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

Perboric acid, sodium salt, mono and tetrahydrate
CAS No.:
11138-47-9
(10332-33-9
10486-00-7)

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1. CONTENTS

2. EXECUTIVE SUMMARY

Sodium perborate tetra and monohydrates are mainly used as bleaching agents in laundry detergents and machine dishwashing products. The amount of sodium perborate that was used in household cleaning products was estimated to be about 280,000 tons in 2000 (calculated as sodium perborate tetrahydrate).

Sodium perborate hydrates readily dissolve in water. In aqueous solution equilibrium between boric acid, hydrogen peroxide and sodium perborate exists. For sodium perborate acute aquatic toxicity data are available for all 3 trophic levels and the LC_{50} values range from 51-125 mg/l for fish, 11 to 30 mg/l for Daphnia magna and 3.3 to 20 mg/l for algae for the mono- and tetrahydrate respectively. The available data show that the acute toxicity of sodium perborate can be explained by the formation of hydrogen peroxide.

In the fabric washing or dishwashing process the hydrogen peroxide is consumed and the equilibrium is shifted to the reaction products. After washing, the active oxygen is rapidly degraded in the sewer so that boric acid is the only relevant species that enters the environment. As boric acid is an inorganic substance it will not be degraded in the sewage treatment plant. Adsorption to sediment is also considered negligible. Consequently the risk assessment is concentrating on boric acid (calculated as boron) in the water compartment.

A large amount of chronic toxicity data for boric acid is available for all trophic levels and a probabilistic PNEC that covers 95% of the species was derived. This PNEC was 3.45, or in a more conservative approach 1.34-mg boron/l. PEC calculations were based on a large amount of monitoring data and the PEC/PNEC ratio is well below 1. Thus it can be concluded with confidence that there is no risk to the environment from the use of sodium perborate containing household cleaning products.

Sodium perborate mono and terahydrates have a long history of safe use in bleach-containing cleaning products, in particular in laundry detergents and machine dishwashing agents. The substances are of low to moderate acute toxicity via the oral and inhalation route and of low toxicity via the dermal route. In aqueous media their toxicological properties are mainly determined by hydrogen peroxide and boric acid.

The local toxicity of sodium perborate hydrates is mediated by hydrogen peroxide. Hydrogen peroxide is known for its local irritant and cytotoxic properties that are also used in the physiological defence systems of the human body. Effective detoxification mechanisms are in place in the body to effectively destroy and detoxify hydrogen peroxide. The detoxification systems are practically unsaturable.

With regard to genotoxicity and carcinogenicity the properties of sodium perborate also resemble those of hydrogen peroxide and it can be concluded that there is no concern for humans with regard to a possible genotoxicity or carcinogenicity of the products.

Boric acid, which is the species that is potentially systemically available from sodium perborate, is also of low acute toxicity and does not have any genotoxic or carcinogenic potential. The systemic availability of boric acid from sodium perborate hydrates is, however, limited by the formation of hydrogen peroxide at the same time.

The toxicologic endpoints of concern for boric acid from studies in rodents were effects on fertility as well as developmental toxicity at high dose levels. The most sensitive endpoint indicative of possible effects on fertility of boric acid are effects on the histology of male sex organs in repeated dose studies. In a repeated dose study in rats with sodium perborate tetrahydrate it was shown that at the maximum tolerated dose levels no test compound related effects on the sex organs were observed.

Effects on developmental toxicity were only observed at maternally toxic dose levels.

Human exposure to products containing sodium perborate hydrates under normal handling conditions is so low, that it will neither lead to significant local irritation nor to any systemic effects.

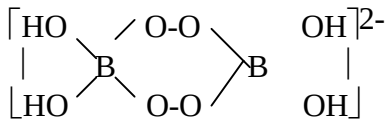
Accidental exposure to eyes may result in transient irritation that is normally readily reversible. Accidental swallowing may lead to irritation of mucous membranes in the gastro-intestinal tract and in some cases vomiting. These effects are normally also readily reversible and no fatal or severe poisoning cases have been reported.

Thus, it can be concluded that no risk for the consumer is anticipated from the use of sodium perborate hydrates in household detergent and cleaning products.

3. SUBSTANCE CHARACTERISATION

3.1 CAS No and Grouping information

Table 1: Substance identification

CAS No.:	**11138-47-9[a]**	
	10332-33-9 (15120-21-5)	10486-00-7 (13517-20-9)
EINECS No.:	**234-390-0[a]**	
	239-172-9	not available
IUPAC Name:	disodium–di-µ- peroxo-bis-(dihydroxoborate) monohydrate	disodium–di-µ- peroxo-bis-(dihydroxoborate) hexahydrate
Synonyms:	**sodium perborate monohydrate** sodium peroxoborate monohydrate perboric acid, sodium salt PBS1; PBSM	**sodium perborate tetrahydrate** sodium peroxoborate tetrahydrate PBS4; PBST
Molecular formula:	$[NaBO_2 \cdot H_2O_2]_2$ or $NaBO_3 \, xH_2O$	$[NaBO_2 \cdot H_2O_2]_2 \cdot 6\ H_2O$ or $NaBO_3$ x 4 H_2O
Structural formula of the peroxoborate anion:		
Molecular weight:	99.8 g/mol	153.9 g/mol

[a] collective CAS/EINECS Number for the mono- and the tetrahydrate of sodium perborate;

3.2 Chemical structure and composition

3.2.1 Molecular description /Macro-molecular description (Physical State/Particle size)

Sodium perborate hydrates are solid salts available either as tetrahydrate or monohydrate form.

The particle sizes of a typical product have been determined by sieve analysis and are identical for the two hydrates: >20 mesh (0,83mm DIN): 0-5%; >35 mesh (0,42mm DIN): 30-80%; >100 mesh (0,15mm DIN): 90-100% (Degussa AG, 1997).

The substance itself consists of coarse crystals > 100 µm.

3.2.2 Physico-chemical data

The most important physico-chemical data are given in table 2.

Table 2: Physico-chemical data

	Sodium perborate monohydrate		**Sodium perborate tetrahydrate**	
	Value	Comment	Value	Comment
Melting point (°C):	-	decomposition (only few data available: > 50 - > 180°C)	ca. 60-65.5	melting in its own crystallisation water; beginning decomposition
Boiling point (°C):	-	decomposition	-	decomposition
Density (20°C):	0.4-0.65	relative density	0.65-0.9	relative density
Vapour pressure (hPa, 20°C):	-	not applicable due to ionic hydrated structure; evaporation of crystal water at reduced pressure	-	not applicable due to ionic hydrated structure; evaporation of crystal water at reduced pressure
Surface tension (mN/m, 20°C):	-	it can be assumed that the surface tension of both hydrates is equal	64.6	aqueous solution of 1 g perborate/l
Water solubility (g/l, 20°C):	ca. 15-16	-	ca. 23	-
Partition coefficient log K_{OW}:	-	not applicable ionic salt	-	not applicable ionic salt
Conversion factor:	dose (monohydrate) x 0.108 = equivalent dose (boron) dose (monohydrate) x 0.341 = equivalent dose (hydrogen peroxide)	-	dose (tetrahydrate) x 0.07 = equivalent dose (boron) dose (tetrahydrate) x 0.221 = equivalent dose (hydrogen peroxide)	-

3.3 Manufacturing route and Production/Volume statistics

For the production of sodium perborate hydrates the boron ore (e.g. rasorite, tincal, borax, and colemanite) is first dissolved by reaction with sodium hydroxide, leading to a sodium metaborate (NaBO2) solution. During this step, heavy metals hydroxides are precipitated, and in ores containing large amounts of calcium, soda ash is added to sodium hydroxide to eliminate calcium as its insoluble carbonate. The metaborate solution, once clarified by e.g. filtration is then contacted with an aqueous solution of hydrogen peroxide, leading to the precipitation of sodium perborate tetrahydrate crystals (NaBO3, 4H2O). The crystals are separated from the mother liquor, dried with air at moderate temperature and shipped. The perborate tetrahydrate crystals can also be sent to an air drier operated at higher temperature, where the tetrahydrate is dehydrated into perborate monohydrate ($NaBO_3xH_2O$) which is also a commercial product.

Production volumes are available for Western Europe from the CEFIC peroxygen sector group (CEFIC 1999a,b ,CEFIC 2002) and are calculated as sodium perborate tetrahydrate, consumption volumes for consumer products (not including institutional use) have been provided by AISE, and were also calculated as sodium perborate tetrahydrate (AISE, 2002).

Table 3: Production and consumption in Western Europe (calculated as tetrahydrate form)

Year	**Consumption (t/y)**	**Production (t/y)**	**Export (t/y)**	**Reference**
1997	ca. 421600	ca. 569600	ca. 153000 [1]	CEFIC (1999a); CEFIC (1999b)

Year	Consumption (t/y)	Production (t/y)	Export (t/y)	Reference
2000	283 849[2]	ca. 537 600	223 375	CEFIC (2002) AISE (2002)

1 (ca. 27 % of the production quantity)
2 use in consumer products only

The volume of 283849 t per year used in consumer detergent products will be used converted to boron (factor 0.07, see table 2) 19.9 kt/year in the EUSES calculations for the environmental risk assessment.

3.4 Use applications summary

More than 90% of the production volume of sodium perborate mono or tetrahydrates are used in formulations for bleach-containing laundry detergents or dishwashing agents. For the perborate content of different product types see chapter 5.1 (table 13).

According to AISE, 1999a 96% of the sodium perborate used in detergent products is used in heavy duty bleach-containing powders or tablets, and 3% in machine dishwashing detergents (powders or tablets).

4. ENVIRONMENTAL ASSESSMENT

4.1 Environmental Exposure Assessment

General discussion

Sodium perborates have only anthropogenic sources. Environmental releases from anthropogenic sources may take place during production, use and consumer use of perborates.

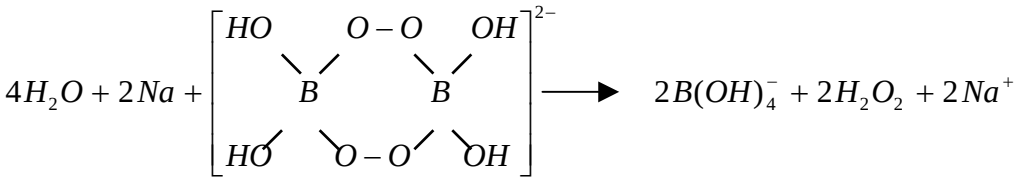
Due to the physico-chemical properties of sodium perborates entries into the atmosphere during its use are not to be expected. Direct emissions from perborate use to the terrestrial compartment are considered negligible in Western Europe.

Based on the high water solubility of perborates (and degradation products) and based on the main use of perborates (detergents), the most important environmental compartment is water. Therefore most attention will be paid to this compartment.

The most important borate species, which will be formed in aqueous solutions, is boric acid (H_3BO_3). Because the ecotoxicology of all borate species is likely to be similar on an equivalent boron basis and because only concentrations of boron can be determined analytically, the environmental emissions will be expressed as boron equivalents.

4.1.1 Environmental fate

If perborates are dissolved in water different perborate species can be found. The nature of perborate species in aqueous solutions has been discussed by Flanagan et al. (1989). One of the aqueous equilibria is presented below:



The aqueous solution of sodium perborate reacts like an alkaline solution of hydrogen peroxide, the active oxygen being catalytically decomposed by heavy-metal ions. The pH of a perborate solution at saturation is 10.1 - 10.4.

As can be seen from the equation, the free hydrogen peroxide cannot be determined by titration, since this continually displaces the equilibrium. The concentration of sodium perborate in a solution cannot be determined analytically. Only the total concentration of hydrogen peroxide (active oxygen) and the boron concentration can be determined analytically. Analytical methods for hydrogen peroxide measurements in water are described in the EU Risk Assessment Report of hydrogen peroxide (EU, 2001). Analytical methods for boron measurements in water are described in ECETOC (1997).

Biotic and abiotic degradability

An adapted closed bottle test has been performed with sodium perborate monohydrate (Jansen et al., 1993). Active sludge (20 mg/l, based on dry weight) was incubated in closed bottles using a sodium perborate monohydrate concentration of 20 mg/l. Based on the measured decrease of the active oxygen concentration, the degradation was 86 % after 48 hours (end of the test). A rapid decrease of the active oxygen content was also found during ecotoxicity tests with sodium perborate and zebra fish and algae (Groeneveld et al., 1993a,c).

Guhl & Berends (2000) tested the decrease of active oxygen after addition of 1-25 mg/l sodium perborate monohydrate and tetrahydrate to domestic raw waste water which was taken from the grit chamber of a wwtp and domestic activated sludge. They found a rapid degradation of active oxygen, both in the wastewater and the activated sludge with half-lives of 1 – 8.5 min and 0.5 – 1.3 min respectively. No significant difference between the two perborate hydrates could be detected. In the same study the degradation behaviour of hydrogen peroxide was determined. Half-lives for this compound in domestic raw wastewater ($t_{1/2}$: 0.5 – 8.2 min) and activated sludge ($t_{1/2}$: 0.5 – 1 min) were exactly in the range of the perborate. This fact supports the conclusion, that the most important species in aqueous solution are hydrogen peroxide and boric acid. These studies demonstrate that in wastewater and biological treatment plants active oxygen released from the use of perborates in laundry detergents will be rapidly degraded and will not enter the aquatic environment. Therefore the exposure assessment of perborate will be based on borate/boric acid concentrations because borates can be considered the long-term degradation product of perborates. It can be assumed that 100% of the active oxygen is degraded while 100% of the boric acid enters the aquatic environment.

