CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name:

Disodiumoctaborate anhydrate

EC Number: **234-541-0**
CAS Number: **12008-41-2**
Index Number: **-**

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Version number: 3.0 **Date: March 2013**

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Disodiumoctaborate anhydrate
EC number:	234-541-0
CAS number:	12008-41-2
Annex VI Index number:	-
Degree of purity:	unknown
Impurities:	unknown

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	None	None
Current proposal for consideration by RAC	Repr 1B, H360FD May damage fertility. May damage the unborn child SCL: Repr. 1B; H360FD: C ≥ 3.7 %	Repr. Cat 2; R60-61 SCL: Repr. Cat. 2; R60-61: C ≥ 3.7 % R52-53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Repr 1B, H360FD May damage fertility. May damage the unborn child SCL: Repr. 1B; H360FD: C ≥ 3.7 %	Repr. Cat 2; R60-61 SCL: Repr. Cat. 2; R60-61: C ≥ 3.7 % R52-53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Based on adverse developmental and fertility effects of borates it is proposed to classify disodium octaborate anhydrate with reproduction category 2 and assign risk phrases R60-61 according to Directive 67/548/EEC (Dangerous Substances Directive (DSD)). Further, a specific concentration limit (SCL) for this classification is proposed in line with the other borates already included in Annex VI

Based on adverse developmental and fertility effects of borates in rats and rabbits, disodium octaborate anhydrate should be classified with Repr 1B, H360FD May damage fertility. May damage the unborn child. according to Regulation EC 1272/2008 (CLP Regulation). Further, an SCL for this classification is proposed in line with the other borates already included in Annex VI.

Classification for the environment based CLP Regulation for aquatic acute and chronic hazards is not proposed because it does not meet the criteria under according to Regulation EC 1272/2008 (CLP Regulation).

Based on lowest aquatic acute toxicity value in invertebrates of 98.9 mg/L and not ready biodegradability of the substance, it is proposed to classify disodium octaborate anhydrate with R52-R53, Harmful to aquatic organisms. May cause long-term adverse effects in the aquatic environment according to Directive 67/548/EEC.

Please note that we propose different CLP and DSD classifications for the environment based on the same dataset because of the second ‘adaptation to technical progress’ or ATP changes in the CLP criteria for classification of substances and mixtures for environmental hazard[1] (see also section 5.6).

[1] New criteria for classification for long term (chronic) aquatic hazard.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	none			Conclusive but not sufficient for classification
2.2.	Flammable gases	none			Conclusive but not sufficient for classification
2.3.	Flammable aerosols	none			Conclusive but not sufficient for classification
2.4.	Oxidising gases	none			Conclusive but not sufficient for classification
2.5.	Gases under pressure	none			Conclusive but not sufficient for classification
2.6.	Flammable liquids	none			Conclusive but not sufficient for classification
2.7.	Flammable solids	none			Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	none			Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	none			Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	none			Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	none			Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	none			Conclusive but not sufficient for classification
2.13.	Oxidising liquids	none			Conclusive but not sufficient for classification
2.14.	Oxidising solids	none			Conclusive but not sufficient for classification
2.15.	Organic peroxides	none			Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	none			Conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	none			Conclusive but not sufficient for classification

	Acute toxicity - dermal	none			Conclusive but not sufficient for classification
	Acute toxicity - inhalation	none			Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	none			Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	none			Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	none			Data lacking
3.4.	Skin sensitisation	none			Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	none			Conclusive but not sufficient for classification
3.6.	Carcinogenicity	none			Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Repr. 1B	**3.7%**		
3.8.	Specific target organ toxicity –single exposure	none			Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	none			Conclusive but not sufficient for classification
3.10.	Aspiration hazard	none			Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Not classified			Conclusive but not sufficient for classification
5.1.	Hazardous to the ozone layer	Not classified			Data lacking

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Danger
Pictogram: GHS08
Hazard statements: H360FD, May damage fertility or the unborn child
Precautionary statements: Not required as precautionary statements according to CLP are not included in Annex VI.

Proposed notes assigned to an entry:

Table 4: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness	none			Conclusive but not sufficient for classification
Oxidising properties	none			Conclusive but not sufficient for classification
Flammability	none			Conclusive but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	none			Conclusive but not sufficient for classification
Thermal stability	none			Conclusive but not sufficient for classification
Acute toxicity	none			Conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	none			Conclusive but not sufficient for classification
Repeated dose toxicity	none			Conclusive but not sufficient for classification
Irritation / Corrosion	none			Conclusive but not sufficient for classification
Sensitisation	none			Conclusive but not sufficient for classification
Carcinogenicity	none			Conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	none			Conclusive but not sufficient for classification
Toxicity to reproduction – fertility	Repr. Cat. 2	**3.7%**		
Toxicity to reproduction – development	Repr. Cat. 2	**3.7%**		
Toxicity to reproduction – breastfed babies. Effects on or via lactation	none			Conclusive but not sufficient for classification
Environment	R52-R53			

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Toxic
R-phrases: R60-R61, May impair fertility. May cause harm to the unborn child.
R52-53, Harmful to aquatic organisms. May cause long-term adverse effects in the environment.
S-phrases: S53, S45, S61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Disodium octaborate anhydrate has not been included in Annex VI of Regulation (EC) No 1272/2008 (CLP). However, several other simple borates (diboron trioxide, boric oxide (EC: 215-125-8); disodium tetraborate, anhydrous boric acid, disodium salt (EC: 215-540-4); tetraboron disodium heptaoxide hydrate (EC: 235-541-3); orthoboric acid, sodium salt (EC: 237-560-2); disodium tetraborate decahydrate, borax decahydrate (EC: 215-540-4) and disodium tetraborate pentahydrate, borax pentahydrate (EC: 215-540-4) and boric acid are included in Annex VI of CLP and classified as Repr. Cat. 2; R60-61 / Repr. 1B; H360FD. For some borates this classification is based on read-across.

Disodium octaborate anhydrate has been registered under REACH (last check 25-06-2012). In addition, for several other borates (boric acid, diboron trioxde, disodium tetraborate and disodium octaborate anhydrate) registrations have been made.
Due to the toxicological similarities of boron compounds classified as toxic to reproduction category 1B the following boron compounds have been included in the Candidate List following their identification as substances of very high concern (SVHC):

- Boric acid (CAS: 10043-35-3);
  covering also
  boric acid, crude natural (CAS: 11113-50-1)
- Disodium tetraborate, anhydrous (CAS: 1330-43-4);
  covering also
  disodium tetraborate pentahydrate (CAS: 12179-04-3),
  disodium tetraborate decahydrate (CAS: 1303-96-4) and
  tetraboron disodium heptaoxide, hydrate (CAS: 12267-73-1)
- Tetraboron disodium heptaoxide, hydrate (CAS: 12267-73-1);
  covering also
  disodium tetraborate, anhydrous (CAS: 1330-43-4),
  disodium tetraborate pentahydrate (CAS: 12179-04-3),
  disodium tetraborate decahydrate (CAS: 1303-96-4)
- Diborontrioxide (CAS: 1303-86-2)

The information from REACH registration dossiers and SVHC dossiers has been considered for the preparation of the disodium octaborate anhydrate CLH dossier and the proposed classification is in line with the classification included in Annex VI (1st ATP) for the other borates.

2.2 Short summary of the scientific justification for the CLH proposal

The proposed classification and labelling of disodium octaborate anhydrate for reproductive toxicity is based on read-across from other tested borates (e.g. boric acid) and borate salts (borax or disodium tetraborate decahydrate) because its hydrolysis results in the formation of the same substances. The resulting classification is comparable to that of the other borates in Annex VI.

Please note that we propose different CLP and DSD classifications for the environment based on the same dataset because of the second ‘adaptation to technical progress’ or ATP changes in the CLP criteria for classification of substances and mixtures for environmental hazard.

Classification for the environment based CLP Regulation for aquatic acute and chronic hazards is not proposed because it does not meet the criteria under according to Regulation EC 1272/2008 (CLP Regulation). However, based on lowest aquatic acute toxicity value in invertebrates of 98.9 mg/L and lack of rapid degradability of the substance, it is proposed to classify disodium octaborate anhydrate with R52-R53,

Harmful to aquatic organisms, May cause long-term adverse effects in the aquatic environment according to Directive 67/548/EEC.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

None

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

None

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Several CLP notifications are available for disodium octaborate anhydrate (searched using CAS number 12008-41-2). The self-classifications differ between the notifiers with respect to the SCL for Repr. 1B. Three different SCLs are used:

- Repr. 1B H360 SCL 3.8%
- Repr. 1B H360 SCL 4.6%
- Repr. 1B H360 no SCL

2.4.2 Current self-classification and labelling based on DSD criteria

The self-classification according to the DSD criteria could not be retrieved but given the difference in CLP classification, comparable differences in DSD classifications are expected.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Disodium octaborate tetrahydrate is an active substance in the meaning of Directive 98/8/EC. Harmonised classification and labelling for all hazard classes and differentiations is normally required for such substances according to Regulation 1272/2008 article 36(2). Normally harmonized classification for disodium octaborate would be proposed as inclusion of the anhydrate in Annex VI also covers the hydrate. However, as different SCLs apply to these two substances due to the difference in boron content, two different proposals are made. The difference in self-classification between the notifiers also reaffirm the need for harmonized classification.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

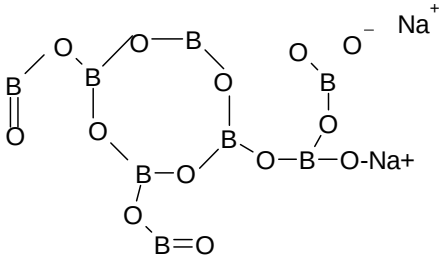
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	234-541-0
EC name:	Disodium octaborate
CAS number (EC inventory):	
CAS number:	12008-41-2
CAS name:	disodium octaborate anhydrous
IUPAC name:	disodium octaborate
CLP Annex VI Index number:	-
Molecular formula:	$Na_2B_8O_{13}$
Molecular weight range:	340.47

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Disodium octaborate anhydrate	unknown		

Current Annex VI entry: none.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
unknown			

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
unknown				

1.2.1 Composition of test material

No tests with disodium octaborate anhydrate are available. The proposed classification is based on read-across from disodium octaborate tetrahydrate and other borates.

1.3 Physico-chemical properties

No information is provided on disodium octaborate anhydrate. The information provided in table 9 is disodium octaborate tetrahydrate.

