or skeletal tissues in the test groups did not differ from the number occurring spontaneously in the control group. These data show that the test compound was not teratogenic in mice at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity. The study is valid with restrictions.
Pregnant Dutch rabbits were treated daily with sodium aluminium silicate (FDRL, 1973 [91]) with 0, 16, 74, 345 or 1600 mg/kg BW on gestation days 6 –18 per gavage. The dams were sacrificed on gestation day 29. The administration of the test compound had no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities

seen in either soft or skeletal tissues in the test groups did not differ from the number occurring spontaneously in the control group. These data show that the test compound was not teratogenic in rabbits at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity. The study is valid with restrictions.
Pregnant New Zealand rabbits were treated daily with sodium aluminium silicate (HENKEL, R 0100169 – 1978 [100]) with 0, 74, 345 or 1600 mg/kg BW on gestation days 6 –18 per gavage (20 animals per dose). The dams were sacrificed on gestation day 29. No significant differences were observed in the incidence of soft tissue malformations or of skeletal defects in the treated animals relative to the controls. In addition, no maternal toxicity or mortality was observed that could be attributed to the test compound. These data show that the test compound was not teratogenic in rabbits at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity in this well documented study.
Pregnant Syrian hamsters were treated daily with sodium aluminium silicate (FDRL, 1973 [91]) with 0, 16, 74, 345 or 1600 mg/kg BW on gestation days 6 –10 per gavage. The dams were sacrificed on gestation day 14. The administration of the test compound had no clearly discernible effect on nidation or on maternal or foetal survival. The number of abnormalities seen in either soft or skeletal tissues in the test groups did not differ from the number occurring spontaneously in the control group. These data show that the test compound was not teratogenic in hamster at the dose levels tested. The NOAEL was 1600 mg/kg BW for maternal toxicity and for teratogenicity. The study is valid with restrictions.

Conclusion

Sodium aluminium silicate was evaluated for teratogenicity in rats, mice, rabbits and hamsters. Although these studies were not performed according to current guidelines and not according to GLP, they are partly well documented. The data show that sodium aluminium silicate is not teratogenic in experimental animals. The NOAEL in the studies performed was 1600 mg/kg BW for maternal toxicity and for teratogenicity.

5.2.1.10 Biokinetics

In a poorly documented study (GLOXHUBER ET AL., 1983), five male Wistar rats received an oral dose of 1000 mg/kg sodium aluminium silicate (Zeolite A-type). Urine and faeces were sampled over 24 hours. The results showed that about 1 % of the silicon administered orally was absorbed and eliminated via the kidney. The aluminium balance indicated that the absorption of this component of the sodium aluminium silicate is poor. The majority of the administered Zeolite A was eliminated via the faeces, as was the silica. Analysis of organs for silicon did not indicate an accumulation potential of sodium aluminium silicate after oral administration.

The rate and extension of urinary excretion of silicon and aluminium was determined in group of adult male Sprague-Dawley Cox rats (4 rats/group) after single oral administration of sodium aluminium silicate of the Zeolite A type (BENKE AND OSBORNE, 1979 [101]). The doses were 0, 40, 200 or 1000 mg/kg BW. Urine was collected in periods of 0 – 24, 24 – 48, 48 – 72 and 72 – 96 hours after dosing. Urine was analysed for silicon and aluminium by induction-coupled RF plasma optical emission spectrometry. Rats dosed with Zeolite A excreted urinary silicon in excess of background levels.

The amount excreted within 96 hours after dosing increased with increasing dose showing saturation kinetics: about 200 µg at low dose, about 800 µg at intermediate dose, and about 1400 µg at high dose animals. The authors explain the saturation kinetics by saturation of the acid mediated hydrolysis in the stomach at high doses.

In contrast, the percentage of the dose excreted decreased with increasing dose: 12.1 % at low dose, 11,4 % at intermediate dose, and 3 % at high dose animals type (BENKE AND OSBORNE, 1979). The majority of silicon was excreted during the first 24 hours after dosing and a half life of 6-8 hours was determined.

Urine of rats dosed with Zeolite A did not show any detectable increase in aluminium. The detection limit of the analytical method would have permitted the detection of 0.01 to 0.2 % of the dose. The authors concluded that the excreted silicon species was not the parent compound and proposed that breakdown of Zeolite A occurred in the gastrointestinal tract via acid hydrolysis. From the resulting breakdown products only the silicon species is soluble and absorbable.

Since the half life was not dose dependent and taking into account additional data on other silicates investigated by the authors they concluded that Zeolite A is hydrolysed in the gastrointestinal tract and that the hydrolysis as prerequisite step for absorption is the rate limiting process.