Adsorption of borates to soil and sediment

Studies quantifying the adsorption of the degradation product boric acid onto soil, sediments or sewage sludge are not available. An elevated concentration of boron due to natural sources (e.g. weathering of rocks) or man-made emissions were not detected in these compartments. There is some evidence, that water-soluble **borates** have a slight tendency for adsorption to soil, sediment particles and sewage sludge, depending e.g. on pH, organic matter content and the number of active adsorption sites (Butterwick et al., 1989). Significant adsorption, however, was only detected at alkaline pH levels of up to 9.5 when boron is mainly present as the **borate ion** (WHO, 1998; Blume et al., 1980). Greatest adsorption was found in soils with high amounts of fine particles particularly with iron and aluminium compounds on the surface (Sprague, 1972). Depending on soil properties the adsorption of boron was mostly found to be reversible and the compound was easily leached. **Boric acid,** the predominant borate species present at acidic pH levels, was found to be mobile in soil and sediment.

At relevant environmental pH values of ≤ 7 no significant adsorption of **boron compounds** in soil and the aquatic compartments are to be expected (EPA, 1975; Koehnlein, 1972).

4.1.2 Monitoring Studies

Aquatic compartment

Boron is present in the form of water-soluble borates in all inland freshwaters, because of the weathering of naturally occurring borate containing rocks and soils. Background concentrations of boron can be relatively low (about 10 µg/l) or very high depending on geological conditions. Concentrations of 20.2-g boron per litre have been measured in thermal springs of the mount Amiata in Tuscany, Italy (Duchi et al., 1987).

An extensive overview of boron concentrations in inland freshwater has been presented by ECETOC (1997), (2002) and IPCS (1998).

Boron levels in aquatic environments have been reported for Germany, with special emphasis on the situation in Bavaria (Lind et al., 1998). In less contaminated surface water sites or in river's upper reaches, boron concentrations in the range 0.03 – 0.05 mg/l were typical. In more contaminated areas, the boron concentration levels usually were in the range of 0.1 – 0.25 mg/l.

In France the boron concentrations in freshwater have been reported by Golaszewski (1996). More than 95 % of the measured values were lower than 0.3 mg/l. More data on other monitoring studies are summarised in table 4.

Additional boron monitoring data of surface water have been generated by the GREAT-ER project (ECETOC, 1999). Extensive monitoring data of boron concentrations in surface water are available for the United Kingdom, Germany and Italy. Highest boron concentrations were found for the United Kingdom. A preliminary analysis of these data showed that the 95 percentile was lower than 0.4 mg/l. For a more detailed description of the data refer to the HERA risk assessment of boric acid. The analysis of the survey will be updated by ECETOC (2002). This analysis shows that the 90 percentile monitoring values in all European rivers with one exception (1.0 mg/l) ranged between <0.1 and 0.3 mg boron/l.

Table 4: Examples of Boron Concentrations in Surface Waters (adapted from ECETOC, 2002)

Country	No. sites/samples	Conc range (mg/l)	Year	Reference
Austria		< 0.02 – 0.6	1985-1989	Schöller and Bolzer 1989; Schöller 1990
France	>300	98% < 0.1	1986-89	DDASS de l'Oise, 1990
Germany	7 rivers,17 sites, 360 samples	0.013 – 0.372	1991-95	Metzner *et al* 1999
Italy	19 sites 166 sites 5 sites	< 0.002 < 0.01 – 0.5 0.1- 0.2	1989 1983-84 1997-98	Benfenati *et al* 1992 Tartari and Camusso, 1988 Gandolfi *et al* . 1999
Luxembourg		0.11 – 0.39	1993	Unilever 1994
Netherlands	 22 analyses	0.04 – 0.09 0.09 – 0.145	1981 1992	Mance *et al* 1988 Unilever 1994
Spain	5 sites	0.20- 0.30	1986	Garcia *et al* 1987
Sweden		<0.005 – 0.069 <0.05	1990 1991	Sveriges Geologiska AB Analys, 1991 KM Lab, 1991
England Scotland	15 sites 59 sites (236 samples)	0.011 – 0.311 (mean values) <0.005 - 0.035	1993-96	Neal *et al*, 1998
Switzerland	8 sites	<0.004 – 0.26	1990	EAWAG, 1990

Due to erosion processes, which result in a continuous flux of boron to the sea, natural concentrations of boron in seawater tend to be higher than mean freshwater concentrations. A boron concentration in seawater of around 5 mg/l has been reported (ECETOC, 1997).

Terrestrial compartment

The natural boron content of soils has been discussed by ECETOC (1997). The average boron content of soils is 10-20 mg/kg, but concentrations up to 100 mg/kg have been reported for specific areas of the world. On the other hand it has been shown that several countries suffer from a boron deficiency in soil. For a more detailed description of the data refer to the HERA risk assessment of boric acid and ECETOC (2002).

4.1.3 EUSES Calculations

Scenario description

The HERA environmental risk assessment of sodium perborate hydrates is based on the Technical Guidance Document for new and existing substances (TGD, 1996). At screening level it makes use of the EUSES program to calculate the local and regional exposure levels. In the European Union the model EUSES has been used to calculate the PEC of organic compounds. In some cases it can also be used for inorganic compounds to obtain a preliminary idea about the order of magnitude of the PEC. Within HERA the EUSES model has been adapted to develop a specific scenario for detergents (HERA, 2002). The total sodium perborate tonnage produced for and used in, detergency was assumed to follow the down-the-drain pathway as boric acid to the environment.

The production and formulation releases, at local level, were not considered because they fall outside the scope of HERA. As outlined above the tonnage was calculated as boron equivalents. For the calculation, the HERA exposure scenario (to assign 7% of the EU tonnage to the standard EU region, instead of the TGD default 10%, and to increase the emissions at local level by a factor of 1.5, instead of the TGD default factor of 4) was adopted. These changes introduced by HERA more realistically represent the regional emissions and the local input of substances used in household detergents, as experimentally demonstrated (Fox, 2001).

More details and justification of this modification can be found in chapter 2.6 of the HERA methodology document (HERA, 2002).

Table 5: HERA exposure scenario

Sodium perborate hydrates calculated as boron equivalents (B)	HERA scenario
Total yearly use in household (HERA scope), kton	19.9
Continental usage going to standard EU region, %	7
Increase factor for local usage	1.5

Substance data used for the exposure calculations

Data used for the exposure calculations following the TGD guidelines and EUSES model are summarised in table 6. As the assessment is based on boric acid and calculated as boron the appropriate data of these two species were used. The data were taken from ECETOC (2002).

Table 6: Data for exposure calculations with EUSES

Name of field	Value
Molecular weight (g/mol, B)	10.81
Octanol-Water partition coefficient (boric acid) log Pow	0.175
Water solubility (boric acid) (mg/l)	8251
Biodegradation rate constants in STP and surface water	0
STP removal %	0
Fraction to air by STP	0
Fraction to water by STP	1
Fraction to sludge by STP	0

4.1.4 PEC Calculations

PEC-calculations using the EUSES model

The relevant values that were obtained using the input parameters outlined above are summarised in table 7.

Table 7: Relevant PEC values from EUSES calculations

Parameter	Value as B
Local concentration STP influent	1.43 mg/l
Local concentration in the STP effluent	1.43 mg/l
Local concentration in sludge	0
Local PEC in STP	1.43 mg/l
Local PEC surface water	0.204 mg/l
Regional PEC surface water	0.062 mg/l

PEC Water calculated from monitoring data:

Many boron monitoring data of surface water are available which can be used to quantify the emission related with consumer use of sodium perborate although it should be realised that other boron sources can have a significant impact on the measured values. ECETOC (2002) uses the most recent available monitoring data to derive a $PEC_{water..}$ The highest 90^{th} percentiles of monitored data for those areas where extensive monitoring datasets exist for boron in surface waters were used. Specific areas of high geological boron where borates are mined or naturally present in e.g. geothermal streams were excluded.

Based on these considerations a value of **0.8-mg/l boron** was considered to be a **conservative estimate of the PEC_{water}.** For further details see ECETOC (2002).

PEC Soil/ PEC Sediment

Direct emissions of perborates to the terrestrial compartment are considered negligible. A terrestrial assessment of boron has been reported by IPCS (1998). A further risk characterisation of boron for the terrestrial compartment will be done by the ECETOC (2002) and in the HERA risk assessment of

boric acid.

Boric acid, the predominant borate species present at acidic pH levels, was found to be mobile in soil and sediment. At relevant environmental pH values of ≤ 7 no significant adsorption of **boron compounds** in soil and the aquatic compartments are to be expected (EPA, 1975; Koehnlein, 1972). Only a sorption to the inorganic constituents of sediment such as clays seems to be possible. Therefore, $PEC_{local,\ sediment}$ cannot be calculated with the estimation method given in the TGD as this method is based on the adsorption of substances to the organic matter of the sediment. From the scientific literature, however, there is no evidence for a significant adsorption of the substances to soil or sediment under environmentally relevant conditions (see section 4.1.1). An accumulation of any of the borate salts in the sediment is not to be expected and the quantification of $PEClocal_{sediment}$ seems to be of minor importance.

PEC STP

In general, the boron content in raw domestic sewage is derived from the use of perborate in household detergent products. During the washing process, perborate is decomposed to hydrogen peroxide and boric acid or borate. Both laboratory and field studies show that peroxide is destroyed prior to the wastewater reaching the STP (Guhl and Berends, 2001). However, the inorganic boron compounds are not removed in the sewer or at the STP. According to the EUSES calculations a **PEC STP** of **1.43 mg/l** was estimated

4.1.5 Indirect exposure via the environment

Indirect contact with sodium perborate itself via the environment is unlikely as it rapidly breaks down to hydrogen peroxide and borate species during use and in the sewage system. The only relevant indirect exposure could be through the boric acid content of drinking water. The uptake of boron (in form of boric acid) via drinking water is reported in the literature without specifying the underlying sources. For Germany, drinking water concentrations of < 0.2 mg boron/l (with a median of 0.02 mg/l) were measured in 1985/86 (Krause et al., 1991) In a world-wide data compilation of WHO (1998) it was found that in most areas boron content in drinking water was clearly below 0.4 mg/l. In contrast, bottled mineral water of different origin showed in a number of cases significantly higher concentrations (up to 4 mg/l) (Allen et al., 1989). These higher levels are caused by boron containing minerals in the surroundings of the springs. The EUSES calculations revealed a concentration of boron in drinking water from perborate hydrates used in detergent products of 0.06 mg/l. However, as the concentrations in surface water are taken as drinking water concentrations neglecting drinking water preparation procedures and this value is therefore considered overconservative.

Boron content of drinking water is limited by the European drinking water directive to 1 mg boron/l of water. (EU, 1998)

4.2 Environmental Effects Assessment

The Reliability of the studies using the criteria of Klimisch (1997) criteria is given in the IUCLID data set (appendix I).

4.2.1 Ecotoxicity – Aquatic: acute test results

Perborates dissociate to borates and hydrogen peroxide in aqueous environments. To enable a comparison with the toxicity of borates and hydrogen peroxide, the results of the ecotoxicity studies

with perborates will be expressed as concentrations of perborate, boron and hydrogen peroxide equivalents. Aquatic toxicity tests with perborates are available but in most cases analytical measurements of the hydrogen peroxide and/or boron content were not conducted during these studies. In several publications EC0 values were reported, which will be considered equal to NOEC values in the following sections.

Toxicity to fish

Results of toxicity tests with perborates and fish are summarised in the Table.8. Only the test with zebra fish (*Brachydanio rerio*) was considered valid without restrictions. During this test the perborate solutions were renewed daily and the hydrogen peroxide concentrations was measured before and after renewal of the test solutions. At nominal perborate concentrations of 25 - 100 mg/l the concentration of hydrogen peroxide remained constant between two renewals but at nominal concentrations of 6.3 mg/l a severe reduction of the hydrogen peroxide concentration was found between two renewals. During the remaining fish tests analytical measurements were not reported. The study with zebra fish had the longest test duration and this study revealed also the lowest NOEC and LC50 values.

Table: 8 Acute toxicity to fish

Species	Duration (days)	PBS	LC50 (mg/l)			NOEC[1] (mg/l)			Reference
			PBS	H_2O_2	B	PBS	H_2O_2	B	
Zebra fish (*Brachydanio rerio*)	4	PBS1	51	16	5.5	25	8.0	2.7	Groeneveld et al. (1993a)
Golden Ide (*Leuciscus idus*)	2	PBS4	125	27	8.8	100	21	7.0	Henkel (1991)
Eel (*Anguilla anguilla*)	1	PBS3				500	125	40	Mann (1973)
Rainbow trout (*Oncorhynchus mykiss*)	1	PBS3				250	63	20	Mann (1973)
Guppy (*Lebistes reticulatus*)	1	PBS3				250	63	20	Mann (1973)

PBS4: sodium perborate tetrahydrate, PBS1: sodium perborate monohydrate, PBS3 sodium perborate trihydrate (?) (substance not exactly specified in the publication), B: boron

[1] Reported NOEC of that study

The acute toxicity of **inorganic borates** for fish has been reviewed by ECETOC (1997). Based on boron concentrations, LC50 values ranged between 14 and 3400 mg/l, but in general the LC50 values were higher than 100 mg/l. The ecotoxicity of **hydrogen peroxide** has been reviewed in the Risk Assessment of hydrogen peroxide (EU, 2001). For acute toxicity values for fish, LC50 values were in general lower than 100 mg/l and a worst case 96h. LC50 value of 16.4 mg/l was reported for pimephales promelas. Therefore the observed acute toxicity of perborates to fish can be explained by the presence of hydrogen peroxide in the test solutions.