Table 9: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Solid white odourless powder (purity not stated)	CAR 2006	
Melting/freezing point	Melting point: 813/803°C at atmospheric pressure (purity 98% (w/w) expressed as $Na_2B_8O_{13}.4H_2O$)	CAR 2006	
Boiling point	Not applicable	CAR 2006	
Relative density	1.874 at 22°C (purity 98% (w/w) expressed as $Na_2B_8O_{13}.4H_2O$)	CAR 2006	
Vapour pressure	Not applicable, because the melting point lies above 300 °C and experimental data indicate that the vapour pressure is less than 10-5 Pa at ambient temperature.	CAR 2006	
Surface tension	Not applicable	CAR 2006	
Water solubility	pH_ 7.64: 223.65 g/L at 20.0°C for a super saturated solution (purity 98.0% (w/w) expressed as $Na_2B_8O_{13}.4H_2O$) The water solubility for disodium octaborate tetrahydrate as such cannot be determined because disodium octaborate tetrahydrate is converted into boric acid/borate upon dissolution in water. Water solubility studies at pH=5, 7, 9 are not possible, because of the strong buffering capacity of boric acid solutions and ion-pair formation in the presence of alkali-metal ions like Na, K. Temperature dependence of water solubility should be investigated Solubility measurements in the liquid, remaining after precipitation of an oversaturated solution are desirable. The effect of temperature on this solubility is also desirable.	CAR 2006	
Partition coefficient n-octanol/water	pH_5: not investigated pH_7: not investigated pH_9: not investigated pH_7.5: -1.09 at 22°C in potassium/sodium phosphate buffer at a concentration of 0.0097 M boron (purity 99.0% w/w expressed as H_3BO_3). pH_unknown: -0.757 at 25 °C in water at concentration levels between 0.16 - 0.89 M boron (purity not indicated) pH_unknown: -0.74 in 2 M KCl at 25 °C pH_unknown: -0.56 in 3 M $NaClO_4$ at 25 °C pH_unknown: -0.55 in 3 M $NaClO_4$ at 35 °C The log P_{ow} for disodium octaborate tetrahydrate as such	CAR 2006	

	cannot be determined because disodium octaborate tetrahydrate is converted into boric acid/borate upon dissolution in water. The log Pow given is the log P_{ow} for boric acid. The difference between log P_{ow} values obtained at different temperatures, different salinity, different concentration and different analysis, is only 0.5 log Pow unit. No further tests are required.		
Flash point	No data	CAR 2006	
Flammability	Not highly flammable.	CAR 2006	
Explosive properties	Not explosive.	CAR 2006	
Self-ignition temperature	No data	CAR 2006	
Oxidising properties	No data	CAR 2006	
Granulometry	No data	CAR 2006	
Stability in organic solvents and identity of relevant degradation products	Not relevant.	CAR 2006	
Dissociation constant	The dissociation constant for disodium octaborate tetrahydrate as such cannot be determined because disodium octaborate tetrahydrate is converted into boric acid/borate upon dissolution in water. The dissociation constant given is the dissociation constant for boric acid. Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton donator). For this purpose the formula for boric acid is best written as $B(OH)_3$. pKa = 9.0 at 25°C for boric acid in dilute solutions only ($B \leq 0.025$ M). At higher boron concentrations, polynuclear complexes are formed and several dissociation/formation constants apply.	CAR 2006	
Viscosity	No data	CAR 2006	

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

There is no identified use of disodium octaborate anhydrate. Disodium octaborate anhydrate and disodium octaborate tetrahydrate will predominantly exist as undissociated boric acid in physiological conditions. Disodium octaborate tetrahydrate is an active substance in the meaning of Directive 98/8/EC. It is used amongst others as a wood preservative.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference

Flammability	No studies available. Conclusion from CAR 2006: Disodium octaborate tetrahydrate is a non-volatile, non-flammable inorganic solid. The product is used as a flame retardant. Product has been classified according to 29 CFR 1910.1200 as a non-flammable solid.		CAR, 2006
Explosive properties	No studies available Conclusion from CAR 2006: The molecular structure of none of the substances indicates that such groups are present. No reactive or instable groups are present. The molecular structure does not indicate that these substances will explode under the conditions of the test as described in Test Guideline A.14 of EC Directive 92/69/EEC.. As the a.s. is known for its flame retardant properties, it is not expected that the a.s. is to be classified as (highly) flammable nor will it self-ignite. Considering the molecular structure and the information that is available in the literature, disodium octaborate tetrahydrate is not expected to have explosive properties in the sense of EC Directive 92/69/EEC.		CAR, 2006
Oxidising properties	No studies available. Conclusion from CAR 2006: A search of available literature has not resulted in any indication of oxidizing properties of disodium octaborate tetrahydrate, neither has it shown any accident data that may be attributed to oxidizing properties.		CAR, 2006

3.1 *[Insert hazard class when relevant and repeat section if needed]*

3.1.1 Summary and discussion of

3.1.2 Comparison with criteria

3.1.3 Conclusions on classification and labelling

No studies have been performed related to the classification for physico-chemical properties. However, seen the molecular structure, no effects are expected. Disodium octaborate anhydrate needs not to be classified for physico-chemical properties according to 67/548/EEC or EC 1272/2008.

4 HUMAN HEALTH HAZARD ASSESSMENT

The summaries included in this proposal on disodium octaborate (anhydrate) are predominantly copied from the draft Competent Authority Report and Proposed Decision (CAR, 2006) of the Netherlands prepared in the context of the possible inclusion of the active substance disodium octaborate tetrahydrate in Annex I of Council Directive 98/8/EEC (CAR, June 2006; rev June 2008). Some details of the summaries were not included when considered not important for a decision on the classification and labelling of this substance. For more details the reader is referred to the CAR. Additional good quality toxicity studies (equivalent to Klimisch score 1 and 2) carried out in line with recognised guideline and reported in the EU RAR were included if effects in these studies were observed at lower doses than those reported in the CAR. In addition, data from the WHO review on boron (EHC 204, 1998) and recent information from public literature are included in the proposal. Where data from EHC 204 or public literature are used this is indicated in the text. Further, information from the registration of other borates was used where these contained additional information for which read-across to disodium octaborate could be justified. If a study is cited in a number of sources, then the study is referenced according to the non-confidential source.

The classification of borates for reprotoxicity was also discussed in the Commision Working Group of Specialized Experts in the field of Reprotoxicity in October 2004 (Summary record ECBI/132/04 Rev. 2).

In aqueous solutions at physiological and acidic pH, low concentrations of simple borates such as boric acid $B(OH)_3$, disodium tetraborate decahydrate ($Na_2B_4O_7 \cdot 10H_2O$; borax), disodium tetraborate pentahydrate ($Na_2B_4O_7 \cdot 5H_2O$; borax pentahydrate), boric oxide (B2O3), disodium octaborate anhydrate ($Na_2B_8O_{13}$) and disodium octaborate tetrahydrate ($Na_2B_8O_{13} \cdot 4H_2O$) will predominantly exist as undissociated boric acid. Above pH 10 the metaborate anion $B(OH)_4$ becomes the main species in solution. The toxicokinetics and toxicological effects of systemic boric acid, disodium tetraborate decahydrate, boric oxide, disodium octaborate anhydrate and disodium octaborate tetrahydrate will be similar on a boron equivalents basis. Conversion factors are given in the table below.

Table 11: Overview of conversion factors of borates to equivalent dose of boron

Substance	**Formula**	**Conversion factor for equivalent dose of B (multiply by)**
Boric acid	H_3BO_3	0.1748
Boric oxide	B_2O_3	0.311
Disodium tetraborate anhydrous	$Na_2B_4O_7$	0.2149
Disodium octaborate anhydrate*	$Na_2B_8O_{13}$	0.2538
Disodium tetraborate pentahydrate	$Na_2B_4O_7•5H_2O$	0.1484
Disodium tetraborate decahydrate	$Na_2B_4O_7•10H_2O$	0.1134
Disodium octaborate tetrahydrate	$Na_2B_8O_{13}·4H_2O$	0.2096
Sodium pentaborate (pentahydrate)	$NaB_5O_8·5H_2O$	0.1832

Reference: WHO, 1998. Guidelines for drinking-water quality, Addendum to Volume 1, 1998
* Conversion factor was derived separately as it was not included in the reference table (WHO, 1998)

Experts from the CL Working Group, the TC-C&L and the ATP Committee agreed that borate substances (boric acid, boric oxide, disodium tetraborate, anhydrous, disodium tetraborate decahydrate and disodium tetraborate) have very similar properties and therefore that read –across can be applied. Moreover, in a report on boron, drawn up in 1998 as part of the International Programme on Chemical Safety established jointly by the World Health Organisation, the International Labour Organisation and the United Nations Environment Programme, the experts stated that the chemical and toxicological properties of borax pentahydrate, borax, boric acid, and other borates are expected to be similar on a mol boron/litre equivalent basis when dissolved in water or biological fluids at the same pH and low concentration. They add that boric oxide will exhibit properties identical to those of boric acid, as it is an anhydride that will hydrolyse to give boric acid. The RAC opinion on new scientific evidence on the use of boric acid and borates in photographic applications by consumers (ECHA, 2010) also used read-across between the different borates as the DNEL was expressed as mg B/kg bw/day. Recent judgment of the European Court of Justice on borate substances concludes that read-across may indeed be used for the assessment of borate substances [2].

Since disodium octaborate tetrahydrate and disodium octaborate anhydrate will also exist as undissociated boric acid in a physiological environment, it can be expected that also for disodium octaborate tetrahydrate and disodium octaborate anhydrate toxicological properties will be similar. Therefore, the data obtained from studies with the borates mentioned above can be read-across in the human health assessment for disodium octaborate anhydrate (see CAR, 2006). It is noted that the dissolution from simple borates to boric acid takes about 15 min. This could lead to differences in acute and local toxicity between the borates. However, for disodium octaborate tetrahydrate acute toxicity studies are available. These results will also be used for read-across to disodium octaborate anhydrate.

[2] Case C-15/10: Judgment of the Court (Fourth Chamber) of 21 July 2011 - Etimine SA v Secretary of State for Work and Pensions; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62010J0015:EN:HTML

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

On the subject of toxicokinetics, only studies from published literature were available (see CAR, 2006), except for one dermal absorption study. The toxicokinetics of boric acid; boric oxide, disodium octaborate anhydrate, disodium octaborate tetrahydrate and the sodium tetraborate (anhydrous; pentahydrate and decahydrate) are similar in rats and humans with respect to absorption, distribution, and metabolism.

ABSORPTION
Oral Absorption
Boric acid and the simple sodium borates given orally are readily and completely absorbed in humans and animals as shown by the levels of boron in urine, blood or tissues. Animals investigated include rats, rabbits, sheep and cattle. In rats fed ^{10}B at a dose of 20 µg 95 % and 4% was recovered from urine and feces respectively within 24 h.

Inhalation Absorption
Inhalation studies suggest that absorption of borates in the respiratory system occurs. In a study in rats, following inhalation of boron oxide aerosol, increased levels of boron were excreted in the urine. In this study high levels of boron were recovered from the lungs, suggesting that absorption was not complete. It should be noted that it is possible that in the inhalation studies part of the boron may have been absorbed orally since particulate matter is cleared from the lungs and subsequently ingested.

Dermal Absorption
Studies from published literature indicate that dermal absorption of borates across intact skin is low in all species evaluated, including human new-born infants (no rise in plasma boron levels), adult humans (no increase in boron excretion in urine), rabbits (minimal and insignificant), and rats (no or slight increases in urine boron concentration). Borates have been demonstrated to penetrate damaged or abraded skin. However, the use of an ointment-based vehicle may prevent or reduce the absorption through diseased skin compared to an aqueous jelly based vehicle. In addition to the studies summarised in the CAR, an in vitro percutaneous study confirmed the low dermal absorption through human skin for several borates including disodium octaborate anhydrate (Hartway et al, 1997).

DISTRIBUTION
There is no substantiated evidence of boron accumulation in humans or animals although bone contains higher levels than other tissues.
Absorbed boron rapidly distributes throughout the body water in humans and animals. Tissue levels of boron generally reached steady-state within three to four days among rats fed boric acid in the diet or drinking water for 28 days or 3 – 4 days. Thus, boron does not accumulate in soft tissues with time in animals.
In both humans and animals, boron levels in soft tissue are comparable to plasma levels, while a greater concentration of boron in bone is observed relative to other tissues. The most complete study of boron distribution conducted to date examined tissue disposition of boron in reproductive organs and other selected tissues in adult male rats fed boric acid, providing approximately 100 mg B/kg bw/day for up to seven days. All tissues examined, except bone and adipose tissue, appeared to reach steady state boron levels by three to four days. Bone achieved the highest concentration of boron (2 to 3 times plasma levels), and bone boron levels continued to increase throughout seven days of dietary administration. In contrast, adipose tissue concentration was approximately 20 % of the plasma level. No other tissues showed any appreciable accumulation of boron over plasma levels.
Boron levels in a number of tissues have been measured. In mice, boron distribution appeared to be homogenous in the tissues examined, except for higher levels in the kidney (bone was not analysed), but higher levels were found in bone in another study.

METABOLISM
Boric acid is not metabolised in either animals or humans, because of the high energy level required (523kJ/mol) to break the B - O bond. Other inorganic borates convert to boric acid at physiological pH in the

aqueous layer overlying the mucosal surfaces prior to absorption. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid.