The authors investigated also the particulate or filterable forms of silicon that were produced during the time of maximum excretion in rats dosed with Zeolite A. This investigation was triggered by the assumption that the kidney and bladder toxicity observed for silicon compounds is due to the calculi formed via silicon polymerisation. Whereas the total amount of silicon excreted increased with dose (see above) the particulate silicon was not increased above control levels. The authors concluded that toxic effects in the urinary tract would not result from single high doses of Zeolite A.

Yokoi and Enomoto (1979) [102] studied the excretion of silicic acid in rats orally treated with different preparations of sodium aluminium silicate gels with known distributions of molecular forms of silicic acid. Urinary silicic acid excretion was regarded as corresponding to silicic acid absorption. The authors concluded from the results that in the digestive tract, the various silicic acids formed upon acid hydrolysis are absorbed through the lipoid membrane pore route. This mechanism is common in the permeation of hydrophilic molecules. Orthosilicic acid in particular was absorbed, while polysilicic acid, regardless of solubility, were hardly absorbable. The authors discuss a possible mechanism of formation of renal and urinary calculi. Silicic acids are absorbed from the gastrointestinal tract, largely by physical or diffusion processes. Consequently, the silicic acids are concentrated in the urine to exceed the saturated concentration, and polymerise. The polymer formed is converted into insoluble precipitates via colloidal silicic acids.
Cefali et al. (1995[103], 1996[104]) studied the toxicokinetics of sodium aluminium silicate (Zeolite A-Type) in beagle dogs. The oral bioavailability was measured for oral doses of 30 mg/kg (as a capsule, oral suspension or oral solution) in comparison to an intravenous dose of 20 mg/kg BW. Plasma silicon and aluminium concentrations were determined by graphite furnace atomic absorption. The bioavailability determined for the capsules, the oral suspension and the oral solution was 2,33, 3,44, and 2.73 % based on the measured silicon values. The mean elimination half-life was 17.5 hrs for silicon. The bioavailability measurements based on aluminium resulted in uptake rates of less than 0.1 %. The mean elimination half-life was 91.2 hrs for aluminium. The interpretation of the study results is difficult due to the large variability observed.

Conclusions

After oral ingestion of sodium aluminium silicate the major part is excreted in the faeces. A smaller part is hydrolysed in the digestive tract and a silicon compound is absorbed and excreted via the urine. The major part of the absorbed silicon is excreted within 24 hours after administration with a half-life of 6 – 8 hours in rats. About 12 % of the administered silicon dose is absorbed at doses between 40 and 200 mg/kg BW in rats (BENKE AND OSBORNE, 1979). The aluminium component of the parent compound is absorbed only to an extent smaller than 0.1 % of the administered dose. The low absorption rate for the aluminium component has also been observed in beagle dogs. In this species, the oral bioavailability for the silicon compound was lower than observed in the rat. For the purpose of this assessment the rat data are more relevant since the effects studies demonstrating the critical effect have been conducted in the rat.
Skin penetration data and data for distribution/excretion of sodium aluminium silicate after dermal absorption are not available. It is questionable, whether sodium aluminium silicate as almost insoluble compound is absorbed at all. If skin absorption occurs, it should be very low (SCHAEFER and REDELMEIER, 1996).

5.2.1.11 Experience from human exposure

Workers in the production plant and in the laboratory have been examined over a period of 15 years. The average number of employees examined was 100 per year. Most of these employees have been examined as often as 10 –15 times since 1955. Examination included a complete history and physical, chest X-ray, OCB an urinalysis. At no time evidence of systemic, generalised or local reactions due to sodium aluminium silicate have been found (IUCLID dataset, 1987)

5.2.2 Identification of critical endpoints

5.2.2.1 Overview on hazard identification

Sodium aluminium silicate has a very low toxicity after oral or dermal application. The LD50 is higher than 5000 mg/kg BW in experimental animals. Reliable data on acute inhalation exposures are not available. Sodium aluminium silicates are not irritating to the skin and slightly to non-irritating to the eyes. The powder of the substance may cause reactions in eyes due to mechanical friction. There is no evidence that sodium aluminium silicate is sensitising by skin contact and there is no indication that sodium aluminium silicates can induce respiratory hypersensitivity. The chemical structure of the compound also does not indicate any potential in this regard. A range of in vitro and in vivo studies on genetic toxicity did not indicate a potential of sodium aluminium silicate to damage the genetic material. This is in line with the results of oral and inhalation long-term studies, which did not indicate any potential of sodium aluminium silicate to induce neoplastic lesions. Chronic oral studies showed that sodium aluminium silicate causes adverse effects in the urogenital tract at high doses. In chronic inhalation studies inflammation reactions in lungs have been observed. Long term dermal studies and studies on reproductive toxicity are not available. The data on developmental toxicity demonstrate that sodium aluminium silicate is not teratogenic in experimental animals.