Toxicity to aquatic invertebrates

The acute toxicity of perborates to aquatic invertebrates is presented in table 9. One valid test (without restriction) with water fleas (*Daphnia magna*) and PBS1 was reported which revealed EC50 and

NOEC values of 11 and 8.0 mg/l, respectively. The perborate solutions of this semi-static test were renewed after 1 day. Analytical results showed that the measured concentration of hydrogen peroxide was at least 89 % of the nominal concentration at nominal perborate concentrations of 2 - 32 mg/l. A guideline study with *Daphnia magna* and PBS4 revealed results, which were not very different from the test with PBS1 (see table). The test with *Gammarus tigrinus* revealed no effect of PBS3 at a concentration of 7500 mg/l, while 100 % mortality was found at 10,000 mg/l.

Table 9: Acute toxicity to Invertebrates

Species	Duration (days)	PBS	EC50 (mg/l)			NOEC[1] (mg/l)			References
			PBS	H_2O_2	Boron	PBS	H_2O_2	Boron	
Daphnia magna	2	PBS1	11	3.5	1.2	8.0	2.6	0.86	Groeneveld et al. (1993b)
Daphnia magna	2	PBS4	30	6.4	2.1	15	3.2	1.1	Henkel (1991)
Gammarus tigrinus	1	PBS3				7500	1900	600	Mann (1973)

[1] Reported NOEC of that study

The EC_{50}.48h of **inorganic borates** to Daphnia magna ranged between 95 and 226 mg boron per litre (ECETOC, 1997). For **hydrogen peroxide** an EC_{50}.24h, value of 2.3 mg/l has been reported (EU, 2001), which shows that the observed acute toxicity of perborates to Daphnia magna can be explained by the presence of hydrogen peroxide in the test solutions.

Toxicity to aquatic plants

The toxicity of perborates to algae is presented in table 10. During the study with the green alga *Selenastrum capricornutum* the hydrogen peroxide content has been measured daily. A severe decrease of the measured active oxygen content was found during the test. Reinitiating of algal cell growth close to control levels between days 2 and 3 at a nominal PBS1 concentration of 5 mg/l could be explained by the dissociation of hydrogen peroxide in the test flasks. A firm NOEC could not be determined because the concentration-response curve was not monotone. Three toxicity tests with *Scenedesmus subspicatus* were reported. Based on EC50 values a good agreement between the results of the tests was found. However a significant difference between the results of the three tests was found based on NOEC values. These differences could be due to variations in the hydrogen peroxide content at the start of the test or due to differences in biomass loading (initial cell density) at the start of the test or even due to control growth variability.

EC0, EC3 and EC10 values of laboratory algal tests with **inorganic borates** ranged between 10 and 24 mg boron per litre (ECETOC, 1997). These values are significantly higher than the NOEC values of perborates (expressed as boron concentrations). The endpoints of the algal tests with perborates, based on H_2O_2 concentrations, were similar to the endpoints of the tests with **hydrogen peroxide** (EU, 2001).

Table. 10: Toxicity to aquatic plants

Species	Dura-tion (h)	PBS	EC50 (mg/l)			NOEC[1] (mg/l)			References
			PBS	H_2O_2	B	PBS	H_2O_2	B	
S. capricornutum	72	PBS 1	3.3	1.1	0.63	2.5	0.80	0.27	Groeneveld et al. (1993c)
S. subspicatus	96	PBS 4	24	5.2	1.7	11	2.3	0.75	Henkel (1991)
S. subspicatus	96	PBS 4	19	4.1	1.4	0.78	0.17	0.055	Henkel (1991)
S. subspicatus	96	PBS 4	27	5.7	1.9	3.5	0.74	0.25	Henkel (1991)

[1] Reported NOEC of that study

Microcosm test

Sodium perborate tetrahydrate has been tested in a so-called microcosm test (Guhl, 1998). The microcosm test system was a multi-species system consisting of a number of different unicellular species of bacteria, algae, protozoans and small multicellular organisms. The organisms were exposed in 150 ml glass beakers (with overflow pipe) containing 100-120 ml test solution and every two hours a volume of 10-ml fresh perborate solution was added. The test duration was 3 weeks. Most of the organisms were located near the bottom of the pipe, which was close to the inflow of the fresh solution, which means that they were exposed at least every two hours to active oxygen. Based on the species composition of the microcosm, the NOEC of the study was 1.4 mg/l (nominal) sodium perborate tetrahydrate, which is equivalent with boron and hydrogen peroxide concentrations of 0.10 and 0.30 mg/l, respectively.

4.2.2 Toxicity to micro-organisms

The effect of perborate on the rate of biodegradation of alkylbenzene sulphonates by pure cultures of *Pseudomonas fluorescens* and *Aspergillus* sp. was studied by Dimkov et al. (1985). Both cultures were isolated from non-adapted sewage effluent. At perborate concentrations of 12 and 48 mg/l the biodegradation by *P. fluorescens* was reduced with 48 % and 75 %, respectively. At the same perborate concentrations the biodegradation by *Aspergillus* sp. was reduced with 7 % and 61 %, respectively. The effect of perborate on the biomass of the microorganisms was smaller than the effect on biodegradation. It is unknown which perborate hydrate was used during the study. No conclusions can be drawn when the toxicity of perborates is compared with the toxicity of inorganic borates and hydrogen peroxide. Endpoints of toxicity tests with microorganisms and hydrogen peroxide and inorganic borates showed a large variation. However, as sodium perborate from household use is degraded prior to entering a sewage treatment plant in the sewer already (Guhl and Berends, 2001) the data of **boric acid** are relevant for assessing this endpoint. The NOEC of *Pseudomonas putida* was 59.5 mgB/l Dyer (2001). The clean-up performance of activated sludge plants is not adversely affected below 40-110 mgB/l (ECETOC, 2002). This is confirmed by the results in the oxygen consumption inhibition test (EC_0=110 mgB/l), a test that is highly relevant to the effect of substances on the performance of activated sludge plants (Guhl and Gode, 1989). This result could be verified by several tests with biocenoses of activated sludge. Up to more than 20 mgB/l there was no difference between test and control. In the next concentration (50 mgB/l), the abundance of *Opercularia bimarginata* decreased, but another species of the same ecological niche (*Opercularia coarctata*) increased. At 110 mg/l, the change of the biocenosis was more evident, but the sludge condition measured by the composition of the ciliates as well as the dry weight of the sludge demonstrated that there is no damage

of the function (Guhl, 1987). Two tests were performed with sludge, which did not *contain Opercularia bimarginata*. No change was found in the biocenosis as well as in the STP function up to the highest tested concentration (110 mgB/l). Hence, a **STP NOEC of 110 mgB/l** is recommended (ECETOC, 2002).

4.2.3 Ecotoxicity – Aquatic: chronic test results

For the assessment of chronic toxicity of sodium perborate hydrates to aquatic organisms only the data of **boric acid** are of relevance. For a more detailed description of the data including statements of the validity and reliability refer to the HERA risk assessment of boric acid.

The ecotoxicology of inorganic borates has been discussed in detail by ECETOC (1997). Based on this review the NOEC borates to all freshwater aquatic life is at least 1 mg boron per litre (ECETOC, 1997). The toxicity of boron has also been reviewed by the International Programme on Chemical Safety (IPCS, 1998). Based on this review the environmental no effect concentration of boron is 1 mg/litre. Other important documents on the ecotoxicity of boron have been published by WRc (1988), Butterwick et al. (1989), Eisler (1990), Guhl (1992), Black et al. (1993), Hovatter et al. (1995), Plassche et al. (1999) and Raymond and Butterwick (1992)).

Results of additional studies with fish have been published. No effect of boron on mortality and length of rainbow trout larvae (*Oncorhynchus mykiss*) was found when they were exposed up to a concentration of 10 mgB/l (Eckhert, 1998). Boron concentrations were determined during this study. A study with zebra fish embryos (*Brachydanio rerio*) revealed a LOAEL of 400 mgB/l after 72 hours of exposure (Rowe et al., 1997). When zebra fish were exposed to a very low level of boron (1.6 µg/l) a reduced survival of the organisms was observed due to boron deficiency.

In 1997 a field study has been performed in the Yellowstone National Park Wyoming, USA to determine the potential effect of boron on trout populations. However, atypical high water flows and concomitant lower than historical temperatures and boron concentrations during summer 1997 preclude conclusions about avoidance of high boron concentrations. Preliminary results indicate that 0.5 mg boron/l did not appear to be avoided by rainbow trout and brown trout (Meyer et al. 1998).

Overall chronic toxicity values for 18 aquatic species covering all trophic levels are available that are reviewed in ECETOC (2002). A probabilistic analysis of the data to derive an aquatic PNEC was therefore conducted by Dyer (2001).

4.2.4 PNEC calculations

PNEC water

In a recent publication Dyer (2001) used a probabilistic approach to derive a $PNEC_{0.05}$ (Predicted No Effect Concentration for 95% of the species) from chronic studies that were available for boron for all trophic levels. Mean toxicity levels per taxa were determined and then converted to a cumulative probability term and curve-fit assuming a log-logistic distribution. The **$PNEC_{0.05}$** derived from this analysis was **3.45 mg B/l** when all species data with uniform chronic toxicity endpoints (NOEC, LC_{10}) were considered. This value will be used for the risk assessment. If in a more conservative approach other effect levels (e.g. EC_3) were considered as well, a $PNEC_{0.05}$ of 1.34-mg B/l was derived. However, this more conservative value is based on data that were insufficiently reported to calculate EC_{10} or NOEC values and is therefore considered overconservative.

PNEC stp

In contrast to the PNEC for surface waters where the objective of protection is each single species, for STP it is important to protect the function, i.e. the degradation or the reduction of organic carbon (COD/BOD), phosphorous and nitrogen. Therefore the most important value for STP is the concentration of a substance which does not damage the function of the STP.

According to the TGD, the PNEC of STP is the NOEC, determined from a chronic test with bacteria. The NOEC of *Pseudomonas putida* is 59.5 mgB/l, i.e. according to TGD, the PNEC = 60 mgB/l.

On the other hand, there was no influence of boron on either the biocenosis or the functional performance up to at least 50 mgB/l. Above 50 mgB/l minor changes in the sewage community occurred but its function was not affected at concentrations up to 110 mgB/l. An assessment factor of 1 is appropriate as the value reflects the situation in the STP itself. Therefore, the **$PNEC_{sewage}$ = 110mgB/l** will be used in the risk assessment.

4.3 Environmental Risk Characterisation

As for the consumer use of detergents only boric acid concentrations are relevant, the PEC/PNEC calculations are based on environmental concentrations measured as boron and ecotoxicological data of boric acid/borates expressed as boron equivalents.

Table. 11: Relevant PEC and PNEC values based on monitoring data

PEC [mg B/l]	**PNEC [mg B/l]**	**PEC/PNEC**
$PEC_{regional\ water}$ = 0.8l[1]	3.45	0.23
	most conservative: 1.34	0.59

[1] based on monitoring data includes boron from other sources (including natural origin)

With the EUSES model an estimate of the contribution of household use of sodium perborate hydrates containing detergent products can be derived.

Table 12 PEC/PNEC calculations using EUSES calculated PECs

PEC [mg B/l]	**PEC/PNEC**	**with most conservative PNEC**
PEC_{STP} = 1.43 mg/l	0.013	
$PEC_{local\ water}$ = 0.204 mg/l	0.059	0.15
$PEC_{regional\ water}$ = 0.17 mg/l	0.049	0.13

The results of the modelling calculations fit relatively well with those of the monitoring data.

4.3.1 Aquatic compartment

Based on the previous reviews on the ecotoxicity of boron, based on the recently published additional fish studies and based on the results of the statistical extrapolation method a $PNEC_{water}$ of 3.45 mg boron per litre, or if a more conservative approach is used of 1.34 mg/B/l can be derived for the environmental assessment of perborates.

Many boron monitoring data of surface water are available which can be used to quantify the emission

related with consumer use of sodium perborate although it should be realised that other boron sources can have a significant impact on the measured values. Based on the monitoring data 0.8 mg/l boron was considered to be a conservative estimate of the PEC_{water}.

Thus the PEC/PNEC ratio is 0.8/3.45 = 0.23 or with the conservative estimate 0.8/1.34 = 0.6. This ratio is well below 1 and indicates that there is no risk for the aquatic compartment from the use of perborates in detergent products. As the PEC/PNEC calculations are based on monitoring in surface waters data that also include boron concentrations from natural and other anthropogenic sources, and a probabilistic PNEC based on an enormous amount of data, this analysis is applicable for all entries of boron to surface waters and seems to be very robust.

4.3.2 Sediment

From the scientific literature, there is no evidence for a significant adsorption of the substances to soil or sediment under environmentally relevant conditions. An accumulation of any of the boric acid or borate species in the sediment is not to be expected and a quantification seems to be of minor importance.

4.3.3 Non compartment specific effects relevant to the food chain

Studies on the potential bioaccumulation of boron have been discussed by IPCS (1998). The studies with aquatic organisms showed that the organisms take up boron in relation to its availability. No bioaccumulation was found for aquatic organisms.

4.3.4 Sewage treatment plant

In general, the boron content in raw domestic sewage is derived from the use of perborate as a bleaching agent in detergent products. During the washing process, perborate is decomposed to hydrogen peroxide and boric acid or borate. Both laboratory and field studies show that peroxide is destroyed prior to the wastewater reaching the STP (Guhl and Berends, 2001). Therefore boric acid is the species to be considered for the assessment of the sewage treatment plant. From consumer use of detergent products a PEC of 1.43 mg B/l was derived and a PNEC of 110 mg B/l from the available data on toxicity to STP organisms. Thus with a PEC/PNEC ratio of 0.013 there is no concern for a misfunction of sewage treatment plants through perborate containing detergent products. This is confirmed by the practical experience.

4.4 Discussion and conclusions

Sodium perborate mono and tetrahydrate are predominantly used in laundry detergents and machine dishwashing detergents. In aqueous solution equilibrium between boric acid, hydrogen peroxide and sodium perborate exists. In the washing or dishwashing process the hydrogen peroxide is consumed and the equilibrium is shifted to the reaction products.