EXCRETION
In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boron is slowly eliminated from bone. Elimination half-lives for animals have not been stated explicitly in the scientific literature, but they can be calculated or estimated from the data in the literature. In mice, assuming first order kinetics for elimination, the half-life was estimated to be approximately one hour, and in rat < 12 hours. In rabbits, 50 to 66% of an orally administered dose of boric acid was excreted in the urine in the first 24 hours after dosing. A recent study indicated that the half-life may be only 3 hours in both pregnant and non-pregnant rats.
The major determinant of boric acid excretion is expected to be renal clearance since boric acid is excreted unchanged in the urine. Rats and mice generally have faster rates of renal clearance than humans since the glomerular filtration rates as a function of body mass are generally higher in rats and mice than in humans. Clearances of 40.4 ± 3.2 ml/min/1.73m^2 for sodium tetraborate in male rats and 40 ml /min/1.73m^2 for boron in mice have been reported, although there are methodological and/or analytical limitations in both studies. In more recent studies boric acid clearance rates in non-pregnant rats and pregnant rats ranged from 29.0 ± 5.7 to 31.0 ± 4.5 and from 32.2 ± 5.1 to35.6 ± 5.7 ml/min/1.73m^2, respectively.

4.1.2 Human information

ABSORPTION
Oral Absorption
Boric acid and the simple sodium borates given orally are readily and completely absorbed in humans and animals as shown by the levels of boron in urine, blood or tissues. In adult human volunteers given a single oral dose of 131 mg B (as boric acid dissolved in water), 94% of the administered dose was excreted in the urine over a 96 hour period. Similar absorption was observed based on urinary excretion of boron in 6 volunteers drinking curative spa water with a high boron content (daily dose of 102 mg B) for two weeks. In another study more than 90% was absorbed in human volunteers taking in 3% boric acid in an aqueous solution or as a waterless emulsifying ointment spread onto biscuits. Reports involving accidental human ingestion, particularly in infants, where new-born infants died after accidentally ingesting boric acid, provide further evidence of virtually complete oral absorption.

Inhalation Absorption
Inhalation studies suggest that absorption of borates in the respiratory system occurs. Inhaled sodium borate dust is readily absorbed as demonstrated by the increased blood and urine levels among groups of workers occupationally exposed through inhalation of various levels of borax. It should be noted that it is possible that in the inhalation studies part of the boron may have been absorbed orally since particulate matter is cleared from the lungs and subsequently ingested. For occupational exposure assessment 100% inhalatory absorption is assumed.

Dermal Absorption
Studies from published literature indicate that dermal absorption of borates across intact skin is low in all species evaluated, including human new-born infants (no rise in plasma boron levels; and adult humans (no increase in boron excretion in urine). For the biocide evaluation (CAR 2006) a skin absorption study in humans, performed with boric acid, disodium tetraborate decahydrate and disodium octaborate tetrahydrate was available. In this study, low levels of boron were recovered from the urine. From the applied doses of boric acid, disodium tetraborate decahydrate and disodium octaborate tetrahydrate respectively 0.226 ± 0.125, 0.210 ± 0.194 and 0.122 ± 0.10 % (mean ± SD) was excreted in urine. This study, however, is seriously flawed, since total recovery of the applied boron was low. In the studies total recovery of the applied dose ranged from 48.8-63.6%. Accordingly 36.4-51.2% of the applied dose is not accounted for.

This may be due to loss to outside clothing and bedding, as suggested by the study authors. However, part of the lost dose may be located in the body or in the skin at the application site, which in that case should be considered as being absorbed. As such, the absorption estimates from this study are unreliable. On the other hand, other toxicokinetic studies also indicate that borates have a low dermal absorption and low potential for accumulation in the body. In this respect the present data are in line with dermal absorption data from other studies. Therefore, based on this study and other data a dermal absorption for borates of 0.5% can be assumed as a reasonable worst case estimate.

DISTRIBUTION
There is no substantiated evidence of boron accumulation in humans or animals although bone contains higher levels than other tissues.
Absorbed boron rapidly distributes throughout the body water in humans. In a study of workers occupationally exposed to 10 mg/m^3 of airborne borax (0.22 mg B/kg bw/day), there was no progressive accumulation of boron in soft tissues during the working week as measured by blood and urine levels. Similarly, it was concluded from pharmacokinetic studies of human volunteers that there was no tendency for boron to accumulate following a single i.v. dose of 600 mg of boric acid (approximately 105 mg B). Thus, boron does not accumulate in soft tissues with time in humans. A poisoning case with boric acid in a pregnant woman indicated that borates can cross the placenta.
In a recent study (Robbins et al., 2010) data were collected on boron exposure/dose measures in workplace inhalable dust, dietary food/fluids, blood, semen, and urine from boron workers and two comparison worker groups (n = 192) over three months. Blood boron averaged 499.2 ppb for boron workers, and 96.1 and 47.9 ppb for workers from high and low environmental boron areas ($p < 0.0001$). Boron concentrated in seminal fluid with average concentrations of 786, 311 and 214 ppb for boron workers, workers from high and low environmental boron, respectively.
A study published by Duydu et al. in 2011 was conducted to investigate the reproductive effects of boron exposure in workers employed in boric acid production plant in Bandirma, Turkey. In order to characterize the external and internal boron exposures, boron was determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. The mean calculated daily boron exposure (DBE) of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg/day. Blood boron levels were 224 ng B/g (<LOQ-454). Semen boron levels were 1876 ng B/g (<LOQ-9522), demonstrating that boron concentrates in seminal fluid.
In both humans and animals, boron levels in soft tissue are comparable to plasma levels, while a greater concentration of boron in bone is observed relative to other tissues. Studies show a greater concentration of boron in sperm fluid relative to other tissues in humans.

METABOLISM
Boric acid is not metabolized in either animals or humans, because of the high energy level required (523kJ/mol) to break the B - O bond. Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Additional support for this comes from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid.

EXCRETION
In both humans and animals, boron is excreted in the urine regardless of the route of administration. It is excreted with a half-life of < 24 hours in humans and animals. Boron is slowly eliminated from bone. In humans, 99 % of a single i.v. dose of boric acid was excreted in the urine; the plasma half-life was calculated to be 21 hours using a three compartment toxicokinetic model.
Following oral intake of an aqueous solution of boric acid, the urinary recovery was 94 %; more than 50 % of the oral dose was eliminated in the first 24 hours, consistent with the 21 hour half-life in the i.v. study. In a boron balance study only 8% of dietary boron is excreted in faeces. Half-lives ranging 13-28.7 hours have also been reported from various poisoning cases.
The major determinant of boric acid excretion is expected to be renal clearance since boric acid is excreted unchanged in the urine.

In humans,a clearance rate of 55 ml/min/1.73m^2 following an i.v. dose of 600 mg of boric acid (105 mg B) was determined. A similar value of 39 ml/min/1.73m^2 in humans given 35 mg B/kg intravenously as sodium pentaborate was reported, although there are methodological and analytical limitations to this 40 year old study. In a more recent study, renal clearance rates in humans were 68.30 ± 35.0ml/min/1.73m^2 for pregnant subjects and 54.31 ± 19.35 ml/min/1.73m^2 for non-pregnant subjects. This might indicates about 20 –25% greater clearance in pregnant humans.
A comparison of the renal clearance between rats and humans in terms of body surface area indicated that humans clear boric acid slightly faster than rats (~1.7 -1.9 times as fast), while a comparison by bodyweight indicates that humans may clear boric acid more slowly than rats (~ 3 - 4 times slower).

4.1.3 Summary and discussion on toxicokinetics

CONCLUSION
Absorption of borates via the oral route is nearly 100%. For the inhalatory route also 100% absorption is assumed. Dermal absorption though intact skin is very low. In the blood boric acid is the main species present. Boric acid is not further metabolised. Borates are distributed rapidly and evenly through the body, with concentrations in bone 2-3 higher than in other tissues. In humans, there is evidence of some concentration in the seminal fluid. Boron is excreted rapidly, and has low potential for accumulation. Boric acid is mainly excreted in the urine.

4.2 Acute toxicity

Table 12: Summary table of relevant acute toxicity studies

Method	Test substance	Results	Remarks	Reference
Acute oral toxicity study, OECD401	disodium octaborate tetrahydrate	2550 mg/kg bw	Supported by other studies with other borates	Doyle, 1988[a]
Acute dermal toxicity study, OECD 402	disodium octaborate tetrahydrate	> 2 g/kg bw	Supported by other studies with other borates	Doyle, 1989a[a]
Acute inhalation toxicity study, OECD 403	disodium octaborate tetrahydrate	> 2.01.mg/L (2010 /m^3)	Highest attainable dose. Supported by inhalation studies with other borates	Wnorowski, 1994d[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

The oral LD50 value for disodium octaborate tetrahydrate in a study in rats was 2250 mg/kg bw. For the biocide evaluation (CAR 2006) also acute oral toxicity studies with other borates were available. The oral LD_{50} value of boric acid in a study in rat was 3450 mg/kg bw. Other acute oral toxicity studies with boric acid in rats also report LD_{50}'s >2000 mg/kg bw. The studies in rats with disodium tetraborate anhydrous, disodium tetraborate pentahydrate, and boric oxide revealed LD_{50}'s of >2000, 3305, and >2600 mg/kg bw respectively.

4.2.1.2 Acute toxicity: inhalation

An inhalation study in rats with disodium octaborate tetrahydrate revealed an LC_{50} of >2.01 mg/L (2 g/m^3). In an inhalation study in which rats were exposed to boric acid at actual concentrations of 2.12 mg/L for 4h no deaths were observed. A study in rats with disodium tetraborate pentahydrate revealed an LC_{50} of >2.04 mg/L (2 g/m^3).

4.2.1.3 Acute toxicity: dermal

In an acute dermal toxicity study in rat performed with disodium octaborate tetrahydrate the LD50 value was >2000 mg/kg bw. Also other borates appear to have low acute dermal toxicity. In a study in rabbits, the dermal LD50 value for boric acid was >2000 mg/kg bw. Acute dermal toxicity studies with disodium tetraborate decahydrate and disodium tetraborate pentahydrate revealed no deaths a limit doses of 2000 mg/kg bw. It must be noted that these studies were flawed since the test material was not moistened, so good contact with the skin was not ensured.

4.2.1.4 Acute toxicity: other routes

No data available.

4.2.2 Human information

Accidental or intentional poisoning incidents with borates have been reported. The potential lethal oral dose of boric acid is reported to be 3 - 6g in children and 15 - 20 g for adults. However, lethal doses are not well documented. Acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse.

4.2.3 Summary and discussion of acute toxicity

No information is available on the acute toxicity of disodium octaborate anhydrate. Acute toxicity results for disodium octaborate tetrahydrate are: LD50 oral rat = 2550 mg/kg; LD50 dermal rat > 2000 mg/kg; LC50 inhalation rat > 2010 mg/m^3. Also boric acid and other borates are of low acute toxicity. Although most of the acute oral studies were not of modern standards and were performed prior to the introduction of GLP, they are reproducible across a number of studies and species and of acceptable quality. For acute dermal and acute inhalation some studies meet the GLP standard.

Using read-across from disodium octaborate tetrahydrate with a correction for the difference in molecular weight is considered correct because no differences in uptake are expected and once taken up the effects will not significantly differ. This correction for differences in molecular weight results in an LD50 of 2105 mg/kg bw for disodium octaborate anhydrate. For acute dermal and inhalation toxicity also no mortality is expected at the limit dose (dermal) or the highest attainable dose (inhalation).

4.2.4 Comparison with criteria

Based on the data from disodium octaborate tetrahydrate, and using a correction for molecular weight the oral and dermal LD50 for disodium tetraborate anhydrate is 2105 and > 1659 mg/kg bw, respectively. Using the same correction for inhalation an LC50> 1.65 mg/l can be derived. The oral value is higher than the limit for classification. For dermal and inhalation the calculated LD50 and LC50 are possibly below the limit values for classification according to 67/548/EEC or EC 1272/2008. However, it is expected that the toxicity of disodium octaborate anhydrate and disodium octaborate tetrahydrate will be similar and that both substances do not need to be classified for acute oral, dermal and inhalation toxicity according to 67/548/EEC or EC 1272/2008.