5.2.2.2 Rational for identification of critical endpoints

Since dermal exposure is the main exposure route for consumers, especially dermal effects have to be considered with regard to the human risk assessment. The local dermal effects are not causing concern since the sodium aluminium silicate is not irritating to skin and not sensitising by skin contact. Since data are lacking, it is not possible to assess the risk of long-term dermal effects on the basis of experimental dermal studies. However, using bridging assumptions systemic effects after dermal exposure may be assessed using the results of the long-term oral studies in experimental animals.
Long-term inhalation exposure may be the result of prolonged use of sodium aluminium silicate in household products. To assess this exposure scenario the data on long term inhalation in monkeys is used.
The eye irritation potential has to be considered, since accidental spillage may cause eye contact of sodium aluminium silicate. For the assessment of accidental exposures via ingestion the data on acute oral toxicity are considered.

5.2.2.3 Adverse effects in the urogenital tract observed in long term oral toxicity studies

Microscopic changes in kidneys and bladder associated with crystalline material in the kidney and excretion of crystalline material in the urine were observed consistently in the oral long-term toxicity studies. These findings are explained by absorption of silicic acids from the gastrointestinal tract, largely by physical or diffusion processes. Consequently, the silicic acid is concentrated in the urine to exceed the saturated concentration, and polymerise. The polymer formed is converted into insoluble precipitates. Calculi are formed and the excretion of this material may cause damage to the kidney and bladder associated with concurrent epithelial hyperplasia in these organs.

5.2.2.4 Local effects in lungs observed in long term inhalation studies

Kidney and bladder effects were not observed in the long term inhalation studies, indicating a lower, if any, systemic bioavailability of the compound responsible for the effects in the urogenital tract when compared with the oral exposure.
The dust particles of sodium aluminium silicate are small enough to reach the lungs. The particles are deposited in the lungs and cause histopathological effects such as macrophage accumulations accompanied by sporadic nonsuppurative bronchiolitis and alveolitis. No evidence of progressive pulmonary fibrosis was observed. Hence, sodium aluminium silicate dust is regarded as a poorly soluble non-fibrogenic dust with regard to human inhalation risk.

5.2.2.5 Adverse effects possible related to accidental exposure

The acute oral toxicity is greater than 5000 mg/kg BW and the acute eye irritation potential is slight to non-irritating.

5.2.3 Determination of NOAEL or quantitative evaluation of data

The NOAEL for the effects in the urogenital tract that have been observed in a two-year rat oral toxicity study is 60 mg/kg BW. This value is used for the risk assessment, since it is the lowest NOAEL determined after oral administration. The NOAEL for maternal toxicity and teratogenicity was much higher, i.e. 1600 mg/kg BW, the highest dose tested. For a quantitative assessment of absorption from the gastrointestinal tract after oral ingestion, a percentage of 12 % of the administered dose was measured at a dose range between 40 and 200 mg/kg BW (BENKE AND OSBORNE, 1979).

For the lung effects, a LOAEL of 1 mg/m³ for inflammation reactions was determined in long-term exposure of monkeys. The effects were reversible at this dose level.

For the quantitative assessment of dermal long-term exposure the following assumptions are made. The percutaneous penetration of salts or ionic compounds is generally considered to be negligible (SCHAEFER and REDELMEIER, 1996). Since acidic conditions leading to hydrolysis and uptake in the digestive tract are not likely to occur upon skin contact, the skin penetration, if any, should be very low. As a worst case assumption a systemic bioavailability of 1 % of the applied amount has been used in the estimation of the systemic exposure dose (see section 5.2). The systemic dose calculated is compared to the systemic dose causing effects observed after oral administration.

For foreseeable and accidental misuse, i.e. intentional or unintentional oral ingestion, a LD50 value of 5000 mg/kg BW is used. The eye irritation potential, if any, is low and probably due to mechanical friction of the dust particles.

5.3 Risk Assessment

5.3.1 Margin of Exposure Calculation

The Margin of Exposure (MOE) is the ratio of the No Observed Adverse Effect Level (NOAEL) or an appropriate substitute to the estimated or actual level of human exposure to a substance.