For sodium perborate itself acute aquatic toxicity are available for all 3 trophic levels. The acute toxicity to aquatic organisms in the laboratory studies, in the absence of catalytic metal ions or organic material that would trigger the degradation of hydrogen peroxide, is mainly due to the latter and matches very good with studies on hydrogen peroxide.

Residual active oxygen is degraded rapidly in the sewer so that boric acid is the only relevant species that enters the environment. As boric acid is an inorganic substance it will not be degraded in the sewage treatment plant. Adsorption to sediment is also considered negligible so that the final compartment for boric acid from perborate use is the surface water. Consequently the risk assessment is concentrating on the water compartment. Many monitoring programmes in Western Europe have

included boron analysis and therefore the PEC calculation could be made using these data.

A great amount of chronic toxicity data for boric acid are available for all trophic levels so that the PNEC calculation could be based on a probabilistic PNEC that covers 95% of the species.

As the PEC/PNEC ratio derived from that data is well below 1 it can be concluded with confidence that there is no risk to the environment from the use of sodium perborate used in laundry detergents.

5. HUMAN HEALTH ASSESSMENT

5.1 Consumer Exposure

In the consumer application, granular preparations containing sodium perborate are used as household detergent products and the possibility of inhalable dust formation is very limited. Dermal contact is more likely to occur with diluted aqueous solutions of sodium perborate-containing preparations. Oral exposure will only occur as accidental exposure.

Indirect contact with sodium perborate itself via the environment is unlikely as it rapidly breaks down to hydrogen peroxide and borate species during use and in the sewage system.

The predominant use of sodium perborate mono- and tetrahydrates is in bleach-containing dry laundry detergents, regular and compact, mainly used for machine laundering and in machine dishwashing products either as powder or tablets. Those products are granulated or in tablet form and formulated specifically to avoid fine powder forms or 'fines' and hence, the potential for exposure to dust is negligible. An assessment of consumer exposure will nevertheless include a scenario on a possible dust exposure during the filling of the washing machine or refilling of washing powder packages. These operations will typically be of very short duration (1 minute) and relatively low frequency. Dermal contact with washing solutions and occasional handwashing with machine wash detergents will also be considered, although they are not the typical products that would be used in handwashing.

The sodium perborate content in the different products has been provided by AISE (2002) and is summarised in table 13.

Table 13: Sodium perborate content in different detergent products

Product	**Content sodium perborate (range) %**	**Typical content %**
LAUNDRY REGULAR powder	15-31	20-31
LAUNDRY COMPACT powder	15-31	20-31
Laundry additive	16-20	19
Machine dishwashing (powder)	4-18	5-18
Machine dishwashing (tablet)	5-18	5-18

5.1.1 Consumer exposure via direct skin contact

Laundry handwashing

Consumers may be exposed to sodium perborate hydrates via solutions if machine-laundering detergents are used for handwashing. Due to the ionic nature of the substance, its water solubility and degradation as well as the water solubility of the degradation products, no residuals are expected to remain on the fabrics.

AISE 2002a has issued an overview of habits and practices for consumer products in Western Europe

that will be used to calculate the possible consumer exposure.

The highest concentration of laundry detergent used in the handwashing solution is approximately 1% (10 g/l), a typical amount is 5 g/l. The highest concentration of sodium perborate hydrates in the laundry detergent is 25 % (AISE 1999) or 31% (AISE, 2002). The content is approximately the same for regular and compact detergents as well as for laundry additives. As those products are used alternatively, no cumulative exposure is calculated.

As for the exposure calculations the maximum concentrations in the products are used these exposures can be considered a conservative worst case estimate of the consumer exposure.

Worst case estimate for handwashing scenario:

Contact time is usually 10 minutes (AISE (2002a)

Frequency of tasks per week is typically 5 (AISE (2002a). In the same document (AISE 2002a) a maximum of 21 tasks per week is mentioned, but this is more related to machine wash and seems to be a very extreme worst case assumption that is not applicable to the handwash scenario.

Using the equations of the HERA guidance document (2002) the following exposure can be derived:

$C_{perborate}$ = Maximum concentration of sodium perborate hydrates: 3.1 g/l (= mg/ml)

T_{der} = Thickness of layer on skin: 100 µm = 0.01 cm (HERA 2002, TGD, 1996)

S_{der} = Exposed Area (hands and forearms according to EPA, 1997): 1980 cm^2 (adult male)

Percutaneous absorption worst case derived from data: 0.4 %,

F =fraction absorbed: 0.004 in (24 h exposure time) (see section 5.2.8).

$EXP_{sys} = C_{perborate} \times T_{der} \times S_{der} \times F$

EXP_{sys} = 3.1 mg/ml (cm^3) x 0.01 cm x 1980 cm^2 x 0.004 =

0.25 mg sodium perborate hydrate or a maximum of 0.027 mg B (assuming use of sodium perborate monohydrate) absorbed in 24 hours

Assuming 10 min contact time per task and a very conservative maximum task frequency of 21 washes per week (3 per day) (AISE 2002a) the total daily contact time adds to 30 min. Assuming such very conservative daily duration of exposure the amount of absorbed sodium perborate per day can be calculated as [(0.25 mg/day) x (30/60 hr) x (1/24 day/hr)] = 5.2 µg. This would correspond to a maximum of 0.56 µg of boron (again using use of sodium perborate monohydrate as the worst case assumption) Assuming a body weight of 60 kg, the resulting estimated systemic dose is:

Worst case estimate

$Exp_{sys\ (direct\ skin\ contact)}$ = 0.087 µg perborate /kg BW /day and

0.009 µg boron/ kg BW/day

A more realistic worst case estimate would use the typical use frequency of 5 times per week for 10 min, this would result in an exposure of (5/7) x 10/60 x 1/24)= 1.2 µg of perborate /day and 0.13 µg boron per day, and for a 60 kg individual 0.02 µg/kg/day as sodium perborate, 0.002 µg boron/kg per day.

Typical frequency and exposure, realistic worst case estimate

$Exp_{sys\ (direct\ skin\ contact)}$ = 0.02 µg perborate /kg BW /day and 0.002 µg boron/ kg BW/day

For the estimation of systemic exposure only boron is considered and not the degradation product hydrogen peroxide that will be present in the aqueous solution as well for the following reason. Hydrogen peroxide coming into contact with skin will be readily degraded by catalases in the skin and the underlying capillaries to oxygen and water and will thus not be systemically available (EU, 2001, ECETOC, 1996). For possible local (irritant) effects only the concentration in water is relevant.

The maximum content of hydrogen peroxide in a handwashing solution will be 1.05% if based on sodium perborate monohydrate (3.1 % perborate monohydrate x 0.341 (see table 2).

Skin contact with solid sodium perborate hydrates

Another scenario would be dermal contact to a fraction of the solid (0.1% best estimate for this risk assessment) when filling the washing or dishwashing machine.

In this case it can be assumed that the contact lasts less than 1 minute (AISE 2002a) and only affects a fraction of the hand surface (palms of the hands). According to EPA, 1997 the surface of the hands would constitute ca. 840 cm^2, the palms would then be one half, 420 cm^2.

The maximum amount of detergent powder used per event was 290 g. With a maximum amount of 31% sodium perborate this would contain 90 g/sodium perborate hydrates. If about 0.1% come into contact with the skin, this would constitute 90 mg. It can be assumed that only a fraction of this will be soluble and available on the skin for absorption.

Given the very short duration of exposure and the very low levels of material expected to be available for skin absorption, this exposure scenario can be expected to be negligible. In the case of the use of tablets the exposure would be even lower as only the thumb and the index finger of one hand (approximately 2 cm^2) are in contact with the products.

5.1.2 Consumer exposure via the inhalation route

The products containing sodium perborate hydrates are either granulated or in tablet form. Dust formation from these products is so small that it can be considered negligible. This assumption has been confirmed for the laundry-washing scenario. According to van de Plassche et al. (1998) studies indicate an average exposure of about 0.27 µg/ cup of product used for machine laundering, of which up to 31% could consist of sodium perborate hydrates, i.e. ca. 0.08 µg. Furthermore the duration of such an operation is less than 1 min and can only be regarded as short term exposure. In a worst case assumption this dust would distribute in about 10 m^3 room, a concentration of 0.008 µg/perborates per m^3 would be obtained of which only a fraction would be respirable. According to CEFIC (1997) 90 to 100% of the sodium perborate hydrates particles have a diameter above 0.15 mm. Assuming that all particles below a diameter of 0.15 mm are in the respirable range, a worst case estimate would include 10% of respirable particles.

$C_{perborate}$= Dust levels: 0.008 µg/m^3

F1 = Particles in the respirable range: 10% (fraction 0.1) (CEFIC, 1997)

F2= Absorbed fraction 75% (default) (TGD, 1996) (factor 0.75)

Q_{inh} = Respiratory volume: (light activity): 0.02 m^3/min (TGD, 1996)

t = Exposure duration: 1 min/ event

n= number of events per day (x 21/7=3) (AISE 2002a)

BW = Body weight: 60 kg

(Dose = 0.008 µg x 0.3 x 0.75 x 0.02 x 3 / 60) = $1.8\ 10^{-6}$ µg perborate hydrate/kg BW or at maximum $1.9\ 10^{-7}$ µg boron per kg BW/day

Worst case inhalation exposure estimate

$Exp_{sys\ (inhal)} = C \times Q_{inh} \times t \times n \times F1 \times F2/BW$

$Exp_{sys\ (inhal)} = 0.008\ µg/m^3 \times 0.02 \times 1 \times 3 \times 0.1 \times .75/\ 60 = 6\ 10^{-7}$µg perborate /kg BW /day and

$6.4\ 10^{-8}$ µg boron/ kg BW/day

This calculation shows that the exposure via inhalation is really negligible and also far below the general threshold of no concern of 1.5 µg day as defined by FDA (2001), or Munro and Kroes(1998).

5.1.3 Consumer exposure via the oral route

Oral uptake of sodium perborate mono or tetrahydrate via the use of household cleaning products is considered negligible under normal handling conditions. Due to the high water solubility and ionic character of the product and the degradation product boric acid/ borax as well as the instability of hydrogen peroxide in the dishwashing solution, possible exposure to residual amounts on dishes from dishwashing applications are considered negligible.

5.1.4 Accidental or intentional exposure

Accidental exposure to sodium perborate hydrates can occur via accidental swallowing of solid detergents or drinking of liquid washing solutions. Typically one would estimate that not more than 5 g of powder detergent (1.5 g of sodium perborate) or 20 ml of washing liquid (62 mg of sodium perborate hydrate) would be swallowed. Accidental exposure to eyes is possible by splashes of dilute washing solutions or to low amounts of the solid from hands into the eyes.

5.2 Hazard assessment

General remark the reliability of the different studies according to Klimisch et al. (1997) and adopted by HERA (2002) is given in the attached IUCLID data set. (Appendix 1)

5.2.1 Acute toxicity

Acute Oral Toxicity

Sodium perborate tetrahydrate was of low toxicity via the oral route in rats as derived from well documented acute studies, the oral LD_{50} in rat was 2567 or 2243 mg/kg bw (Degussa, 1987, Dufour, 1971). Sodium perborate monohydrate was of moderate toxicity with an oral LD_{50} in rat of 1120 to 1800 mg/kg bw (Interox, 1987a). The higher toxicity of the monohydrate is consistent with the lower water content of the salt and the administration as a very concentrated suspension that could give rise to local irritant effects that are rather concentration than dose related. Typical histopathological findings were distended gastrointestinal tract, probably due to the liberation of oxygen from hydrogen peroxide and signs of irritation in the stomach. Beagle dogs receiving 50 mg/kg bw of sodium perborate tetrahydrate showed a strong vomiting reflex due to hydrogen peroxide production and

subsequent release of oxygen in the stomach. No mortality or histopathological lesions were observed in anaesthetised dogs receiving up to 500 mg/kg bw of sodium perborate (Dufour et al., 1971).

Acute Inhalation Toxicity

In an acute inhalation study (DuPont, 1987) male Crl:CD®BR rats were exposed to 160, 480,1100 and 2900 mg/m^3 of micronised sodiumperborate tetrahydrate (particle size: MMAD 3.3.-4.2 µm). All exposed animals exhibited gasping and red nasal discharge. At concentrations higher than 480 mg/m3 also laboured breathing was observed. Surviving animals showed slight to severe body weight losses. 3 of 6 animals died at 1100 mg/m^3. Probit analysis of the experimental data revealed an LC_{50} of 1164 mg/m^3.

Silajew (1984) reported on inhalation studies in rats at concentrations between 3.7 and 74 mg/m^3. At 39 to 74 mg/m^3 the authors described symptoms of respiratory irritation (reduced respiration rate and an increase in total cell number in lung lavage fluid). The study is however poorly described since no details of exposure conditions, exposure time, number of animals or effects were given.

Acute Dermal Toxicity

After 24-h occlusive dermal application of 2000 mg/kg sodium perborate monohydrate to 5 male and 5 female rabbits, 9 of 10 animals survived and the death of one animal was not related to treatment according to the authors. Clinical signs reported in the survivors were diarrhoea, yellow nasal discharge and soiling of the anogenital area. Body weight changes of the survivors were generally normal. Apart from mild to moderate skin irritation on day 1 which decreased in severity during the 14 day observation period and distended intestines in 2 animals no histopathological abnormalities were noted. (Interox, 1987b):

Acute toxicity – other routes

Studies with i.v. administration are available and summarised together with the studies for relevant exposure routes in Table 14.