4.2.5 Conclusions on classification and labelling

No information is available on the acute toxicity of disodium octaborate anhydrate. Considering the fact that disodium octaborate tetrahydrate and disodium octaborate anhydrate will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of disodium octaborate tetrahydrate and disodium octaborate anhydrate are expected to be similar. Therefore, read across from disodium octaborate tetrahydrate to disodium octaborate anhydrate is applied. Disodium octaborate anhydrate therefore does not need to be classified for acute oral, dermal and inhalation toxicity according to 67/548/EEC or EC 1272/2008.

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

There are no indications that disodium octaborate tetrahydrate induces a specific target organ toxicity following single oral, dermal or inhalation exposure in animals. Details on the effects observed in the acute toxicity studies cannot be provided because these details were not included in the CAR and we do not have access to the study reports. In humans accidental or intentional poisoning incidents with borates have been reported. The potential lethal oral dose of boric acid was reported to be 3 - 6g in children and 15 - 20 g for adults. However, lethal doses are not well documented. Acute effects may include nausea, vomiting, gastric discomfort, skin flushing, excitation, convulsions, depression and vascular collapse. It is considered likely that the observed clinical signs reflect aspecific toxicity rather than a specific target organ toxicity.

4.3.2 Comparison with criteria

There are no indications that disodium octaborate tetrahydrate induces a specific target organ toxicity following single oral, dermal or inhalation exposure. Based on read-across, the same applies to disodium octaborate anhydrate.

4.3.3 Conclusions on classification and labelling

Disodium octaborate anhydrate does not need to be classified for specific target organ toxicity – single exposure (STOT-SE) according to 67/548/EEC or EC 1272/2008.

4.4 Irritation

4.4.1 Skin irritation

Table 13: Summary table of relevant skin irritation studies

Method	Test substance	Results	Remarks	Reference
FIFRA (40 CFR 163) Acceptable protocol at the time of testing.	disodium octaborate tetrahydrate	Not irritant average erythema scores at 24, 48 and 72h: 0.22 average edema scores at 24, 48 and 72h: 0	Supported by studies with other borates	Doyle, 1989b[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

4.4.1.1 Non-human information

In a study in rabbits, boric acid did not cause skin irritation when applied to the intact or abraded skin at a dose of 0.5 g. Similarly, in studies in rabbits, boric oxide, disodium octaborate tetrahydrate, sodium tetraborate decahydrate and sodium tetraborate pentahydrate did not cause skin irritation at doses of 0.5 g.

4.4.1.2 Human information

No data available

4.4.1.3 Summary and discussion of skin irritation

Limited skin irritation occurs following exposure to disodium octaborate tetrahydrate. No data are available for disodiumoctaborate anhydrate. Based on the results for disodium octaborate tetrahydrate, it is also expected that disodium octaborate anhydrate only has limited irritating properties, because the substances differ only by the amount of water of crystallisation.

4.4.1.4 Comparison with criteria

The skin irritation observed following exposure to disodium octaborate tetrahydrate is below the criteria for classification according to 67/548/EEC and EC 1272/2008. The same is expected for disodium octaborate anhydrate.

4.4.1.5 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Therefore, read across from disodium octaborate tetrahydrate to disodium octaborate anhydrate is applied because the substances differ only by the amount of water of crystallisation. Based on the results for disodium octaborate tetrahydrate, it is also expected that disodium octaborate anhydrate only has limited irritating properties, Disodium octaborate anhydrate does not need to be classified for skin irritation according to 67/548/EEC or EC 1272/2008.

4.4.2 Eye irritation

Table 14: Summary table of relevant eye irritation studies

Method	Test substance	Results	Remarks	Reference
FIFRA (40 CFR 158, 162); TSCA (40 CFR 798). The study was considered acceptable.	disodium octaborate tetrahydrate	Not irritating	Studies with boric acid and boric oxide also showed no eye irritating properties. Sodium tetraborate decahydrate and sodium tetraborate pentahydrate did cause eye irritation, possibly due to the crystalline nature of these compounds.	Doyle, 1989d[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

4.4.2.1 Non-human information

In studies with boric oxide and disodium octaborate tetrahydrate, no eye irritation was observed. Disodium tetraborate decahydrate and sodium tetraborate pentahydrate did cause eye irritation, possibly due to the crystalline nature of these compounds. Boric acid induced conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days.

4.4.2.2 Human information

Workers exposed occupationally to borax dust (disodium tetraborate decahydrate, average air concentration 4.1 mg/m^3) reported eye irritation, dry mouth, nose or throat, sore throat and productive cough. No data on eye irritation due to exposure of humans to disodium octaborate tetrahydrate were available. All concentrations as were determined using a total dust sampler.

4.4.2.3 Summary and discussion of eye irritation

Disodium octaborate tetrahydrate is not an eye irritant in a study in animals. No data on eye irritation due to exposure of humans to disodium octaborate anhydrate were available. Based on the negative results for disodium octaborate tetrahydrate, it is also expected that disodium octaborate anhydrate has no irritating properties, because the substances differ only by the amount of water of crystallisation.

4.4.2.4 Comparison with criteria

No eye irritation occurs following exposure to disodium octaborate tetrahydrate at the limit values for classification set by 67/548/EEC or EC 1272/2008. No data on eye irritation due to exposure of humans to disodium octaborate tetrahydrate were available. Also no eye irritation is expected for disodium octaborate anhydrate.

4.4.2.5 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Therefore, read across from disodium octaborate tetrahydrate to disodium octaborate anhydrate is applied because the substances differ only by the amount of water of crystallisation. Based on the results for disodium octaborate tetrahydrate, it is also expected that disodium octaborate anhydrate only has limited irritating properties. Disodium octaborate anhydrate does not need to be classified for eye irritation according to 67/548/EEC or EC 1272/2008.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

No data available in CAR or EHC 204.

4.4.3.2 Human information

No data on human inhalation exposure to disodium octaborate anhydrate or tetrahydrate were available. Exposure to borax induced acute and chronic respiratory irritation at levels ≥ 4.5 mg/m^3 Concentrations ≥ 4 mg/m^3 induced eye irritation. From a prospective cohort study it was concluded that a threshold limit value (TLV) of 10 mg/m^3 was protective of workers' health. All concentrations as were determined using a total dust sampler.

4.4.3.3 Summary and discussion of respiratory tract irritation

In humans respiratory irritation was observed following exposure to borax at concentrations ≥ 4.5 mg/m3. It is considered likely that the respiratory irritation is due to physical/mechanical irritation of the inhaled borax dust.

4.4.3.4 Comparison with criteria

In the guidance on application of the CLP criteria it is stated that a solid substance which causes RTI due to physical/mechanical irritation when inhaled as a dust should not be classified for respiratory tract irritation.

4.4.3.5 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate.
No classification for respiratory tract irritation is proposed for disodium octaborate anhydrate due to lack of data.

4.5 Corrosivity

Table 15: Summary table of relevant corrosivity studies

Method	Results	Remarks	Reference
No data			

4.5.1 Non-human information

In studies in animals no skin and eye irritation were observed after exposure to borates.

4.5.2 Human information

No reports on corrosive effects of borates were found.

4.5.3 Summary and discussion of corrosivity

There are no indications that borates have corrosive properties.

4.5.4 Comparison with criteria

There are no indications that borates have corrosive properties.

4.5.5 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Therefore, read across from disodium octaborate tetrahydrate to disodium octaborate anhydrate is applied because the substances differ only by the amount of water of crystallisation. Based on the results for disodium octaborate tetrahydrate, it is also expected that disodium octaborate anhydrate only has limited irritating properties.
It is not necessary to classify disodium octaborate anhydrate for corrosive effects according to 67/548/EEC or EC 1272/2008.

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 16: Summary table of relevant skin sensitisation studies

Method	Test substance	Results	Remarks	Reference
OECD 406	Disodium octaborate tetrahydrate	Non-sensitizer	Buehler test	Wnorowksi, 1994h[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

4.6.1.1 Non-human information

Disodium octaborate tetrahydrate was tested in a Buehler method skin sensitization test. Disodium octaborate tetrahydrate was applied at a concentration of 95% (powder moistened with water) during both the induction and challenge phase of the test. No signs of skin sensitization were observed. In the induction phase no signs of skin irritation were observed, and as such the test does not meet the guideline requirements. Also for other borates no sensitising properties were reported in animal studies and also no evidence of skin sensitization in humans exposed occupationally to borates has been reported.

4.6.1.2 Human information

No evidence of skin sensitization in humans exposed occupationally to borates has been reported.

4.6.1.3 Summary and discussion of skin sensitisation

There are no indications that disodium octaborate anhydrate has skin sensitizing properties.

4.6.1.4 Comparison with criteria

There are no indications that disodium octaborate anhydrate has skin sensitizing properties.

4.6.1.5 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Considering the fact that disodium octaborate tetrahydrate and disodium octaborate anhydrate will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of disodium octaborate tetrahydrate and disodium octaborate anhydrate are expected to be similar. Therefore, read across from disodium octaborate tetrahydrate to disodium octaborate anhydrate is applied.
It is not necessary to classify disodium octaborate anhydrate for skin sensitization according to 67/548/EEC or EC 1272/2008.

4.6.2 Respiratory sensitisation

Table 17: Summary table of relevant respiratory sensitisation studies

Method	Results	Remarks	Reference
No data			

4.6.2.1 Non-human information

No data that indicate that disodium octaborate anhydrate causes respiratory sensitization in animals were found.

4.6.2.2 Human information

No data that indicate that disodium octaborate anhydrate causes respiratory sensitization in humans were found.

4.6.2.3 Summary and discussion of respiratory sensitisation

There is no indication that disodium octaborate anhydrate causes respiratory sensitization.

4.6.2.4 Comparison with criteria

There is no indication that disodium octaborate anhydrate causes respiratory sensitization.

4.6.2.5 Conclusions on classification and labelling

Disodium octaborate anhydrate should not be classified for respiratory sensitization according to EC 1272/2008 based on absence of data.

4.7 Repeated dose toxicity

Table 18: Summary table of relevant repeated dose toxicity studies

Method	Test substance	Results	Remarks	Reference
13-weeks oral study in mouse	Boric acid	LOAEL 1200 ppm, equivalent to 194(34) mg boric acid(B)/kg bw/day (lowest dose tested	At all dose levels extra medullary haematopoiesis of the spleen. At ≥ 5000 ppm: degeneration and atrophy of the seminiferous tubules was observed.	NTP, 1987[a]
13 weeks oral study in rat	Boric acid	NOAEL is 8.8 mg B/kg bw/day LOAEL 26 mg B/kg bw/day	At ≥ 88 mg B/kg bw/day: Reduction bodyweight; clinical signs of toxicity; testicular atrophy At 26 mg B/kg bw/day on male exhibited partial testicular atrophy	Weir, 1962[b]
2-year oral study in rat	Boric acid	NOAEL is 2000 ppm equivalent to 100 (17.5) boric acid (B)/kg bw/day. LOAEL is 6690 ppm, equivalent to 334 (58.5) mg boric acid (B)/kg bw/day	Reduction bodyweight; clinical sign of toxicity; in males testicular atrophy and reductions in red cell volume and Hb	Weir, 1966a[a]
30 and 60 days drinking water study in rats	Disodium tetraborate decahydrate	LOAEL is 25 mg B/kg bw/day	Significant reduction in epididymal weight in all dose groups after 30 days In all dosed groups increase of plasma FSH levels and decrease of diameter of the seminiferous tubules. 60 days: reductions in testes and liver weights ≥ 50 mg B/kg bw/day; 60 days > 30 days: significant loss of germinal elements and testicular atrophy ≥ 50 mg B/kg bw/day Changes of testicular enzyme activities ≥ 50 mg B/kg bw/day	Dixon, 1979[b]
13 weeks oral study in rat	Disodium tetraborate decahydrate		2.6 & 88 mg B/kg bw/day: atrophied testes (not seen at 8.8	Weir, 1962b[b]