5.3.1.1 Exposure scenario: direct skin contact by hand washed laundry

To reach a conclusion for this exposure scenario, a systemic NOAEL is determined using the chronic oral NOAEL for urogenital effects of 60 mg/kg BW/day in the rat and a bioavailability of 12 % (BENKE AND OSBORNE, 1979) following gastrointestinal absorption. For calculation of the MOE, the resulting systemic NOAEL of 7.2 mg/kg BW/day is divided by the daily systemic dose of 1.4 µg/kg BW/day estimated for the dermal exposure to sodium aluminium silicate by hand washed laundry.

$MOE_{direct\ skin}$ = systemic oral NOAEL /estimated systemic dose =
7200/1.4 [µg/kg BW/day] = **5142**

All other possible direct skin contact scenarios, such as short direct contact with laundry powder or laundry tablets result in even lower estimated systemic doses and will give larger MOE. These are not further considered in this risk assessment.

5.3.1.2 Exposure scenario: indirect skin contact wearing clothes

To reach a conclusion for this exposure scenario, a systemic NOAEL has to be determined using the chronic oral NOAEL of 60 mg/kg BW/day in the rat and a bioavailability of 12 % following gastrointestinal absorption (BENKE AND OSBORNE, 1979 [101]). For calculation of the MOE, the resulting systemic NOAEL of 7.2 mg/kg BW/day is divided by the daily systemic dose of 10.8 µg/kg BW/day estimated for the dermal exposure to sodium aluminium silicate via residues on clothes.

$MOE_{indirect\ skin}$ = systemic oral NOAEL /estimated systemic dose =
7200/10.8[µg/kg BW/day] = **667**

5.3.1.3 Exposure scenario: inhalation of detergent dust during washing processes (powder detergents)

About 0.27 µg dust is estimated to emit during the washing loading process. Assuming this dust consists solely of sodium aluminium silicate and is available for inhalation in one cubic meter the resulting concentration is 0.27 µg/m³. This concentration is about 3700 times lower than the LOAEL of 1mg/m3 determined in a long–term monkey study. In addition, the exposure time during the washing loading process is estimated to be in the range of several minutes further reducing the inhalation risk.

5.3.1.4 Exposure scenario: oral route via drinking water containing sodium aluminium silicates

To reach a conclusion for this exposure scenario, a systemic NOAEL is determined using the chronic oral NOAEL for urogenital effects of 60 mg/kg BW/day in the rat and a bioavailability of 12 % (BENKE AND OSBORNE, 1979) following gastrointestinal absorption. For calculation of the MOE, the resulting systemic NOAEL of 7.2 mg/kg BW/day is divided by the daily systemic dose of 0.5 µg/kg BW/day estimated for the oral route via drinking water containing sodium aluminium silicates.

$\mathbf{MOE_{oral\ route}}$ = systemic oral NOAEL /estimated systemic dose =
7200/0.5[µg/kg BW/day] = **14400**

5.3.1.5 Exposure scenario: oral ingestion via case of poisoning and accidental contact with the eyes

The oral ingestion of 100 g of washing powder results in an oral uptake of about 35 g sodium aluminium silicate. For an adult person a dose of 583 mg/kg is calculated (body weight 60 kg). For a child this dose may be as high as 3500 mg/kg (body weight 10 kg). Compared to the experimentally determined LD50 value of > 5000 mg/kg, there is still no reason for concern, especially since no toxic effects were reported at 5000 mg/kg or higher. In addition, the poison centres in Germany have not reported a case of lethal poisoning with detergents containing sodium aluminium silicate.

Accidental contact of sodium aluminium silicate with the eyes is not expected to cause more than a slight irritation on the basis of the experimental data.

5.3.1.6 Total Consumer Exposure

The consumer exposure via direct and indirect skin contact as well as via oral route in drinking water results in an estimated total body burden of 10.8 + 1.4 + 0.5 = 12.7 µg/kg BW/day. Comparison with the systemic NOAEL of 7200 µg/kg BW/day yields an MOE of 567. Due to the inert characteristics of the sodium aluminium dust particles it is assumed that inhalation does not contribute to the systemic total consumer exposure.