Table 14: Summary of acute toxicity data

Compound	Species Strain No. per Group, Sex	Details of administration	LD_{50} [mg/kg bw]	Dose [mg/kg bw]	Toxicological Effects	Reference
oral						
PBS1	rat Wistar 5 m, 5 f	concentrated aqueous suspension	1800 2100 (m) 1700 (f)		lethargy, ptosis, chromorhinorrhea, ataxia, prostration, bloated abdomen, diarrhoea, abnormalities of the lungs, liver, kidneys, spleen and gastrointestinal tract	Interox, 1987a
PBS1	rat n.g. 10-33 per dose	1.3 % aqueous solution		130 260 325	1/36 animals: hyperaemia of stomach mucosa	Mulinos et al., 1952
		2.6 % aqueous solution		260 520 650	27/61 animals: hyperaemia of stomach mucosa (no differentiation between the three doses)	
PBS4	rat, Wistar 9 m 9 f	in 1 % aqueous Tragant-suspension, limit test	2567 2670 (m) 2360 (f)		stomach enlarged, hyperaemia, reversible within 14 days, diarrhoea, salivation	Degussa, 1987
PBS4	rat n.g. n.g.	20 % aqueous solution	1600		not stated	Procter & Gamble, 1965
		50 % aqueous solution	1200			
PBS n.sp	rat Wistar 25 m, 25 f	in 2 % gummi arabicum,	2243		diarrhoea, salivation, apathy, hyperaemia of stomach, with white foam, females more susceptible	Dufour et al., 1971
PBS n.sp	rat Wistar 10 m	in 2 % gummi arabicum		2000	reduced weight gain; reversible hyperaemia of stomach serosa with reversible(within 10 days) superficial necrosis; no lesions in histopathological examinations, no pathological change in liver, kidneys and intestines no controls	Dufour et al., 1971

Table 14: Summary of acute toxicity data

Compound	**Species Strain No. per Group, Sex**	**Details of administration**	**LD_{50} [mg/kg bw]**	**Dose [mg/kg bw]**	**Toxicological Effects**	**Reference**
PBS n.sp	rat ChR-CD 5 m	not stated	3600 (m)		not stated	DuPont, 1972
PBS n.sp	mouse ddY 10m, 10f		3600 (m) 3250 (f)		diarrhoea, stomach bloated, hyperaemia in stomach, brain, lung	Momma et al., 1986
PBS n.sp	dogs beagle 1 m	in 10 % gummi arabicum		25, 50, 100, 250, 500	50, 250, 500: vomiting 100, 500: congestion's of mucosa of stomach	Dufour et al., 1971
Inhalation						
PBS4	Rat Crl:CD®BR 6 m	4h MMAD: 3.3 – 4.2 µm Diameter: 86-94 % < 10µm	1164 mg/m^3	160, 480, 1100, 2900	Lethality: 0/6, 1/6, 3/6, 5/6 during exposure: $\geq$ 160 mg/m^3: gasping, red nasal discharge $\geq$ 480 mg/m^3: laboured breathing $\geq$ 1100 mg/m^3: no startle response during postexposure period: in some surviving rats: red ocular, nasal or oral discharges, diarrhoea, gasping, lung noise slight to severe body weight losses within 24 hours of exposure	Du Pont, 1987;
PBS4	n.g.	n.g.		3.7, 11.3 mg/m^3	no effect	Silajev, 1984
				39 mg/m^3	reduced respiration rate, increase in total cell number in lavage from nasopharynx	
				58 mg/m^3	reduction in nervo-muscular excitability, increase in number of cells in lung lavage	
				74 mg/m^3	toxic effects, not further specified	
dermal						

Table 14: Summary of acute toxicity data

Compound	**Species Strain No. per Group, Sex**	**Details of administration**	**LD_{50} [mg/kg bw]**	**Dose [mg/kg bw]**	**Toxicological Effects**	**Reference**
PBS1	rabbit New Zealand 5 m, 5 f	OECD 402 24 h occlusive application of original substance slightly moistened with water,		2000	9/10 animals survived, 1 male died on day 13 after a 3-days-period of diarrhoea, from day 5-9 no signs of illness animal that died: diarrhoea, yellow nasal discharge, soiling of anogenital area, abnormalities of lungs, liver, spleen, gastro-intestinal tract 1 animal: distended intestines. 1 animal: skin reactions	Interox, 1987b
Intravenous						
PBS1	cat 5, sex n.g.	3 % in water		700-900	Injection from a burette at 1 cc per minute increased respiratory effort, dark colour of blood, death	Mulinos et al., 1952
PBS1	rabbit 1-11 per group, sex n.g.	2 % in water	78	22 50-56 60-68 70-80	deep cyanosis, asphyxia death	Mulinos et al., 1952
PBS n.sp.	dog beagle 1 m	dogs anaesthetised to avoid vomiting, after intravenous infusion oral application of the same dose (exception: animal that received 500 mg/kg bw) in physiologic saline		25 50	no effects	Dufour et al., 1971
				100 250	irritation of stomach mucosa, vomiting	
				500	death	

PBS n.sp. Sodium perborate, compound not specified
PBS1: Sodium perborate monohydrate
PBS4: Sodium perborate tetrahydrate
MMAD: mass median aerodynamic diameter, d: diameter

Conclusion:

Sodium perborate hydrates are of low to moderate acute toxicity via the oral, dermal and inhalation route in experimental animals. The most reliable studies that were performed according to modern standards (although not under GLP) and well reported are taken forward to the risk characterisation: LD_{50}, oral, rat: 2360 mg/kg bw (Tetrahydrate) and 1120 mg/kg for sodium perborate monohydrate, LD_{50} dermal, rabbit: > 2000 mg/kg bw, LC_{50} inhalation, rat: 1164 mg/m^3.

5.2.2 Corrosiveness/irritation

Skin Irritation

Sodium perborate tetrahydrate was non-irritant in a rabbit skin irritation study after 4 h of occlusive exposure. No erythema or oedema was observed in any of the animals. (ICI, 1986a). Slight irritation was observed after 4 h semi-occlusive exposure of 3 rabbits to sodium perborate monohydrate (Interox 1987c) and no irritation (no erythema or oedema) in another study in rabbits after 4 h occlusive exposure (ICI, 1986b). The applied dose in every study was 500 mg.

A human patch test was conducted in 26 volunteers (healthy humans aged 18 to 65). A sequential single patch test procedure was used applying 0.2 g of the test material on to a 25 mm plain hill top chamber containing a moistured Webril pad to the upper outer arm progressively from 15 min to 4 h. Treatment sites were assessed for the presence of irritation using a 4-point scale. A positive skin reaction included irritation of all grades at any time point. When irritation occurred the test was stopped on that person. Sodium dodecyl sulphate (SDS) was included as a weak positive control substance. 1 of 26 test persons showed a positive skin reaction while 21 of the 26 reacted to the positive control. On the basis of this result the material was evaluated as non-irritant to human skin (York et al., 1996).

Conclusion

In conclusion, both sodium perborate tetrahydrate and monohydrate should not be considered as skin irritants.

Eye Irritation

In a study with sodium perborate tetrahydrate, which used only two rabbits, one rabbit experienced severe pain and corneal opacity grade 3; the other rabbit had a corneal opacity grade 1.67; both had redness grade 3. One animal was killed for humane reasons on day 3, in the other animal the effects (corneal opacity, conjunctivae redness) were not completely reversible within 21 days. In this study severe eye irritation was observed. (ICI, 1986a). Similar results were reported by Momma et al., 1986, but the identity of the test substance is not clearly stated, while only slight irritation was reported for sodium perborate tetrahydrate by Procter and Gamble, 1965.

Momma et al. (1986) also investigated the effect of an eye washing procedure on the irritant effect of sodium perborate. After instilling 100 mg of sodium perborate into the left eye of 3 rabbits the eye was washed 4 or 30 seconds later. No irritant effects were observed in the washed eyes

Sodium perborate monohydrate when instilled into rabbit eyes (3 test animals) showed moderate to severe irritation. The results are shown below:

Table 15: Irritation scores Momma et al, (1986)

Effect	Score	Number Animals affected
Cornea opacity	2	3
Iris	1	3
Conjunctivae redness	3	3
Chemosis	2	1
	2.33	1
	2.7	1

The effects were reversible in two animals after 21 days, but one animal had persistent corneal opacity and conjunctival chemosis after 21 days. (Interox, 1987d). Severe eye irritation with the monohydrate was also demonstrated after instillation into the eye of one of 3 intended animals in which corneal opacity grade (2.7), iris reaction grade 1.3, conjunctival redness grade 3 and chemosis grade 2.7 was observed and the effects were not completely reversible within the 21 day observation period. (ICI, 1986b). Bagley et al, 1994 reported that sodium perborate (test substance not specified) was highly irritating to rabbit eye and the effects were not reversible within 35 days. It should be noted, however that the solution used was strongly alkaline.

It is most likely that **hydrogen peroxide** is the irritating principle of sodium perborate hydrates. For hydrogen peroxide several concentrations were tested in eye irritation studies to determine the threshold of irritation. 5 and 6% solutions of hydrogen peroxide were non-irritant or only slightly irritant to rabbit eye, while a concentration of 8% hydrogen peroxide caused severe irritation to eyes. Concentrations of 5% would correspond to concentrations of ca. 23 % sodium perborate tetrahydrate and 15 % sodium perborate monohydrate respectively, while a concentration of 8% hydrogen peroxide would correspond to a concentration of ca. 36 % sodium perborate tetrahydrate or 24 % sodium perborate monohydrate.

Evaluation:

Both sodium perborate monohydrate and tetrahydrate when applied undiluted to rabbit eyes revealed irritating effects. The severity of the effects varied considerably between the studies. Reasons for the variability of the results could be related to the test substance (mono- or tetra-hydrate) or the particle size distribution or a variation of hydrogen peroxide concentrations due to solubility differences. Furthermore different pH values and variable local concentrations due to differences in solubility of the solid substance in the conjunctival sac could play a role.

Conclusion

It can be concluded that sodium perborate mono- and tetrahydrate are moderate to severe eye irritants under certain conditions.

Using the data of diluted hydrogen peroxide solutions a threshold of irritation for sodium perborate tetrahydrate of ca. 23 % and for monohydrate of ca.15% could be derived. The concentration that would cause severe effects to eyes could be extrapolated to be about 36% sodium perborate tetrahydrate or 24% sodium perborate monohydrate.

5.2.3 Sensitisation

Sodium perborate monohydrate was tested in a Bühler Test in 10 guinea pigs (5 males, 5 females) receiving an irritant induction concentration (6 h/d, occlusive) once every seven days for a total of three applications. 14 days after the last induction the animals were challenged with a 5% solution in water (maximum non-irritant concentration). 10 untreated animals served as controls. One of 10 test group animals as well as one of 10 control group animals showed a very slight erythema after 24 h. The test substance was not skin sensitising in this test. (Interox, 1987e).

Conclusion:

Sodium perborate hydrates were not sensitising to skin in an appropriate animal test.

5.2.4 Repeated Dose Toxicity

Oral administration

Groups of 20 or 12 male rats were treated by gavage for 6 days with 200 or 1000 mg/kg bw of sodium perborate (quality not given), respectively. After administration of 1000 mg/kg bw, body weight gain and food consumption was comparable to that of control animals. Very slight haematological changes were observed in this dose group, which were, however in the range of the historical controls. No macroscopic or histopathological alterations were observed in the organs examined (liver, kidney, stomach, intestine). At 200 mg/kg no toxic effects were observed. (Dufour et al., 1971).

In a 28 day study conducted under GLP and in accordance with OECD guidelines, groups of 5 male and 5 female Wistar rats were treated, by gavage, with a limit dose of 1000 mg/kg/day of sodium perborate tetrahydrate administered in 1% aqueous tylose (methyl cellulose) suspension. Controls were administered 1- % aqueous tylose suspension. The administration volume was 4.64 ml/kg (concentration 215 mg/ml). The only clinical signs observed were salivation in all animals treated with sodium perborate immediately after administration, caused by local contact of the test substance with the mucus membranes of the mouth and the gastro-intestinal tract. Hypersalivation for up to 70 minutes was observed in some animals. A 15% reduction in body weight gain and food consumption was observed by the end of the study in males. The absolute weights of the testes, heart, brain, and kidneys were reduced in males, but the relative organ weights were not affected. Slight increased relative adrenal weights in males and liver weight in females were observed. The only alteration recorded in the macroscopic examination was a reduced spleen size observed in two male animals. Microscopic examination indicated a mild reduction of the splenic parenchyma only in males. Effects on the gastric mucosa were also observed in both males and females (slight acanthosis and hyperkeratosis in the forestomach, and hyperplasia of the fundic mucosa). Detailed testicular examination was carried out and no microscopic changes were observed. A slight decrease in red blood cell parameters and increase in platelets was observed in both males and females. A significant decrease in white blood cell count (due to an absolute reduction in lymphocyte numbers) seen in males may be associated with the reduction of splenic parenchyma. However, all the haematological changes were in physiological range and although possibly treatment related, were not considered to be of toxicological significance (Degussa, 1989).

Studies with hydrogen peroxide illustrating the local irritation effect after repeated oral administration

In a 90 day study with hydrogen peroxide mild duodenal mucosal hyperplasia was seen in catalase deficient mice given H_2O_2 in drinking water in concentrations of 100, 300, 1000 and 3000 ppm resulting in doses between 26 and 370 mg/kg bw per day. Both males and females receiving 3000 ppm exhibited significant reductions in body weight and food and water consumption; animals receiving 300 and 1000 ppm displayed intermittent reductions in food and water consumption. No

biologically significant differences in haematology parameters were noted among treated animals relative to controls. Males receiving 3000 ppm displayed significant reductions in total protein and globulin levels (clinical chemistry parameters) in the blood possibly attributable to reduced food consumption or reduced protein absorption caused by mucosal hyperplasia observed in the duodenum of these animals. No treatment-related significant differences in absolute or relative organ weights were noted. Necropsy revealed no treatment-related gross lesions. Macroscopic evaluation of tissue slides indicated an increase in the cross sectional diameter and wall thickness of the duodenum. Subsequent microscopic evaluation of the duodenum revealed minimal to mild mucosal hyperplasia in eight of nine males receiving 3000 ppm and in seven of ten males receiving 1000 ppm; minimal mucosal hyperplasia was noted in one of ten males receiving 300 ppm. Minimal to mild mucosal hyperplasia was also noted in ten of ten females receiving 3000 ppm and in eight of ten females receiving 1000 ppm. No duodenal mucosal hyperplasia was noted among females receiving 300 ppm or among males or females receiving 100 ppm. Duodenal mucosal hyperplasia is defined as an increase in mucosal area and an increase of villi size. No other areas of the gastrointestinal tract were affected. Microscopically, no evidence of cellular atypia or architectural disruptions nor any other indications of pre-neoplastic changes were observed; therefore, the treatment-related mucosal hyperplasia noted in this study was not considered to be a pre-neoplastic lesion.