			& 26 mg B/kg bw/day) 26 mg B/kg bw/day: Spermatogenic arrests	
2-year oral study in rat	Disodium tetraborate decahydrate	NOAEL is 3080 ppm, equivalent to 155 (17.5) mg disodium tetraborate decahydrate (B)/kg bw. LOAEL is 10300 ppm, equivalent to 516 (58.5) mg disodium tetraborate decahydrate (B)/kg bw	Reduction bodyweight; clinical signs of toxicity; reductions in red cell volume and Hb; testicular atrophy	Weir, 1966b[a]
90 day oral study in dogs	Boric acid	NOAEL is 100 ppm equivalent to 2.6 (0.46) boric acid (B)/kg bw/day. LOAEL is 1000 ppm, equivalent to 24 (4.2) mg boric acid (B)/kg bw/day	Reduction in testes weight, artifactual distortion of the tubules in the outer one-third of the glands, slight extramedullary haematopoiesis at ≥ 100 ppm. At 1000 ppm: testicular atrophy	Paynter, 1963a[a]
90 day oral study in dogs	Disodium tetraborate decahydrate	NOAEL is 154 ppm, equivalent to 3.5 (0.39) mg disodium tetraborate decahydrate (B)/kg bw. LOAEL is 1540 ppm, equivalent to 42 (4.7) mg disodium tetraborate decahydrate (B)/kg bw	Reduction in testes weight, artifactual distortion of the tubules in the outer one-third of the glands, slight extramedullary haematopoiesis at ≥ 154 ppm. At 1540 ppm: testicular atrophy	Paynter, 1963b[a]
2 year oral study in dogs	Boric acid		Testes effects (not specified). Study had major methodological deficiencies and was not acceptable.	[a]
2 year oral study in dogs	Disodium tetraborate decahydrate		Testes effects (not specified). Study had major methodological deficiencies and was not acceptable.	[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). (2007).

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

In repeated dose toxicity studies with disodium tetraborate decahydrate the observed effects were similar to those seen in the boric acid studies.

In a 30/60 day study in rats of disodium tetraborate decahydrate administered in drinking water (0, 500, 1000, 2000 ppm equivalent to 0, 25, 50, 100 mg B/kg bw/day) no reduction of bodyweight or organ weights were observed, with the exception of significantly reduced epididymal weights in all dosed groups after 30 days. After 60 days the weight of testes and liver at 50 and 100 mg B/kg bw/day was also reduced. At these doses a significant loss of spermatocytes and spermatogenic cells and testicular atrophy (60 days > 30 days) concomitant with reduced enzyme activities of hyaluronidase, SDH (dehydrogenase of sorbitol) and LDH-X (lactate dehydrogenase isoenzyme X) and increased enzyme activities of G3P-DH (glyceraldehye-3-phosphate dehydrogenase) and M-DH (malate dehydrogenase) were observed, correlating well with dose and duration of exposure. Plasma levels of FSH (follicle stimulating hormone) were increased in all treated groups, with both a dose-response and an exposure time-response apparent. LH (luteinizing hormone) and testosterone levels were not significantly altered. The NOAEL in this study was 25 mg B/kg bw/day (Dixon et al., 1979, as summarised in EU-RAR).

In a 13 weeks study with boric acid in the mouse at all dose levels extra medullary haematopoiesis of the spleen was observed. This may be indicative of an increased destruction or loss of red blood cells induced by boric acid. Based on the extra medullary haematopoiesis of the spleen at all dose levels, a NOAEL could not be determined. The LOAEL in this study was 1200 ppm, equivalent to 194 and 169 mg/kg bw/day in males and females respectively. It should be noted that in a mouse carcinogenicity study, also in the males an increased incidence of extramedullary haematopoiesis in the spleen was reported at boric acid doses of 2500 and 5000 ppm (275 and 550mg/kg bw/day respectively). In addition, in the 90 days study at doses of 5000 ppm (811mg/kg bw/day) and above, degeneration and atrophy of the seminiferous tubules was observed (NTP, 1987, as summarised in CAR, 2006).

In a 90 days study in dogs with boric acid a 17 and 40% reduction in absolute testes weight was observed respectively at 0.1% (1000 ppm, 24.2 mg/kg bw/day) and 1% (10000 ppm, 201 mg/kg bw/day) of boric acid in the diet. Relative testes weight at 0.1 and 1.0% were statistically significantly reduced by 25 and 40% respectively. Histopathological examination of the testes of the 0.1% group revealed that the spermatogenic epithelium was intact and active. However, at this dose, in the testes histological changes, described as ‘artifactual distortion of the tubules in the outer one-third of the glands’ were observed. Although these changes are described as artifactual, it is striking that they were found in all males at this dose, but not in males of the control or the low dose groups. Therefore these histological changes observed at the mid-dose are considered by the authors of the CAR to be a consequences of a boron-related alteration of the structure of the testes. Since at this dose also the testes weights were reduced, the histological changes are considered to be toxicologically relevant. At 1% severe testicular atrophy was reported. In addition, slight extramedullary haematopoiesis was reported in the 0.1 and 1% groups, although no further details were provided. At the end of the treatment period, haematology in the 1 % group revealed reductions in cell volume (11-14%) and Hb levels (16-17%). The extramedullary haematopoiesis and haematological findings in the high dose animals are indicative of an increased red blood cell destruction at this dose. Since the testes are the primary target organ for boron, the findings at 0.1% cannot be discarded. Based on the effects on testicular weight the NOAEL in this study was 0.01% (100 ppm), equal to a boric acid dose of 2.6 mg/kg bw/day (0.46 mg B/kg bw/day). This conclusion is supported by data from dose-response modeling. At the Technical Meeting (TMIII07) this study was not considered acceptable for quantitative evaluation within the biocide evaluation because it had several deficiencies. However, it is considered a qualitative confirmation in an additional species of the effects on sexual function and fertility (Paynter, 1963a, as summarised in CAR, 2006).

Although not conforming to modern protocols, data on several effects can be obtained from a 90 day study in rats fed 0, 52.5, 175, 525, 1750, 5250 ppm equivalent boron (as boric acid) equal to 0, 2.6, 8.8, 26, 88 and

260 mg B/kg bw/day. All the animals in the top dose died by week 6. Animals at the top two doses displayed rapid respiration, hunched position, bloody nasal discharge, urine stains on the abdomen, inflamed eyes, desquamation and swollen paws and tail. These animals exhibited reduced food consumption and body weight gain. At 88 mg B/kg bw/day, in females, reduced weight for livers, spleens and ovaries were observed, while for males only the kidney and adrenal weights were reduced. The adrenals in 4 males at 88 mg B/kg bw/day displayed minor increases in lipid content and size of the cells in the zona reticularis. All the male rats at 88 mg B/kg bw/day had atrophied testis, a histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. One male at 26 mg B/kg bw/day exhibited partial testicular atrophy. The NOAEL was determined to be 8,8 mg B/kg bw/day (Weir 1962, as summarised in EU RAR).

In a 90 days study in dogs with disodium tetraborate decahydrate reductions in testes weight of 16, 8 and 44% were observed respectively at dietary levels of 0.0154, 0.154 and 1.54% (equal to respectively, 154, 1540 and 15400 ppm or 3.5, 42 and 374 mg/kg bw/day). Relative testes weights at 0.0154, 0.154 and 1.54% were reduced by 20, 15 and 50% respectively. At the mid-dose, histopathological examination of the testes revealed that the spermatogenic epithelium was intact and active. At this dose, however, in the testes histological changes, described as ‘artifactual distortion of the tubules in the outer one-third of the glands’ were observed. Although these changes are described as artifactual, they were found in all males at this dose, but not in males of the control or the low dose groups. Therefore these histological changes observed at the mid-dose are considered by the authors of the CAR to be a consequence of a boron-related alteration of the structure of the testes. Since at this dose also the testes weights were reduced, and similar effects were observed in a study with boric acid at an equimolar boron dose, the histological changes are considered to be toxicologically relevant. At 1.54% severe atrophy of the testes was observed. Slight extramedullary haematopoiesis was reported in the 0.154 and 1.54 % groups, although no further details were provided. At the highest dose the presence of haemosiderin in reticular cells of the liver and spleen and the proximal tubule of the kidney indicate increased red blood cell destruction. At the end of the treatment period, haematology in the 1.54 % group revealed reductions in cell volume (6-14%) and Hb levels (10-11%). Based on the reduction in absolute and relative testes weight and the histological changes in the testes, the NOAEL in this study was 0.0154%, equal to a disodium tetraborate decahydrate dose of 3.5 mg/kg bw/day (0.39 mg B/kg bw/day). This conclusion is supported by data from dose-response modeling. At the Technical Meeting (TMIII07) this study was not considered acceptable for quantitative evaluation within the biocide evaluation because it had several deficiencies. However, it is considered a qualitative confirmation in an additional species of the effects on sexual function and fertility (Paynter, 1963b, as summarised in CAR, 2006).

In a 2 year feeding study in rats with boric acid, marked reductions in body weights were observed (19 and 32% in males and females respectively) at boric acid levels in the food of 6690 ppm, equivalent to a boric acid dose of 334 mg/kg bw/day (58.5 mg B/kg bw/day). These reductions in body weight may have been the result of a decreased food consumption in these animals. In males of this dose group testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months (absolute testis weight reduced by about 75%). The extent of the testicular effects did not increase over the course of the treatment period. No effect on relative testes weight were observed at the other dose groups at 26, 52 or 104 weeks. In addition, haemoglobine levels (decrease up to 19%) and cell volume (decrease up to 18%) were consistently reduced in males of the high dose groups throughout the study. Occasionally, significant reductions in these parameters were found in males of the low- and mid-dose groups. Significant reductions in white blood cell counts were observed in males of the high dose group at 30 days and 24 months. In the high dose group hunched position, swollen pads, inflamed bleeding eyes, desquamation of the skin of the tail and the pads of the paws and marked respiratory involvement, were observed. In all males of the high dose group the scrotum appeared shrunken.
Based on the effects observed at 6690 ppm, the NOAEL in this study was 2000 ppm, equivalent to boric acid doses of 100 mg/kg bw/day (equal to 17.5 mg B/kg bw/day) (Weir 1966a, as summarised in CAR, 2006).

In a 2 year oral toxicity study with sodium tetraborate decahydrate in rats, reductions in body weights were observed in males (16%) and females (33%) fed on a diet containing 10300 ppm of sodium tetraborate decahydrate, equivalent to 516 mg/kg bw/day (58.5 mg B/kg bw/day). In females fed on 1030 and 3080 ppm of sodium tetraborate decahydrate body weight was reduced by 17 and 9% respectively. The reductions in

body weight may be the result of a decreased food consumption in these animals. In the high dose animals coarse hair coats, hunched position, inflamed bleeding eyes, desquamation of the skin of the tail and the pads of the paws, swollen pads and marked respiratory involvement were observed. In both males and females, cell volume was consistently reduced in the high dose group at all time points (reduction up to 13%), reaching statistical significance at 60 and 545 days in males and at 60, 90, 365 and 545 days in females. Haemoglobine also was consistently reduced in males and females of the high-dose group (reduction up to 16%), reaching statistical significance at 60, 180, 365 and 545 days in males and at 2 years in females. Marked reductions (ranging from 16 to 49%) in white blood cell count were observed in males and females of the high dose group at all time points, except for females at 545 days. Occasionally reductions (not statistically significant) in white blood cell count were observed in the low and mid-dose groups. Since only 5 animals per group were sampled the statistical power is low. Testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level. Absolute testis weight was reduced by about 75%. The extent of the lesion did not increase over the course of the treatment period. No effect on relative testes weight were observed at the other dose groups at 26, 52 or 104 weeks. Based on the clinical and haematological effects and the testicular atrophy observed at 10300 ppm (equivalent to borax intake of 516 mg/kg bw/day or 58.5 mg B/kg bw/day) the NOAEL in this study was 3080 ppm, equivalent to a borax intake of 155 mg/kg bw/day or 17.5 mg B/kg bw/day (Weir 1966b, as summarised in CAR, 2006)..