$\mathbf{MOE_{total}}$ = systemic oral NOAEL /estimated systemic dose =
7200/12.7 [µg/kg BW/day] = **567**

5.3.2 Risk Characterisation

Scenarios relevant to the consumer exposure to sodium aluminium silicate have been identified and assessed using the margin of exposure or equivalent assessments. Due to the lack of irritant and sensitising effects the local effects of dermal exposure do not cause concerns. The Margin of Exposure for the combined estimated systemic dose is 567.
The MOE has to be assessed in view of all available evidence. The scientific uncertainty and variability caused by the extrapolation of limited animal data to the diverse human population is usually addressed by assessment factors. In the absence of specific data such default factors are used for extrapolation. A combined assessment factor of 100 consists of a factor of 10 for possible interspecies differences in toxicodynamics and toxicokinetics (extrapolation of animal data to man) and a factor of 10 for inter–individual differences in the human population. There is no need to use additional assessment factors since:

- a well documented chronic toxicity study is available
- a clear NOAEL for the critical adverse systemic effect has been determined
- the uncertainty of this NOAEL appears to be low due to corroborating results from other studies
- the extrapolation between the oral and dermal exposure route is facilitated by the existence of oral toxicokinetic data
- sensitivity differences in the human population are not regarded as unusually high for the urogenital effects observed.

In addition, the factor of 567 has been derived from a number of worst case assumptions. A replacement of these worst case assumption by real world data would lower the exposure estimation considerably and thereby result in a higher MOE. The MOE of 567 is therefore considered to provide sufficient protection of consumers exposed to sodium aluminium silicate.
Assessment of the possible effects of inhaled sodium aluminium silicate dust is based on a LOAEL of a long-term monkey study. The estimated exposure concentration is about 3700 lower than the LOAEL. Therefore, this exposure scenario does not cause concern.
Accidental exposure scenarios such as ingestion or contact to eyes were also assessed. Due to the lack of acute toxicity effects of sodium aluminium silicates, these scenarios also do not cause concern.
In view of the outcome of this assessment further experimental data are not required.

5.3.3 Conclusions

Sodium aluminium silicate is used in laundry regular and compact powder as well as in laundry tablets. Typical concentration ranges of sodium aluminium silicate are between 19.6 to 34.2 % in these products. As relevant consumer contact scenarios the direct contact via hand washed laundry and the indirect skin contact via wearing clothes were identified and assessed. In addition, inhalation of detergent dust during washing processes has been assessed. Indirect exposure via drinking water may also contribute to the total body burden and has been taken into account.

Sodium aluminium silicate has a very low toxicity after oral or dermal application. The LD50 is higher than 5000 mg/kg BW in experimental animals. Reliable data on acute inhalation exposures are not available. Sodium aluminium silicates are not irritating to the skin and slightly to non-irritating to the eyes. The powder of the substance may cause reactions in eyes due to mechanical friction. There is no evidence that sodium aluminium silicate is sensitising by skin contact and there is no indication that sodium aluminium silicates can induce respiratory hypersensitivity. The chemical structure of the compound also does not indicate any potential in this regard. A range of in vitro and in vivo studies on genetic toxicity did not indicate a potential of sodium aluminium silicate to damage the genetic material. This is in line with the results of oral and inhalation long-term studies, which did not indicate any potential of sodium aluminium silicate to induce neoplastic lesions. Chronic oral studies demonstrate that sodium aluminium silicate causes adverse effects in the urogenital tract at high doses. Long-term inhalation studies in monkeys revealed reversible inflammation reactions in the lungs after 24 months of exposure to 1 mg/m³. There was no evidence of progressive pulmonary fibrosis. Long term dermal studies and studies on reproductive toxicity are not available. The data on developmental toxicity demonstrate that sodium aluminium silicate is not teratogenic in experimental animals.

Due to the lack of irritant and sensitising effects the local effects of dermal exposure do not cause concerns. The dermal direct exposure scenario results in an estimated systemic dose of less than 1.4 µg/kg BW/day. The dermal indirect exposure scenario results in an estimated systemic dose of 10.8 µg/kg BW/day. The oral route scenario via drinking water containing sodium aluminium silicates showed an estimated systemic dose of 0.5 µg/kg BW and day. The combined exposure doses were assessed using a NOAEL for effects in the urogenital tract of 60 mg/kg BW/day determined in a chronic oral toxicity study in rats and using a systemic bioavailability of 12 % (BENKE an OSBORNE, 1979). The resulting Margin of Exposure of 567 is considered to provide sufficient protection of consumers exposed to sodium aluminium silicate. The same conclusion has been reached in assessing the possible effects of inhaled sodium aluminium silicate dust. Comparison of the possible exposure concentration in the household (0.27 µg/m³) with the LOAEL of 1 mg/m³ determined in a chronic inhalation study in monkeys did not indicate a concern. Accidental exposure scenarios such as ingestion or contact to eyes were also assessed. Due to the lack of acute toxicity effects of sodium aluminium silicates, these scenarios also do not cause concern.

In summary, the human risk assessment has demonstrated that the use of sodium aluminium silicate in household detergents does not cause concern with regard to consumer use.

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