After a 6-week recovery period no significant differences in haematology, clinical chemistry or organ weight parameters were noted among recovery animals. No treatment-related gross lesions were noted during necropsy of animals following the recovery period. No histopathological findings were noted that were attributed to previous treatment among any recovery animals following the recovery period. No mucosal hyperplasia was noted among recovery animals.

Based on dose-related reductions in food and water consumption, and the observation of duodenal mucosal hyperplasia for hydrogen peroxide, the Lowest Observed Adverse Effect Level (LOAEL) was 300 ppm and the No Observed Adverse Effect Level (NOAEL) was 100 ppm (26 and 37 mg/kg bwday for males and females, respectively). The food and water consumption decreases among animals receiving 300 and 1000 ppm were intermittent and reversible. Histopathological effects were not present in any organ other than the duodenum. Microscopically, neither evidence of cellular atypia or architectural disruptions nor any other indications of preneoplastic lesions were observed.

All effects noted during the treatment period of the study were reversible; animals sacrificed following the recovery period were considered biologically normal. No clinical signs of toxicity or morphological effects on any organ systems other than the local effects on the gastrointestinal tract were noted during the study (Freeman et al, 1997).

In another study on hydrogen peroxide, in rats given 56, 169 and 506 mg/kg bw per day of hydrogen peroxide by gavage (as 0.1 to 1.1 % (v/w) solution in water, 6d/weekfor 12 weeks), lesions of the gastric mucosa were reported in the high dose group (NOAEL 169 mg/kg bw per day (0.34 %)) (Ito et al., 1976).

Evaluation and conclusions

Sodium perborate tetrahydrate breaks down to boric acid and H_2O_2 under physiological conditions (see 4.1.2.1). An administered dose of 1000 mg/kg sodium perborate tetrahydrate if completely broken down would give rise to 220.8 mg/kg H_2O_2 according to the following equation:

$NaBO_3.4\ H_2O = NaOH + B(OH)_3 + H_2O_2 + H_2O$

(i.e. 1 mole $NaBO_3.4\ H_2O$ (mol wt 154) gives 1 mole H_2O_2 (mol wt 34), that is 154 mg $NaBO_3.4\ H_2O$ gives 34 mg H_2O_2).

When considering sodium perborate, males appeared to be more sensitive to the toxic effects as indicated by the accompanied 15% reduction in body weights gain and food consumption. However,

most of the observed effects are considered as secondary effects resulting from the local effects on the gastric mucosa. The reduction of splenic parenchyma in the treated males may have been caused by the reduced body weight gain of these animals. This is a common finding in starved animals (inanition atrophy) and is expected to be more pronounced in growing animals.

Thus a NOAEL for systemic effects of about 1000 mg/kg bw can be derived from the 28 day gavage study with sodium perborate while the local irritation observed is likely to be more concentration related (high local concentrations after bolus dosing). The clinical signs of hypersalivation and the histologic changes observed in the gastric mucosa are consistent with a local irritant effect probably related to the production of H_2O_2 as shown in studies on H_2O_2 summarised above. For local effects 1000 mg/kg bw (215 mg/ml) was a LOEL in this study.

Dermal application

Two dermal studies on sodium perborate with limited reporting are available. In the first study a 20% aqueous solution of sodium perborate monohydrate was spread on the clipped back of 3 male and 3 female New Zealand white rabbits covering approximately 10% of the body surface. The administered dose was 200 mg/kg bw per day applied daily for 20 days. Skin from animals in either group (control-water and test group) was near normal with individual animals showing mild irritation. There were indications of liver parasites (2 animals in test group) and gastritis and enteritis (1 animal in control group). No statistically significant differences between the two groups in growth, organ/body weight ratios, blood parameters, gross pathology, or histopathology were observed (Procter and Gamble, 1966a).

In the second study, groups of 3 male and 3 female rabbits received dermal doses of 50 mg/kg bw of sodium perborate tetrahydrate as a 2.5% solution in water 5 times per week for 13 weeks. Control animals were treated with water. No skin irritation was observed in either the control or test group. There were no statistically significant differences between the two groups in growth, organ/body weight ratios, blood parameters, gross pathology, or histopathology (Procter and Gamble, 1966b).

Conclusions

No systemic toxicity was observed after dermal application of up to 200 mg/kg bw of sodium perborate monohydrate, which is consistent with the low dermal absorption rate as described in section 5.2.8. As no higher dose level was tested, no clear conclusion on a NOAEL can be drawn from this studies, apart from the fact that the NOAEL is greater than 200 mg/kg bw per day after repeated dermal application for 20 days.

5.2.5 Genetic Toxicity

In vitro

A bacterial mutation test (Ames test) was conducted using strains TA 98, TA 100 and TA 102, both in the presence and absence of a metabolising system (S9) at doses of 10 – 2000 µg/plate and with and without catalase, to reduce/abolish any mutagenic effect due to generation of hydrogen peroxide. Strain TA 102 was included since this strain is receptive to oxidative substances. Positive responses were obtained with strains TA 100 and TA 102 in the absence of metabolic activation. Survival was reduced with TA100 above 20 µg/plate. At 100 µg/plate the number of revertants was increased by a factor of 1.5 whereas the survival rate was reduced to less than 15%. Both the mutation effect and the toxicity of sodium perborate were reduced by the presence of S9 fraction or catalase (10 µg/plate). This suggests that the rat liver mix or catalase provide a means of inactivating the mutagenic and toxic effects of perborate, possibly due to decomposition of the peroxygen constituents. (Seiler, 1989).

A DNA repair assay was conducted using E coli repair deficient and repair proficient strains at

concentrations of 0.0015 and 0.0033 µmoles (equivalent to 0.0002 and 0.0004 µg/ml). A positive response was obtained suggesting the perborate was capable of inducing preferential DNA repair. However, this test system did not include a metabolic activation process, and, the addition of catalase (50 µg/ml) reduced the effect suggesting that the perborate is inactivated by catalase (Rosenkranz, 1973).

Using Chinese hamster ovary mammalian cells (CHO-K1) the effects of perborate on chromosomal aberrations both in the presence and absence of S9 was investigated in concentrations between 10 and 100 µg/ml. As with the bacterial assay, a positive response was obtained in the absence of S9 which was abolished in the presence of S9 (Seiler, 1989).

In vivo

An in vivo genetic toxicity assay was not undertaken since it is unlikely that perborate administered in vivo would cause an increase in chromosomal aberrations or gene mutation. The rationale for this is that the in vitro profile observed is remarkably similar to that seen with hydrogen peroxide (EU, 2001). Hydrogen peroxide is produced under physiological conditions and would therefore be formed in the test organisms. Studies with hydrogen peroxide are therefore relevant for the assessment of the in vivo genotoxic potential sodium perborate hydrates as well. The most important studies on hydrogen peroxide are summarised below.

Studies with hydrogen peroxide

Hydrogen peroxide has been examined for its mutagenic potential in vivo in the mouse micronucleus assay after single i.p. administration of up to 1000 mg/kg body weight (Molinier, 1995), and after repeated oral administration of mice exposed to up to 6000 mg/l hydrogen peroxide (maximum applicable concentration) in drinking water for 14 days (Ross, 1995). In both cases, no evidence of micronucleus formation was observed. Negative results were also reported in a rat bone marrow chromosomal aberration assay (Kawasaki et al., 1969) and in an in vivo sex linked recessive lethal assay in Drosophila. (Di Paolo, 1952).

An in vivo UDS assay was conducted in Wistar rats with i.v. doses of 25 and 50 mg/kg hydrogen peroxide, 50 mg/kg being the maximum tolerated dose. Preparation of the hepatocytes was performed 2 to 4 or 12 to 14 hours after dosing to assess unscheduled DNA synthesis. There was no evidence of a UDS response. (Clare, 1996).

Hydrogen peroxide was evaluated for the ability to produce DNA damage (8-OH-dG), ha-ras mutations, and sustained epidermal hyperplasia in a study designed to establish a pre-screen for the carcinogenicity of organic peroxides.

Hydrogen peroxide (70%) was applied to the skin of female Sencar mice (10/group) at dose levels of 10, 100 and 200 µmol (in 200 µl of ethanol) twice weekly for four weeks. DMBA (10 and 100 µmol) and ethanol (200 µl) were used concurrently as positive and negative controls. The animals were sacrificed on days 2 or 4 after the end of treatment (5 animals/day). After fixing and staining, epithelial and dermal thickness, and dermal cellularity was determined visually by light microscopy. Non-phenol extraction of fresh frozen tissue was used to isolate DNA from animals killed 2 days after the last dosing, and following digestions to nucleosides, 8-OH-dG was quantified by HPLC. Mutations in codon 61 of HA-ras were determined using DNA isolated from paraffin blocks of whole skin. Hydrogen peroxide caused no changes in any end-point and was therefore considered not being of concern for carcinogenicity (Slaga, 1997).

Evaluation and conclusions

The effects seen in vitro with sodium perborate are similar to those observed for hydrogen peroxide. For hydrogen peroxide it has been concluded that the presence of exogenous metabolising agents or

catalase reduces or abolishes the effect seen in the absence of a metabolising system and that the potential genotoxicity is not manifested in vivo. It can therefore be concluded that sodium perborate is similar to hydrogen peroxide and like hydrogen peroxide would not cause an effect in vivo.

5.2.6 Carcinogenicity

No studies on the carcinogenicity of sodium perborate itself are available. The relevant degradation products hydrogen peroxide and boric acid have been evaluated for a possible carcinogenic effect and are therefore reviewed in brief in this report. For recent reviews on hydrogen peroxide see ECETOC, 1996, and EU, 2001, for reviews of boric acid see WHO, 1998 and Hubbard, 1998.

Studies with hydrogen peroxide

For hydrogen peroxide several studies show that long-term oral administration of 0.1-0.4 % H2O2 causes an inflammatory response in gastroduodenal tissue of mice. The response is limited to the glandular stomach and, to a lesser extent, to the peri-pyloric and proximal portion of the duodenum. No inflammatory response was observed in the oral cavity, forestomach or distal intestinal tract. The incidence was higher in strains of mice with a low catalase activity. Studies by Ito et al (1982) revealed that cessation of H_2O_2 administration causes a regression of lesions induced by prolonged (up to 180d) administration of H_2O_2 in drinking water. The investigations by Ito et al (1981a,b) suggest that this inflammatory response may progress to carcinogenic changes in mice that are catalase deficient. In rats, H_2O_2 induced only papillomas; no malignant tumours of the forestomach were seen, even at nearly lethal concentrations (1-1.5% H_2O_2 in drinking water) (Ishikawa and Takayama, 1984) Initiation-promotion studies suggest that H_2O_2 is not an initiator in skin, but may be a weak promoter of tumours in the rat at high (>15%) concentrations on the skin, or nearly lethal concentrations (1.5%) in drinking water (ECETOC, 1996).

In the 90-d study performed on catalase-deficient, C57BL/6NCrlBR mice that received constant concentrations of 0, 100, 300, 1000, or 3000 ppm of hydrogen peroxide (H2O2) in distilled drinking water for approximately 90 days, microscopically, no evidence of cellular atypia or architectural disruptions nor any other indications of pre-neoplastic changes were observed. Therefore, the treatment-related mucosal hyperplasia noted in this study is not considered to be a pre-neoplastic lesion (Freeman et al., 1997). This reinforces the conclusion from the data of Ito (1982) suggesting that only inflammatory changes seen at nearly lethal concentrations in particularly catalase-deficient species or individuals could possibly lead to local tumours.

In vivo data currently point strongly to the fact that hydrogen peroxide is not an in vivo genotoxin. The induction of carcinogenicity by a non-genotoxic mechanism has been proposed (Troll and Wiesner, 1985, ECETOC, 1991). The fact that tumours were induced only at the sites where high concentrations of H_2O_2 came directly into contact with the tissues and that the tumours were associated with persistent local inflammation supports a non-genotoxic mechanism for the gastrointestinal tract tumours in test animals with impaired repair mechanisms. It can be underlined also here that four recent studies demonstrated the lack of genotoxicity of hydrogen peroxide when administered in vivo at the maximally tolerated dose by different routes (intra-peritoneal, oral (2-wk via drinking water), i.v. or dermal). Consequently it can be concluded that hydrogen peroxide is unlikely to be carcinogenic under relevant human exposure conditions.

All recent evaluations have concluded that hydrogen peroxide is of no concern with regard to a possible carcinogenicity in humans (ACGIH, 1995, US FDA, 1991, EU, 2001, EPA 2002)

Studies with boric acid and borax

Boric acid and borax were negative in carcinogenicity studies with rats, dogs and mice (Hubbard, 1998; WHO, 1998).

Conclusions

No studies on carcinogenicity are available for sodium perborate hydrates themselves. However, the degradation products hydrogen peroxide and boric acid have been evaluated with regard to their carcinogenicity and it was concluded that there is no concern for a possible carcinogenic effect in humans. Therefore it can be concluded that there is also no concern with regard to a possible carcinogenicity of sodium perborate hydrates.