In a 2 year oral toxicity study with boric acid in dogs the testes were identified as a major target for boron treatment. However, this study had major methodological deficiencies and was considered not acceptable for the biocide evaluation. The study does support the notion that the testis is a major target organ for boron (as summarised in CAR, 2006).

In a 2 year oral toxicity study in dogs, performed with sodium tetraborate decahydrate, the testes were identified as a major target for boron treatment. However, this study had major methodological deficiencies and was considered not acceptable for the biocide evaluation. The study does support the notion that the testis is a major target organ for boron (as summarised in CAR, 2006).

4.7.1.2 Repeated dose toxicity: inhalation

No data available.

4.7.1.3 Repeated dose toxicity: dermal

No data available.

4.7.1.4 Repeated dose toxicity: other routes

No data available.

4.7.1.5 Human information

Human Data from Poison Control Centres and Literature Cases
Accidental or intentional poisoning incidents with borates have been reported. Multiple exposure (high levels > 1g) results in various symptoms which may appear singly or together and include dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system irritation or convulsions. A 28 year old woman who ingested around 0.5 g of boric acid (in baby powder) every day for two years suffered from anaemia, which reversed on ceasing ingestion. It is not clear from the study whether the observed effects are due to boron exposure or exposure to other substances or to nutritional deficiency. Infants aged from 6 to 19.5 weeks ingested borax (as a honey-borax mixture which had been applied to

pacifiers) for periods of 4 to 12 weeks. The mean intake was 0.98 g boric acid/day (range 0.55 g to 2 g) for a 10 kg child. The observed effects were convulsions, generalised seizures and focal seizures. There were no dermal effects. Minor occurrences of vomiting and loose stools were also described.

4.7.1.6 Other relevant information

No data available.

4.7.1.7 Summary and discussion of repeated dose toxicity

In the repeated dose studies with mouse, rat and dog, consistently effects on the testes and on blood parameters were found. Boric acid induced a decrease in testes weight, testicular atrophy, and haematological effects (extramedullary haematopoiesis, decreased Hb and cell volume, presence of haemosiderin in reticular cells of the liver and proximal tubules of the kidney) indicative of increased red blood cell destruction. In the 90 days study in the mouse and the 2 year study in the rat the animals appeared to be more sensitive to the effects on the haematopoietic system (LOAEL 17.5 mg boron/kg bw/day) than on the testes. The dogs appeared to be more sensitive to the effects of boric acid on the testes. Similar results were obtained from studies with disodium tetraborate decyhadrate. The 90 days feeding study with boric acid in dogs yielded an overall NOAEL (2.6 mg/kg bw, equal to 0.46 mg B/kg bw/day), based on reduced testes weight and histological changes in the testes at a dose of 24 mg/kg bw/day, (4.2 mgB/kg bw/day). This finding is supported by the study with disodium tetraborate decahydrate, in which a (statistically non-significant) reduction in testicular weight and histological changes in the testes were observed at 42 mg/kg bw/day (4.7 mg B/kg bw/day) and severe testicular atrophy at 341 mg/kg bw/day (38 mg B/kg bw/day).

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Borates (boric acid and disodium tetrahydrate decahydrate) induced effects on the testes (decrease in testes weight, testicular atrophy) in mice, rats and dogs. Based on these observations and on effects in studies of reproductive toxicity it is proposed to classifiy disodium octaborate anhydrate for reproductive toxicity (see 4.11).
In addition, boric acid and disodium tetraborate decahydrate induced haematological effects (extramedullary haematopoiesis, decreased Hb and cell volume, presence of hemosiderin in reticular cells of the liver and proximal tubules of the kidney) indicative of increased red blood cell destruction. In a 90 day oral study with boric acid the LOAEL for haematological effects was 1200 ppm, equivalent to 194(34) mg boric acid(B)/kg bw/day (lowest dose tested). In a 2 year oral study the NOAEL for boric acid was 2000 ppm, equivalent to boric acid doses of 100 mg/kg bw/day (equal to 17.5 mg B/kg bw/day). The NOAEL for disodium tetraborate decahydrate in a 2 year oral study was 3080 ppm, equivalent to 155 (17.5) mg disodium tetraborate decahydrate (B)/kg bw/day.
No data on the haematological effects of disodium octaborate anhydrate were available. For boric acid and disodium tetraborate decahydrate the NOAEL in 2-year oral studies was 17.5 boron mg/kg bw/day. Assuming that the toxicological effects of systemic boric acid, disodium tetraborate decahydrate and disodium octaborate tetrahydrate (Molecular formula: $Na_2B_8O_{13}.4H_2O$; MW 412.52) will be similar on a boron equivalents basis, it can be be assumed that the NOAEL of disodium octaborate anhydrate will be approximately 69 mg/kg bw/day and the LOAEL above 100 mg/kg bw/day. The corresponding values for a 90-day study are approximately two times higher.

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

Borates (boric acid and disodium tetrahydrate decahydrate) induced effects on the testes (decrease in testes weight, testicular atrophy) in mice, rats and dogs. Based on these observations and on effects in studies of

reproductive toxicity it is proposed to classify disodium octaborate anhydrate for reproductive toxicity (see 4.11).
The LOAEL for haematological effects of disodium octaborate anhydrate after chronic exposure is expected to be > 100 mg/kg bw/day. According to 67/548/EEC substances should be classification with R48 (Danger of serious damage to health by prolonged exposure) when these effects are observed in the rat at oral exposure levels < 50 mg/kg bw/day in a 90-day study.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

No information is available for disodium octaborate anhydrate. Considering the fact that borates (including disodium octaborate anhydrate) will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of borates are expected to be similar. Therefore, read across to disodium octaborate anhydrate is applied.
Borates induced effects on the testes (decrease in testes weight, testicular atrophy) in mice, rats and dogs. Based on these observations and on effects in studies of reproductive toxicity it is proposed to classify disodium octaborate anhydrate for reproductive toxicity (see 4.11).
Since haematological effects following repeated exposure to disodium octaborate anhydrate are expected to occur at oral exposure levels >100 mg/kg bw/day it is not necessary to classify this substance with R48.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

Borates induced effects on the testes (decrease in testes weight, testicular atrophy) in mice, rats and dogs. Based on these observations and on effects in studies of reproductive toxicity it is proposed to classifiy disodium octaborate anhydrate for reproductive toxicity (see 4.11).
No data on the haematological effects of disodium octaborate anhydrate were available. For boric acid and disodium tetraborate decahydrate the NOAEL in 2-year oral studies was 17.5 mg boron /kg bw/day and 34 boron mg/kg bw/day in a 90-day study. Assuming that the toxicological effects of systemic boric acid, disodium tetraborate decahydrate and disodium octaborate anhydrate will be similar on a boron equivalents basis, it can be be assumed that the NOAEL of disodium octaborate anhydrate in a 2-year study would be approximately 69 mg/kg bw/day. It is likely that the LOAEL for haematological effects of disodium octaborate anhydrate in repeated dose studies will be > 100 mg/kg bw/day.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

Since it is proposed to classify disodium octaborate anhydrate for effects on reproductive toxicity it is not necessary to classify disodium octaborate anhydrate as STOT-RE for testes effects.
Apart from effects on the testes borates induce haematological effects after repeated dosing. Since it is likely that disodium octaborate anhydrate would induce such effects at doses >100 mg/kg bw/day it is considered not necessary to classify this substance as STOT-RE according to EC 1272/2008 as the oral limit is 100 mg/kg bw/day for a 90 day study and even lower for longer studies.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

No information is available for disodium octaborate anhydrate. Considering the fact that borates (including disodium octaborate anhydrate) will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of borates are expected to be similar. Therefore, read across to disodium octaborate anhydrate is applied. It is not necessary to classify disodium octaborate anhydrate as STOT-RE according to EC 1272/2008.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 19: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Test substance	Results	Remarks	Reference
US EPA 40 CRF Part 158; FIFRA, Section 158.340, Guideline 84-2. Comparable to OECD 471	Boric acid	not genotoxic	S. typhimurium:TA 1535, TA 1537,TA 97, TA 98, TA 100, TA 1538 Tested at 10; 50; 100; 1000; 2500 µg/plate	Stewart 1991[a]
40 CFR Part 158 US-EPAFIFRA, Section 156.340; Complies with OECD 476	Boric acid	not genotoxic	Mouse lymphoma L5178Y cells Tested at 0, 1.2, 1.7, 2.45, 3.5, and 5.0 mg/ml boric acid	Rudd, 1991[a]
NTP protocol. resembles OECD 473	Boric acid	not genotoxic	Tested with S9 at 1000;1600;2000;2500 µg/ml Tested without S9 at 500; 1500; 2000 µg/ml	NTP, 1987[a]
Comet assay in human sperm cells of workers exposed borates	Borates	no increase in DNA-strand breaks		Duydu, 2011a[b]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the REACH registration for disodium octaborate, accessed on October 5, 2012

4.9.1 Non-human information

4.9.1.1 In vitro data

For the biocide evaluation of boric acid 3 genotoxicity studies were available: a bacterial reverse mutation test with *S. typhimurium*, an *in vitro* mammalian cell gene mutation test with mouse lymphoma cells and an *in vitro* mammalian chromosome aberration test in Chinese hamster ovary cells. All these studies were negative. In an NTP study (1987) boric acid is also reported to be negative in another in vitro mouse lymphoma test. In vitro genotoxicity studies with other borates also show no evidence of genotoxicity.

4.9.1.2 In vivo data

No original study reports on in vivo mutagenicity tests with borates were available. In a US-EPA report on "Boron and Compounds" the following is decribed: *O'Loughlin (1991) performed a micronucleus assay on Swiss-Webster mice (10 animals/sex/dose). Boric acid was administered in deionized water orally (no verification of stability, concentration, or homogeneity was made of the boric acid by the investigators) for 2 consecutive days at 900, 1800, or 3500 mg/kg. Five mice/sex/dose were sacrificed 24 hours after the final dose, and 5/sex/dose were sacrificed 48 hours after the final dose. A deionized water vehicle control (10/sex) and a urethane positive control (10 males) were also tested. Boric acid did not induce chromosomal or mitotic spindle abnormalities in bone marrow erythrocytes in the micronucleus assay in Swiss-Webster mice.*

4.9.2 Human information

In a comet assay in boron exposed workers, the relation between DNA-strand breaks (COMET assay, neutral and alkaline version) in sperm cells and previously described sperm quality parameters was investigated. A correlation between blood boron levels and mean DNA-strand breaks in sperm was weak, and DNA-strand breaks in sperm were statistically not different between control and exposed groups (Duydu, 2011a).

4.9.3 Other relevant information

No data available

4.9.4 Summary and discussion of mutagenicity

In vitro studies do not indicate that boric acid induces gene mutations or chromosome aberrations. No original study reports on in vivo genotoxicity effects of borates were available. In a US-EPA report an in vivo micronucleus test with boric acid in mice is described. It is reported that boric acid did not induce chromosomal and spindle abnormalities in bone marrow erythrocytes. In chronic studies in mice and rats with borates (boric acid and disodium tetrahydrate decahydrate) there are no indications that these compounds have carcinogenic properties. Based on the available data it is concluded that boric acid is unlikely to be genotoxic. Human exposure to undefined borates did not result in an increase in DNA-strand breaks of sperm cells.
Since in aqueous solutions at physiological and acidic pH, low concentrations of simple borates, like disodium octaborate anhydrate, will predominantly exist as undissociated boric acid it is considered justified to conclude that disodium octaborate anhydrate is unlikely to be genotoxic.

4.9.5 Comparison with criteria

The available database indicates that disodium octaborate anhydrate is not genotoxic.