5.2.7 Toxicity to reproduction

Fertility

Studies with boric acid and borax administered in high doses to rodents revealed some effects on fertility. The most sensitive effects observed in studies with boric acid and borates were however, the histopathological changes in the testes that occurred already after relative short exposure periods and were detectable with normal histopathological examination. With regard to possible effects on fertility of sodium perborate hydrates a detailed histopathological examination of the testes was therefore included in the 28 day study (Degussa, 1989), described in section 5.2.4 in order to enable comparison with the effects of borates in studies of comparable duration, rather than following the general approach (fertility study) for the evaluation of effects on fertility.

Studies with boric acid

Testicular effects and effects on spermiation have been observed in rats already after very short exposures to high doses of boric acid (even single doses of 1000 mg/kg bw. caused some effects (Lindner et al. 1990). The damage to the testes with boric acid increased over 7 to 10 to 14, and 21days, with the maximum occurring in all animals of the group at 28 days. This is the optimal time to detect testicular damage.

In a study of Treinen and Chapin (1991) inhibition of spermiation was already observed after 7 days of treatment with doses of 61 mg boron/kg bw in the diet. In this study after 28 days extreme epithelial disorganisation and sperm cell loss was evident. Ku et al. (1993) observed testicular toxicity after application of boric acid from concentrations corresponding to 26 B/kg bw, which was apparent after 4 weeks of treatment by histopathological analysis including staging.
Even in 1962 Caujolle et al. were able to detect the effects after 30 days of gavage in rats with boric acid doses corresponding to boron levels between 35 and 140 mg/kg bw.
In the studies with boric acid the testicular pathology associated with boric acid exposure was severe, with cell death, cell sloughing, and epithelial disorganisation evident. These severe pathologies are easily detectable in testis tissues fixed in formalin and sectioned for H&E examination.

In a number of studies with boric acid or borax of longer duration, the NOAEL and LOEL levels for testicular damage did not change with the study duration (ECETOC, 1995).

Study with sodium perborate tetrahydrate

In the 28 day limit dose study reviewed in 5.2.4 (Degussa, 1989), a 15% decrease in absolute testicular weight was recorded, but the relative testis weight was not reduced. This apparent reduction in weight was attributed to a generalised weight reduction, which could be related to reduced food intake since several other organ weights appeared to be similarly affected. A study of Feron et al. 1973 on the influence of dietary restriction on testicular weight clearly demonstrated that the effect of diet restriction on even relative testicular weight is dependent on the study duration “the relative weight of the testis decreased with increasing growth retardation after the feeding of the diets for a period of 4 wk, but the opposite effect occurred after feeding for 13 wk”. With regard to specific boron-effects Ku et al. 1993 demonstrated that effects on testicular weight due to boron only occurred secondary to severe histopathological lesions in the testes. The weight of evidence from these considerations

suggests that the effects on testicular weight seen in the 28-day study were secondary to reduced food consumption and not treatment related.

A detailed histopathological examination of the testis in the Degussa (1989) study revealed no adverse effects. In particular effects observed with boric acid in comparable 28 day repeated dose studies (see above) (Treinen and Chapin, 1991, Ku et al., 1993) were not present. An occasional minimal inhibition of spermiation was present in some tubules of both treated and control animals and was consistent with normal background findings in this strain of rats (Harleman, J.H. 1999).

Since the perborate exposure (1000 mg/kg bw/day corresponding to 70 mg/kg bw per day of boron) in the Degussa study was three times the boric acid exposure that produced the severe testicular pathologies, the lack of any cell death, cell sloughing, and epithelial disorganisation reasonably indicates that there was no testicular toxicity due to the perborate exposure.

The NOAEL for this endpoint is therefore 1000 mg/kg bw sodium perborate tetrahydrate (the maximum tolerated dose), corresponding to 70 mg/kg bw per day of boron.

Evaluation and conclusions

At doses of boric acid of 61 mg/kg bw. of boron, Treinen and Chapin, (1991) and from 26 mg/kg bw of boron Ku et al. (1993) effects on the testes have been observed after 7 to 28 days of treatment. These are the lead effects and most sensitive endpoints indicating possible effects on fertility for boron compounds. In studies with boric acid or borax of longer duration, the NOAEL and LOEL levels for testicular damage did not change with the study duration (ECETOC, 1995). These data provide evidence that a study duration of 28 days and normal histopathology of the testes should be sufficient to detect indications for boron related effects on fertility in the form of histopathological changes in the testes. No effects on the testes indicative of boron toxicity were observed in the 28 day study with sodium perborate tetrahydrate at a maximum tolerated dose of 1000 mg/kg/day sodium perborate tetrahydrate corresponding to a dose of 70 mg/kg bw per day of boron. This result suggests a reduced availability of boron to the target organ and therefore no effects of sodium perborate on the testis. Thus it can be concluded that at doses which caused already some local toxicity no effects on the reproductive organs were observed and the NOAEL of sodium perborate tetrahydrate with regard to possible effects on fertility is 1000 mg/kg bw and day or an external dose of 70 mg B /kg bw and day.

Developmental effects

Groups of 25 mated Charles River (Italy) Sprague Dawley rats, Crl.CD (SD) BR, were given doses of 0, 100, 300 and 1000 mg/kg bw of sodium perborate tetrahydrate by gavage from days 6 - 15 of gestation (vaginal smear positive = day 0). The controls were given 10 ml/kg bw 1% aqueous methylcellulose which was used as the vehicle. All animals were killed on day 20 of gestation for examination of the pregnancy and foetal parameters. External examination of all foetuses was carried out and one half of the foetuses were stained with alizarin and examined for skeletal effects, and the other half of the foetuses examined for visceral effects using the Wilson slicing technique (Bussi, 1995; Bussi et al., 1996).

Of the 25 rats in each group, the numbers pregnant at term were 21, 20, 20 and 19 in the 0, 100, 300 and 1000 mg/kg bw respectively. In these groups, complete resorption of the entire litter were observed in 2/20 and 1/19 litters in the mid and high dose groups.

The results were presented as Group A which includes all pregnant animals including those which had 100% resorptions, and Group B which includes only those pregnant animals with live foetuses on day 20. Group A data are preferred for analysis of pregnancy data, where as Group B are more appropriate for effects on dams such as body weight gain.

Maternal Effects

Since no clinical signs of toxicity were reported, the only criteria for assessment of maternal toxicity are effects on body weight gain and food intake. Body weight gain data are summarised in table 16 Significant reductions in bodyweight gain were observed at the two top doses.

Table 16: Summary of % reduction in body weight gains over control animals

	Group A		**Group B**	
	300 mg/kg bw	**1000 mg/kg bw**	**300 mg/kg bw**	**1000 mg/kg bw**
gd 0 –20	↓ 22.5%	↓ 28%	↓ 16%	↓ 25.4%
gd 6-20	↓ 24.9%	↓ 31.4%	↓ 18.4%	↓ 29%
gd 6-15	ns 14.3%	↓ 28%	ns 7.6%	↓ 25.7%

Group A - all pregnant animals including those which had 100% resorptions; Group B includes only those pregnant animals with live foetuses on day 20; gd – gestation day.

↓ - Statistically significant effect $P < 0.01$; ns – non-statistically significant effect Statistical analysis by Chi-squared and Fischer's exact test.

A significant reduction in food intake was observed in the top dose group (1000 mg/kg). At 300 mg/kg a reduction in body weight and body weight gain was observed over gd 6-20.

The NOAEL for maternal toxicity is therefore 100 mg/kg

Foetal effects

A statistically significant increase in resorptions at the high dose level of 1000 mg/kg bw was observed when analysed on both a per litter and a per foetus basis. The preimplantation and postimplantation losses were 20.7% and 10.66% respectively compared to controls of 13.3 % and 2.81% respectively. The effect at 300 mg/kg bw is less clear, with no increases in resorptions being observed when litter data were analysed. A small postimplantation loss (5.88% compared to 2.81% in controls) was observed when foetal data were analysed. However this is largely due to the complete resorptions seen in two of the litters. If the two animals with complete resorptions are excluded, then there are no significant effects at 300 mg/kg. In addition, the preimplantation loss is very close to the historical control value of the laboratory of 5.14%.

At the highest dose, 1000 mg/kg bw, there was a statistically significant reduction in foetal body weight (35 % reduction compared to controls); litter weight (40% reduction compared to controls) and placental weight (26% reduction compared to controls). A smaller, but statistically significant reduction in foetal weight only (11% compared to controls) was seen at the mid dose, 300 mg/kg bw.

Statistically significant increases in visceral malformations (11 foetuses in 9 litters treated; 0 in controls) and skeletal (95% treated; 59% in controls) and visceral anomalies (11 foetuses in 6 litters treated; 1 foetus in 1 litter in controls) and visceral variants (55% treated; 18% in controls) were observed at the top dose level of 1000 mg/kg. At 300 and 100 mg/kg the only significant increase was in visceral variants (34% and 37% at 300 and 100 mg/kg respectively; 18% in controls). These were considered incidental as they fell within the range of variability for this strain of rats. A non-significant increase in external malformations (6 foetuses from 2 litters) at the lowest dose only was not treatment related.

Evaluation and conclusions

At 1000 mg/kg bw, there is clear evidence of maternal toxicity, together with foetal toxicity and an increased incidence of malformations. At the mid dose of 300 mg/kg bw some evidence of maternal

toxicity was observed but it was not severe. At this dose there was a small, but significant reduction in foetal body weight. At 100 mg/kg bw and day no biological significant changes were observed.

As sodium perborate tetrahydrate breaks down to boric acid and H_2O_2 under physiological conditions, the released hydrogen peroxide is likely to cause irritation of the mucous membranes of the gastro-intestinal tract that could be the cause for the observed maternal toxicity. The low dose of 100 mg/kg bw of sodium perborate tetrahydrate can be regarded as the NOAEL for both maternal and developmental toxicity.

5.2.8 Additional data

Toxicokinetic information

Sodium perborate mono- or tetrahydrate is an inorganic water-soluble solid of relatively low molecular weight. In aqueous solutions, an equilibrium between sodium perborate, hydrogen peroxide and borate species exists. However, it will be difficult to determine the equilibrium constant or equilibrium concentrations of the different species under physiological conditions in different tissues.

Dermal absorption is assumed to be low due to the hydrophilic character and ionic structure of the substance. This assumption is corroborated by studies with different borates with absorption rates in the range of around 0.1 to 0.2 % based on human in vivo dermal absorption studies (boric acid 0.226 ± 0.125; disodium tetraborate decahydrate (borax) 0.210 ± 0.194; disodium octaborate tetrahydrate 0.122 ± 0.10) (Wester et al., 1998). Even if the confidence limits are taken into account the maximum dermal absorption should be lower than 0.4%. It is unlikely that sodium perborate is absorbed to a higher amount, because hydrogen peroxide will inhibit rather than enhance absorption (see below).

After oral or inhalation (in the case of respirable dust) exposure, absorption may be limited by local irritation at the site of contact. Absorption at higher concentrations may further be reduced by the degradation product hydrogen peroxide, which is rapidly degraded by local tissue enzymes (catalase, peroxidase, superoxide dismutase etc.), to water and oxygen. At high concentrations (equivalent to about 3% hydrogen peroxide) the latter forms gaseous oxygen bubbles causing reversible capillary microembolism and preventing irrigation of the tissues by blood.

No data are available on the distribution of sodium perborate in the body. Distribution of the ultimate degradation products (water, oxygen and borates) is expected throughout the body water, and no accumulation in organs or fatty tissues is anticipated (EU, 2001).

No data on metabolism of sodium perborate itself are available. However, equilibrium between sodium perborate, hydrogen peroxide and borate species exists in aqueous solutions. Effective detoxification mechanisms are in place in the body to effectively destroy and detoxify hydrogen peroxide. The detoxification systems are practically unsaturable. Hydrogen peroxide will be rapidly metabolised to water and oxygen by local oxidation reactions or by local tissue enzymes (catalase, superoxide dismutase, and peroxidases) at the site of contact or in the blood, which results in a net degradation of perborate. Boric acid is not further metabolised due to the high energy needed to break the O-H bond (Emsley, 1989) and is eliminated as un-dissociated boric acid in urine as demonstrated in studies with borate in different species including humans (for example in ECETOC, 1995). This information will be reviewed in the HERA risk assessment on boric acid, including data on a comparison between rat and human renal clearance.

More information is available about the essentiality of boron, including the recent assignment of a Tolerable Upper Intake Level for boron of 20 mg/day by the US Food and Nutrition Board (2001). Again this will be reviewed in the HERA risk assessment on boric acid.

5.2.9 Experience with Human Exposure

No adverse effects have been reported from the use of sodium perborate in washing detergents. Some human experience has been reported from human health surveillance in production workers of two production plants. Two plants covered a total of 67 workers of which 46 were working in sodium perborate mono and/or tetrahydrate production for 9 or more years. No alterations in lung function or other symptoms of upper respiratory tract irritation related to sodium perborate mono or tetrahydrate exposure were observed in their workforce. In one plant 2 workers suffering from respiratory allergy to platinum salts and 3 workers with a hyperreactive bronchial system were employed in the sodium perborate mono and/or tetrahydrate production without further impairment of their disease. There was no abnormal development in lung function parameters (FVC (forced vital capacity) and PEF peak expiratory flow) over time in the surveyed work forces. The physicians confirmed that no other clinical symptoms were observed in the workers, which could be related to sodium perborate mono and/or tetrahydrate exposure. (Degussa, 1999).

A poison centre report under the UK home accidents surveillance scheme has been kindly provided by Unilever (DTI, 1998). It summarises an analysis of accidents with household products for the year 1998, which were the most recent data available. However, the report included a survey from 1991 to 1998, which showed that the numbers were relatively constant. Of a total number of accident records of 145361, 717 were related to cleaning products. Of those 59 were related to laundry and dishwashing agents: 30 to detergents/wash powder (4%), 21 to dishwasher products (3%), 8 to clothes wash liquid. Most of the injuries were categorised as “chemical injury” (40), in 17 cases no injury was diagnosed, 9 cases of non-injurious foreign body reactions and 6 cases of injurious foreign body reactions were reported other injuries (unspecified or soft tissue) were reported in 8 cases, one case of specific injury and 5 cases were categorised as unspecific injuries. Poisoning was reported in 9 cases for detergents/wash powder, 11 cases each for dishwasher products and 2 for wash liquid. Corrosion was stated in 2 cases for detergents/wash powder, dishwashing agents. No allergic reactions were observed with those products. The age distribution of the accidents with laundry detergents and dishwashing agents is largely biased towards small children between 0-4 years: 5 accidents occurred with wash liquid, 17 with wash powder, and 15 with dishwasher products. In the age group 5 to 14 years only 1 accident each with laundry detergents and dishwashing liquids occurred. For the age group of 15 to 64 years 2 accidents with washing liquids, 10 with laundry detergents, 5 with dishwashing agents were reported. The age group of 65 to 74 had one accident with washing liquid, while in the age group of 75+ 2 accidents with laundry detergents were observed. Poisoning, ingestion and skin contact (referred to as chemical injury) were the main causes of these accidents (69% of the accidents in children of 0-4 years related to washing or dishwashing, while only 23% were reported to have chemical injury in the age group of 15 to 64 and no cases were reported in people above 65 years. Foreign body/eye injuries were reported in very few people 4 cases for washing or dishwasher detergents, thereof 3 in children aged 0-4 and one in the age group of 15-64. The severity of the accidents seems rather low. No fatalities were reported and 59% of the accidents involving laundry and dishwashing agents could be treated at home. Further 46% could be treated ambulantly by a doctor. None of the patients involved in laundry detergent/dishwashing agent accidents was treated in a hospital. The majority of the accidents in the household with products that could contain sodium perborates consist of accidental ingestion or skin contact in particular of small children with seemingly slight effects only. No firm conclusions on the involvement of perborate can be drawn, but it is noteworthy that only very few cases of eye irritation were observed.

5.2.10 Identification of critical endpoints

Sodium perborate hydrates are of low to moderate acute toxicity via the oral, dermal and inhalation route in experimental animals. They are non-irritant to skin and are moderate to severe eye irritants. They are no skin sensitisers and because of their mechanism of action via hydrogen peroxide are not considered mutagenic or carcinogenic.

With regard to toxicity to reproduction, no formal fertility studies are available, but the most critical

endpoint related to that endpoint for boron compounds, histopathological changes in the testes after repeated exposure for 28 days has been investigated. No effects on the testes indicative of boron toxicity were observed in the 28 day study with sodium perborate tetrahydrate at a maximum tolerated dose of 1000 mg/kg/day sodium perborate tetrahydrate corresponding to a dose of 70 mg/kg bw per day of boron.

Sodium perborate tetrahydrate was did not reveal developmental toxicity at dose levels that were not maternally toxic. The NOAEL for both maternal and developmental toxicity was 100 mg sodium perborate tetrahydrate/kg bw per day(corresponding to 7 mg B/kg bw per day.

The most important endpoints with regard to possible consumer exposure are local irritating effects in particular on the eyes and mucous membranes. However, the following data will be considered in order to include all relevant endpoints in the risk assessment.

Determination of NOAEL or quantitative evaluation of data

The relevant quantitative data and NOAELs that are used for the risk characterisation are summarised in table 17.

Table 17: Data to be used in the risk evaluation

Endpoint	**Value**	effect/remarks
LD50, oral, rat	2360 mg/kg (Tetrahydrate) 1120 mg/kg (monohydrate)	development of oxygen
acute inhalation, rat LC50, inhal. rat:	39-74 mg/m^3 1164 mg/m^3	respiratory irritation threshold
LD50, dermal, rabbit	> 2000 mg/kg	
28 day repeated dose oral, rat	LOAEL 1000 mg/kg bw day (conc. 215 g/l) for local effects NOAEL for systemic effects: , 1000 mg/kg bw day	local irritation, reduced bw gain , but no clear systemic toxicity
Fertility, repeated dose study, rat	highest limit dose NOAEL 1000 mg/kg bw (corresponding to 70 mg/kg bw as boron) per day	from 28 day oral gavage study
Developmental toxicity	maternal and foetal NOAEL: 100 mg/kg bw, (corresponding to 7 mg/kg bw as boron)	Developmental oral study, rat
Local skin irritation (hydrogen peroxide)	35 % (w/V)	irritation threshold of H_2O_2
Local eye irritation (hydrogen peroxide)	5% (w/V)	irritation threshold of H_2O_2
Respiratory irritation (repeated exposure, hydrogen peroxide)	2 mg/m^3 of H_2O_2 corresponding to ca. 10 mg/m^3 of sodium perborate monohydrate	irritation threshold of H_2O_2

5.3 Risk Assessment

5.3.1 Margins of exposure

Local effects

Skin or eye contact to the solid product:

Sodium perborate hydrates themselves were not or only slightly irritating to skin. Contact with the solid product should not lead to local irritation. Eye and mucous membrane irritation are due to the formation of hydrogen peroxide in aqueous solutions have a steep dose response curve.

If 0.1 g of a solid detergent were brought into the eye, this would correspond to 0.034 g of hydrogen peroxide. If this would be diluted in 0.5 ml of tear liquid this would result in a solution of around 7%, which would be expected to be irritant, but would not cause irreversible damage to the eye. This is in accordance with the reports of poison centres that report rather slight irritation effects from detergent spills into the eyes (DTI, 1998).

Skin or eye contact to solutions

As in aqueous solution hydrogen peroxide is formed that may be irritant to skin in concentrations from about 35%, it may be useful to look at the concentration of hydrogen peroxide that could be reached in a handwashing solution. Some eye irritation can occur from about 6% of hydrogen peroxide, while 8% did already cause irreversible effects in rabbit eyes. The maximum content of hydrogen peroxide in a handwashing solution will be 1.05 %. This concentration should not lead to skin or eye irritation.

Inhalation exposure

As dust inhalation is very low and occurs infrequently as a typical acute exposure situation there is no concern with regard to possible local effects. The exposure estimate gave sodium perborate levels in the range of 8 ng/m^3 of inhalable dust they will not lead to local irritation. The acute irritation threshold was in the range of 39 to 74 mg/m^3, which would give a margin of exposure of 10 orders of magnitude. Even if repeated exposure is considered and the long term irritation threshold of hydrogen peroxide (approximately 2 mg/m^3 corresponding to about 10 mg/m^3 of sodium perborate monohydrate) is considered, this will still lead to a margin of exposure of 8 orders of magnitude.

Systemic effects

Consumer exposure via direct skin contact

The worst case exposure estimate for skin contact via the use of sodium perborate containing detergents for hand washing leads to a maximum systemic exposure of sodium perborate mono- or tetrahydrate of 0.087 µg/kg bw/day or 0.009 µg/kg bw per day of boron (if based on sodium perborate monohydrate). The possible critical effects from repeated exposure would be effects on fertility or developmental toxicity with a NOAEL in the animal models of 1000 mg/kg bw per day of sodium perborate tetrahydrate (70 mg B/kg bw and day) and 100 mg/kg bw per day (7 mg B /kg bw and day) respectively. The margin of exposure is thus 1000/ $8.7x\ 10^{-5} = 1.1x10^7$ (based on perborate) or 70/ $9x10^{-6} = 7.7\ x10^6$ (based on B) for possible effects on male sex organs. The margin of exposure for developmental toxicity is $1.1x10^6$ based on perborate or 7/ $9\ x\ 10^{-6} = 7.7\ 10^5$ based on Boron. As the margins of exposure are very high it can be concluded that there is no risk for systemic and reproductive effects from dermal contact to detergents containing sodium perborate.

Consumer exposure via inhalation

As the dust levels are extremely low and a worst case estimate gives an exposure in the range of 6 x 10^{-7} mg perborate per kg bw and day (6.4 x10^{-8} mg B/kg bw per day) which is clearly negligible and there is no risk to consumers with regard to that exposure. The Margins of exposure resulting are 1.6 x 10^{9} (based on sodium perborate tetrahydrate) (1.1 x10^{9} based on boron) for systemic effects and fertility and 1.6 x 10^{8} (based on sodium perborate tetrahydrate) or 1.1 10^{8} (based on boron) for possible developmental toxicity.

Combined exposure

As the contribution of inhalation exposure is 2 orders of magnitude lower then that after skin exposure the skin margins of safety for the latter also apply to combined exposure.

Accidental exposures via ingestion

Accidental swallowing is typically an acute exposure situation. Unfortunately the amounts swallowed are not recorded in the poison centre reports. Typically one would estimate that not more than 5 g of detergent or 1.5 g of sodium perborate hydrate could be swallowed. For a 10 kg child this would result in a dose of 150 mg/kg bw. Lethal effects in animals occur from 1000 to 2000 mg/kg bw in rodents. However, it is likely that due to the liberation of hydrogen peroxide in the stomach humans will vomit and not be able to take up lethal amounts of detergents. The poison centre records that have not registered any fatal poisonings due to the swallowing of detergents corroborate this. They have only reported immediately reversible irritation reactions of relatively benign nature (DTI, 1998).

5.3.2 Consumer Risk characterisation

The different exposure scenarios for the handling and use of detergent products containing sodium perborate hydrates did not reveal any risk for consumers from the use of these materials. Consumers will normally not be exposed to irritant concentrations of the products and the systemic dose is extremely low with margins of safety of several orders of magnitude. Systemic dose levels of boron resulting from detergent use are far below the natural levels in the diet that were estimated to lead to daily intakes of 1.6 to 7 mg per day (26 µg/kg per day to 117 µg/kg per day for a 60 kg individual) in Western Europe (ECETOC, 1995).

Accidental exposure may lead to transient irritation of eyes and mucous membranes, but despite the widespread use of those products, such accidents were never reported to have fatal consequences.

Therefore it can be concluded that household detergents containing sodium perborate terahydrates can be safely used by consumers.

5.3.3 Indirect exposure via the environment

Indirect exposure via the environment to perborate itself will not occur. Indirect exposure via the environment will only occur to the degradation product be boric acid. Boron level in drinking water is the only relevant sources that have been related to the use of sodium perborate in bleach containing detergent products. As many other sources, including natural levels contribute to the boron level in drinking water a sensible assessment can only be made on the total levels. In an overconservative estimate the boron concentration in drinking water resulting of the use of perborate hydrates in household detergent products was calculated by EUSES to be 0.06 mg B/l which seems a relative low contribution to the total amount in drinking water.

Based on the data of boron compounds a drinking water limit of 1 mg/l has been set in the (EU, 1998).

5.3.4 Discussion and conclusions

Sodium perborate mono and terahydrates have a long history of safe use in bleach-containing detergent products in particular in laundry detergents and machine dishwashing agents. The substances are of low to moderate acute toxicity via the oral and inhalation route and of low toxicity via the dermal route.

In aqueous media hydrogen peroxide and boric acid, which are both physiological substances mainly determine the toxicological properties of perborates.

Hydrogen peroxide is known for its local irritant and cytotoxic properties that are also at play in the physiological defence systems of the human body. Effective detoxification mechanisms are in place in the body to effectively destroy and detoxify hydrogen peroxide. The detoxification systems are practically unsaturable. The local toxicity of sodium perborate hydrates is mediated by hydrogen peroxide.

With regard to genotoxicity and carcinogenicity the properties of sodium perborate also resemble those of hydrogen peroxide and it can be concluded that there is no concern for humans with regard to a possible genotoxicity or carcinogenicity of the products.

Boric acid, which is the species that may be systemically available from sodium perborate, is also of low acute toxicity and does not have any genotoxic or carcinogenic potential.

The toxicologic endpoints of concern for boric acid from studies in rodents were effects on fertility, with the most sensitive endpoint being histopathological changes in male sex organs, and developmental toxicity at high dose levels. Consequently possible effects of sodium perborate concerning these endpoints were studied. A repeated dose study in rats was conducted with the maximum tolerated dose of sodium perborate tetra hydrate. With sodium perborate no effects on the testes suggestive of boron toxicity were observed and the highest dose was considered a no effect level for this systemic effect. Effects on developmental toxicity were only observed at maternally toxic dose levels of sodium perborate and, at the mid dose level that caused already significant maternal toxicity, these could be attributed to secondary effects due to maternal toxicity.

Indirect exposure to perborate itself via the environment does not occur due to its rapid abiotic and biotic degradation. Consumer use of sodium perborate containing detergent products contributes to the content of boron in drinking water, which is however also determined by natural sources. Boron content of drinking water is regulated in the EU by the drinking water directive with a limit of 1 mg B/l. (EU, 1998).

Human exposure to products containing sodium perborate hydrates under normal handling conditions are so low (0.09 µg sodium perborate/ kg bw per day, maximum concentration in a handwashing solution 3.1 mg/l or 1.05 mg hydrogen peroxide/l), that they will neither lead to local irritation nor to any systemic effects. The margins of safety are several orders of magnitude for 10^6 to 10^7 for possible systemic effects including fertility and developmental toxicity.

Accidental exposure to eyes may result in transient irritation that is normally readily reversible. Accidental swallowing may lead to irritation of mucous membranes in the gastro-intestinal tract and in some cases vomiting. These effects are normally also readily reversible and no fatal or severe poisoning cases have been reported.

Thus it can be concluded that no risk for human health is anticipated from the consumer use of sodium perborate hydrates in detergent products.

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7. CONTRIBUTORS TO THE REPORT

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