4.9.6 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Considering the fact that borates (including disodium octaborate anhydrate) will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of borates are expected to be similar. Therefore, read across to disodium octaborate anhydrate is applied. It is not necessary to classify disodium octaborate anhydrate for mutagenicity according to 67/548/EEC or EC 1272/2008.

4.10 Carcinogenicity

Table 20: Summary table of relevant carcinogenicity studies

Method	Test substance	Results	Remarks	Reference
2-year oral study in rat	Boric acid	No evidence of carcinogenicity was found.	Animals received doses up to 6690 ppm in food equivalent to 334 mg boric acid/kg bw/d Only 10 animals/sex were used for macroscopic and histopathologic al examination	Weir, 1966a[a]
2-year oral study in rat	Disodium tetraborate decahydrate	No evidence of carcinogenicity was found.	Animals received doses up to 10300 ppm in food equivalent to 516 mg boric acid/kg bw/d Only 10 animals/sex were used for macroscopic and histopathologic al examination	Weir, 1966b[a]
2-year carcinogenicity study in mice	Boric acid	No evidence of carcinogenicity was found. At both doses: In males haematopoiesis in the spleen. Other effects in testes: At the high dose increased testicular atrophy and interstitial cell hyperplasia, variable loss of spermatogenia, and various stages of spermatogenesis from the seminiferous tubules	Animals received doses of 0, 2500, 5000 ppm in food equivalent to 0, 446 and 1150 mg boric acid/kg bw/d	NTP, 1987[a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

In a carcinogenicity study in mice no evidence of a carcinogenic effect of boric acid (275 and 550 mg/kg bw/day) was observed. In 2 chronic toxicity study with rats, performed with boric acid (334 mg/kg bw/day)

and sodium tetraborate decahydrate (516 mg/kg bw/day) no indication for a carcinogenic effect of these substances were found. However, it should be noted that in these rat studies only 10 animals/sex were used for macroscopic and histopathological examination (Weir, 1966a; Weir, 1966b).

4.10.1.2 Carcinogenicity: inhalation

No data available.

4.10.1.3 Carcinogenicity: dermal

No data available.

4.10.2 Human information

No data available.

4.10.3 Other relevant information

None

4.10.4 Summary and discussion of carcinogenicity

There are no indications that boric acid is carcinogenic or genotoxic.
Since in aqueous solutions at physiological and acidic pH, low concentrations of simple borates, like disodium octaborate anhydrate, will predominantly exist as undissociated boric acid it is considered justified to conclude that disodium octaborate anhydrate is unlikely to be carcinogenic.

4.10.5 Comparison with criteria

There are no indications that disodium octaborate anhydrate is carcinogenic.

4.10.6 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Considering the fact that borates (including disodium octaborate anhydrate) will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of borates are expected to be similar. Therefore, read across to disodium octaborate anhydrate is applied. Disodium octaborate anhydrate does not have to be classified for carcinogenic effects.

4.11 Toxicity for reproduction

Table 21: Summary table of relevant reproductive toxicity studies

Method	Test substance	Results	Remarks	Reference
90-day dietary study in mouse	Boric acid	degeneration and atrophy of the seminiferous tubules at LOAEL of 811 mg/kg bw/day, equal to 142 mg B/kg bw/day. NOAEL is 405 mg/kg bw/day, equal to 71mg B/kg bw/day	Doses: 0,1200, 2500, 5000, 10000, 20000 ppm of boric acid. Equivalent to 0, 194 (34), 405 (71), 811 (142), 1622 (284), 3246 (568) mg boric acid (mg B)/kg bw/day males; and 0, 169 (47), 560 (98), 1120 (196), 2240 (392), 4480 (784) mg boric acid (mg B)/kg bw per day females 5 days/week	NTP, 1987[a]
90-day dietary study in dog	Boric acid	Reduction in testicular weight at 24 mg/kg bw/day, equal to 4.2 mg B/kg bw/day NOAEL is 2.6 mg/kg bw /day, equal to 0.46 mgB/kg bw/day	Doses: 0, 100, 1000, 10000 ppm equal to doses of 2.6 (0.46), 24 (4.2) and 201 (35) mg boric acid (B)/kg bw/day.	Paynter, 1963a[a]
90-day dietary study in dog	Disodium tetraborate decahydrate	Reduction in testicular weight at 42 mg/kg bw, equal to 4.7 mg B/kg bw/day and severe testicular atrophy at 341mg/kg bw/day, equal to 38 mg B/kg bw/day NOAEL is 3.5 mg/kg bw /day, equal to 0.39 mg B/kg bw/day	Doses: 0, 154, 1540, 15400 ppm equal to doses of 0, 3.5 (0.39), 42 (4.7) and 374 (41.7) mg boric acid (B)/kg bw/day.	Paynter, 1963b[a]
2-year dietary study in rat	Boric acid	Testicular atrophy at 334 mg/kg bw/day, equal to 58.5 mg/kg bw /day. NOAELis 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day	0, 670, 2000, 6690 ppm, equivalent to 0, 33 (5.9), 100 (17.5), 334 (58.5) mg boric acid (B)/kg bw/day	Weir, 1966a[a] Weir and Fisher, 1972[b]
2-year dietary study in rat	Disodium tetraborate decahydrate	testicular atrophy and seminiferous tubule degeneration at 516 mg/kg bw/day (58.5 mg B/kg bw/day) NOAEL is 155 mg/kg	0, 52, 155 and 516 mg/kg bw/day, equal to 0, 5.9, 17.5 and 58.5 mg B/kg bw/day.	Weir, 1966b[a]

		bw/day (17.5 mg B/kg bw/day		
2-year dietary study in dog	Boric acid	No details	The study has serious flaws	[a]
2-year dietary study in dog	Disodium tetraborate decahydrate	No details	The study has serious flaws	[a]
3 generation study in rat	Boric acid	severely impaired reproduction, decreased ovulation and testes atrophy at 336 mg/kg bw/day	0, 670, 2000 and 6700 ppm, equivalent to 0, 34, 100 and 336 mg/kg bw/day The study has serious flaws	Weir and Fisher, 1972[a] and b
Multigeneration study in rat	disodium tetraborate decahydrate	severely impaired reproduction, decreased ovulation and testes atrophy at 518 mg/kg bw/day	0, 1030, 3080 and 10300 ppm, equivalent to 0, 50, 155 and 518 mg/kg bw/day The study has serious flaws	Weir, 1966a[a] Weir and Fisher, 1972[b]
Prenatal developmental toxicity study in rat (compliant with OECD TG 414)	Boric acid	Dams: no toxicity. NOAEL is 2000 ppm. Fetuses: at 1000 ppm reduced bodyweight; short 13th rib; wavy rib; not seen postnatally. NOAEL is 750 ppm	Doses: 0, 250, 500, 750,1000, 2000 ppm), equivalent to 19 (3.3), 36 (6.3), 55(9.6), 76 (13.3) and 143 (25) mg boric acid (mg B)/kg bw/day	Price, 1994[a] Price, 1996[b]
Prenatal developmental toxicity study in rabbit (compliant with OECD TG 414)	Boric acid	Dams: Reduced bodyweight and food intake at high dose level with abortions and resorptions. NOAEL is 125 mg/kg bw/day. Fetuses: Resorptions and cardiovascular malformations at high dose level. NOAEL is 125 mg/kg bw/day.	Boric acid doses (gavage) 0, 62.5,125 or 250 mg/kg bw/day, equivalent to 0, 10.9, 21.8 and 43.5 mg B/kg bw/day	Price, 1991[a] Price, 1996[b]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] Environmental Health Criteria 204. Boron. International Program on Chemical Safety (WHO) 1998.

4.11.1 Effects on fertility

4.11.1.1 Non-human information

There are no fertility studies with disodium octaborate (tetrahydrate). In the CAR of 2006 the following effects were reported. In a rat 3 generation reproduction study males and females fed on a diet containing 6700 ppm boric acid (336 mg/kg bw/day) had a severely impaired reproductive potency. At this dose, none of the males produced offspring. The males had atrophied testes (up to 70% reduction in relative testes weight). In females at this dose, only one of 16 produced a litter when mated with control males. In about half of all ovaries evidence of decreased ovulation was observed. At 670 and 2000 ppm (34 and 100 mg/kg

bw/day) no effects on fertility were reported. It should be noted that this study had serious flaws. Only 8 males per dose were used. Histopathology of ovaries and uterus was only performed for females of the high dose group. Mating index (number of pregnancies/number of matings) generally was low, including in control animals (about 60%). The high post-natal mortality of the pups (up to 52% in the control group) casts further doubt on the quality of the study (Weir and Fisher 1972 as summarised in CAR 2006 and EHC 1998).
In a parallel multigeneration study with disodium tetraborate decahydrate similar results were found, i.e. at a dose of 10300 ppm boric acid (518 mg/kg bw/day) both males and females had a severely impaired reproductive potency. At this dose, none of the males produced offspring and the males had atrophied testes. In the females there was evidence of decreased ovulation in about half of the ovaries examined and only two of 16 females produced a litter when mated with control males. At 1030 and 3080 ppm (50 and 155 mg/kg bw/day) no effects on fertility were reported. The criticism on the boric acid study also applies for the disodium tetraborate decahydrate study (Weir 1966, Weir and Fisher 1972 as summarised in CAR 2006 and EHC, 1998).

With respect to fertility, repeated dose studies in rats, mice and dogs consistently demonstrate that the testes are the principle target for borates.
In a 90-day study in mice, in males treated with boric acid at doses of 5000 ppm (811mg/kg bw/day) and above, degeneration and atrophy of the seminiferous tubules was observed (NTP, 1987, as summarised in CAR, 2006).
In a 90-days and a 2-year oral toxicity studies with boric acid in dogs the testes were identified as a major target for boron treatment. However, these studies were considered not acceptable for quantitative evaluation for the biocide regulation (Paynter 1963a and unknown, as summarised in CAR 2006).
In a 2-year oral toxicity study with boric acid in rats, testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at the highest dose level (334 mg/kg bw/day). No effects on testes were observed at 33 and 100 mg/kg bw/day (Weir 1966, Weir and Fisher 1972 as summarised in CAR 2006 and EHC, 1998).

Studies with disodium tetraborate decahydrate in the rat and the dog also show that the testes are the principle target for boron.
In a 90-days and a 2-year oral toxicity studies with disodium tetraborate decahydrate in dogs again the testes were identified as a major target for boron treatment. However, these studies were considered not acceptable (Paynter 1963b and unknown, as summarised in CAR 2006).
In a 2-year oral toxicity study with sodium tetraborate decahydrate in rats, testicular atrophy and seminiferous tubule degeneration was observed at 6, 12 and 24 months at 516 mg/kg bw/day (58.5 mg B/kg bw/day). The extent of the lesion did not increase over the course of the treatment period. No effects on the testes were observed in animals treated with disodium tetraborate decahydrate at 52 and 155 mg/kg bw/day (5.9 and 17.5 mg B/kg bw/day) (Weir 1966b, as summarised in CAR 2006).

In addition to the studies reported in the CAR (2006) a number of studies with borates demonstrating testes effects were reported (Boron, EHC 204, 1998). For instance, in the rat, inhibition of spermiation was already observed after 7 days of treatment with doses of 61 mg B/kg bw in the diet and after 28 days extreme epithelial disorganisation and sperm cell loss was evident. Early effects were seen after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day), but at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects seen by histopathological analysis take about 28 days to manifest. Another study in rats showed that inhibited spermiation was reversed after a 16 weeks recovery period, but focal atrophy did not recover up to 32 weeks post-treatment (Treinen and Chapin 1991, as summarised in EHC 1998).
In a multigeneration continuous-breeding experiment Swiss CD-1 mice (F0 generation) were fed boric acid in the diet at 0, 1000, 4500, or 9000 mg/kg feed (0, 19, 105, and 222 mg B/kg bw/day for males and 0, 32, 148, and 291 mg B/kg bw/day for females) for 27 weeks. Treatment with boric acid significantly impaired fertility: no males or females in the high-dose groups were fertile. At the middle dose, the number of litters per pair, number of live pups per litter, proportion of pups born alive, and pup weight adjusted for litter size were all decreased. The lower fertility index at 4500 mg/kg feed progressed in severity with subsequent matings. Cross-mating of animals at 4500 mg/kg bw/day with controls showed that males were affected at this dose. Sperm motility was significantly reduced in all exposed groups (by 12%, 32%, and 47%, from low- to high-dose groups, respectively) (Fail 1990/1991, as summarised in EHC 1998).

In the registration dossier of boric acid, the following (additional) studies were found:
In a fertility study in rats with boric acid (gavage) males were treated for 21 days and mated with untreated females. The NOAEL was 8.75 mg B/kg bw/day (LOAEL 26.25 mg/kg bw/day). Fertility effects were observed at ≥ 26.25 mg B/kg bw/day (Yoshizaki 1999, as summarised in the registration file of boric acid).
In a fertility study in male rats with Borax (feed) for 30 or 60 days, the NOAEL was 50 mg B/kg bw/day (LOAEL 100 mg/kg bw/day). After 30 days exposure a reduction in spermatocytes, spermatids and mature spermatozoa was observed. After 60 days exposure most germinal elements were absent (Lee 1978, as summarised in the registration file of boric acid).
Rats were exposed to 0, 3000, 4500, 6000, 9000 ppm boric acid (equivalent to 0. 26, 38, 52.5 or 68 mg B/kg bw/day) for 9 weeks. Animals exposed to 52 and 68 mg B/kg bw showed severe inhibition of spermiation by week 2 followed by testis and epididymis weight loss and finally, progression to atrophy in week 9 and 6, respectively. Rats exposed to 38 mg B/kg bw showed severe inhibition of spermiation by week 2 with some germ cell exfoliation observed only at week 9 and epididymis weight loss. The animals exposed to 26 mg B/kg bw showed only mildly inhibited spermiation by week 5 and this continued variably until the end of the exposure period. After a 32 week recovery period, mild inhibition of spermiation was demonstrated at 3,000 ppm with 25-50% of tubules with retained spermatid at stage IX, and severe widespread inhibition of spermiation at 4,500 ppm. Testicular atrophy occurred at 6,000 ppm (Ku 1993, as summarised in the registration file of boric acid).

4.11.1.2 Human information

In human epidemiological cohort study in Turkey (Sayli et al., 1998) no effects on the number of children born over a period of 15 years were observed in populations exposed to high levels of boron through drinking water (up to 29 mg B/l)). Other endpoints such as time to pregnancy were not included.
In a study in the USA, the fertility of male workers of a borax mine was studied. The study revealed that the workers exposed to low (<0.82 mg/m^3) or high (>5.05 mg/m^3) levels of boron in dust fathered more live births than was estimated on the basis of the data of the US general population. The extent to which the workers are comparable to the US general population however was not clear. Also in this study other endpoints such as time to pregnancy were not established.
In a recent study (Robbins et al., 2010) data were collected on boron exposure/dose measures in workplace inhalable dust, dietary food/fluids, blood, semen, and urine from boron workers and two comparison worker groups (n = 192) over three months and correlations between boron and semen parameters (total sperm count, sperm concentration, motility, morphology, DNA breakage, apoptosis and aneuploidy) were determined. Blood boron averaged 499.2 ppb for boron workers, 96.1 and 47.9 ppb for workers from high and low environmental boron areas ($p < 0.0001$). Boron concentrated in seminal fluid. No significant correlations were found between blood or urine boron and adverse effects on semen parameters. Exposures did not reach those causing adverse effects published in animal toxicology work but exceeded those previously published for boron occupational groups.
In another recent publication (Scialli et al, 2010) data from new studies in Chinese workers working in boron mining or processing are reported. Employed men living in the same community and in a remote community were used as controls. Boron workers (n = 75) had a mean daily boron intake of 31.3mg B/day, and a subset of 16 of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125mg B/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25mg B/day and 1.40 mg/day, respectively. Reproductive outcomes in the wives of 945 boron workers were not significantly different from outcomes in the wives of 249 background control men after adjustment for potential confounders. There were no statistically significant differences in semen characteristics between exposure groups, including in the highly exposed subset, except that sperm Y:X ratio was reduced in boron workers. Within exposure groups the Y:X ratio did not correlate with the boron concentration in blood, semen and urine. Thus, while boron has been shown to adversely affect male reproduction in laboratory animals, in the study of Scialli et al. (2010) there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers. It is noted, however, that in these studies human the estimated exposure levels are lower than the overall NOAEL for testis effects in rats.

A study published in 2011 by Duydu et al. was conducted to investigate the reproductive effects of boron exposure in workers employed in boric acid production plant in Bandirma, Turkey. In order to characterize the external and internal boron exposures, boron was determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. Unfavorable effects of boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone) were not observed, even when the data were re-evaluated versus semen boron and urine boron levels (unpublished data). The mean calculated daily boron exposure (DBE) of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg/day, i.e. ~ 0.2 mg/kg bw/day. These human exposures represent worst-case exposure conditions to boric acid/borates in Turkey (Duydu 2011b, Basaran 2012). It is noted that these exposure levels and the exposure assessed in the Bandirma boric acid production plant (Duydu, 2012) are considerably lower than exposures, which have previously led to reproductive effects in experimental animals.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Boric acid has been tested in developmental studies in rat and rabbit. In a study in rats the NOAEL for embryotoxic/teratogenic effects was 55 mg/kg bw/day (9.6 mg B/kg bw/day), based on a reduction in mean fetal body weight/litter and an increased incidence in short rib X111 (considered to be a malformation, see also “Boron, EHC 204, 1998”) at 76 mg/kg bw/day (13.3 mg B/kg bw/day). The percentages of fetuses showing the malformations at control, 3.3, 6.3, 9.6, 13.3 and 25 mg B/kg bw/day were 0.7, 0.6, 0.6, 0.7, 1.2 and 1.5% respectively. The maternal NOAEL in this study was 143 mg/kg bw/day (highest dose tested) (Price 1994/1996 as summarised in CAR 2006 and EHC 1998).
The CAR and EHC204 reviews on boron reports a study by Heindel et al. (1992) in which the developmental toxicity and teratogenicity of boric acid was investigated in Sprague-Dawley rats at 0, 13.6, 28.5, and 57.7 mg boron/kg bw/day as boric acid from gestation days 0 to 20). Maternal effects included a significant and dose-related increase in relative liver and kidney weights at >28.5 mg boron/kg bw/day. Treatment with 94.2 mg boron/kg bw/day significantly increased prenatal mortality. Average fetal body weight per litter was significantly reduced in a dose-related manner in all treated groups compared with controls. The percentage of malformed fetuses per litter and the percentage of litters with at least one malformed fetus were significantly increased at >28.5 mg boron/kg bw/day. Malformations consisted primarily of anomalies of the eyes, the CNS, the cardiovascular system, and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. The percentage of fetuses with variations per litter was reduced relative to controls at 13.6 and 28.5 mg boron/kg bw/day (due to a reduction in the incidence of rudimentary or full ribs at lumbar 1) but was significantly increased in rats exposed to 94.2 mg boron/kg bw/day. The variation with the highest incidence among fetuses was wavy ribs. The LOAEL of 13.6 mg boron/kg bw/day (lowest dose tested) for rats occurred in the absence of maternal toxicity; a NOAEL was not found in this study (Heindel 1992, as summarised in CAR 2006 and EHC 1998).
In a developmental toxicity study in rabbits, the NOAEL for maternal and embryotoxicity/teratogenicity was 125 mg/kg bw/day (see EHC204). At 250 mg/kg bw/day the dams showed a reduction in body weight and food consumption. At this dose the number of resorptions per litter was 90%, as compared to 6% in controls. In the surviving foetuses a highly increased incidence in major heart and/or great vessel malformations was observed. The extent and severity of the effects at the LOAEL are remarkable, in view of the small dose spacing between the NOAEL and LOAEL in this study. In a study in rats that was not available for the present evaluation, a slight reduction in fetal body weight was observed at 78 mg/kg bw/day (lowest dose tested). At 163 mg/kg bw/day skeletal malformations were observed (Price 1991/1996, as summarised in CAR 2006 and EHC 1998).
The CAR and EHC204 reviews on boron reports a study by Heindel et al. (1992) in which the developmental toxicity and teratogenicity of boric acid was investigated in mice at 0, 43, 79, or 175 mg boron/kg bw/day in the diet. There was a significant dose-related decrease in average fetal body weight per litter at 79 and 175 mg boron/kg bw/day. In offspring of mice exposed to 79 or 175 mg boron/kg bw/day during gestation days 0-17, there was an increased incidence of skeletal (rib) malformations. These changes occurred at doses for

which there were also signs of maternal toxicity (increased kidney weight and pathology); the LOAEL for developmental effects (decreased fetal body weight per litter) was 79 mg boron/kg bw/day, and the NOAEL for developmental effects was 43 mg boron/kg bw/day (Heindel 1992, as summarised in CAR 2006 and EHC 1998).

In rats exposed to 0.1, 0.2 or 0.4 % boric acid in feed on GD0-20 or 0.8% on GD6-15 (78, 163, 330 and 539 mg/kg/day) prenatal mortality was significantly increased in the 0.8 % group relative to the control group (4 % vs. 36 % non-live implants per litter for controls vs. 0.8 % boric acid). Significant increases in both the percent resorptions per litter and the percent late foetal deaths per litter contributed to the observed increase in prenatal mortality. A corresponding decrease in live litter size was observed in the 0.8 % group (15.4 vs. 9.7 live foetuses per litter for controls vs 0.8 % boric acid). Average foetal body weight per litter was significantly reduced in all boric acid treatment groups. Mean foetal weights were 94 %, 87 %, 63 % and 46 % of the corresponding control means for the 0.1 %, 0.2 %, 0.4 % and 0.8 % groups, respectively.
An increase in the incidence of malformations was observed at 0.2 %, 0.4 % and 0.8 % boric acid relative to controls. The percent foetuses malformed per litter was 2 %, 3 %, 8 % and 50 % for control through 0.4 % boric acid on GD 0 to 20; following exposure on GD 6 to 15 , the control level was 3 % malformed/litter as compared to 73 % for the 0.8 % boric acid group. The percentage of litters containing at least 1 malformed foetus were 21 % (GD 0 to 20 coontrols and 0.1 % boric acid), 29 % (GD 6 to 15 controls), 50 % (0.2 % boric acid) and 100 % (0.4 % and 0.8 % boric acid). The incidence of litters with at least 1 skeletal malformation was significantly increased at 0.2 - 0.8 % boric acid; the incidence of litters with at least 1 visceral malformation was increased at 0.4 - 0.8 % boric acid. The incidence of litters with at least one gross external malformation was increased only at 0.8 %. (Confidential 1990, as summarised in the registration file of boric acid).

4.11.2.2 Human information

In a prospective study of > 50000 pregnancies the association of exposure to several drugs, among which topical exposure to boric acid during pregnancy, on the incidence of malformations was studied. The standardized relative risk for the incidence of malformations after topical exposure to boric acid was 1.69 (0.95-2.76). The hospital standardized relative risk for the incidence of cataract was 13.6 after exposure in the first 4 months of pregnancy and 7.9 after exposure anytime during pregnancy (Heinonen, 1977).

Tuccar et al., (1998) studied the health effects of boron in human subpopulations in Turkey with low or high boron exposure. Spontaneous abortions, stillbirths, and congenital malformations in addition to early infant mortality were questioned in the field by home visits. The rates related to spontaneous abortions and stillbirths from high B exposure vs low B exposure subpopulations revealed no significant differences. The study authors noted that the number of families that were questioned was rather small. Only an abstract of this study was available. In view of the small number of families involved, the study has limited value.

Çöl et al. (2000) investigated reproductive effects, developmental effects, and effects on the sex ratio on environmentally and occupationally exposed male workers families in a cross-sectional design at three areas in Turkey. There were no differences in infertility rates, sex ratios and possible developmental effects between the production workers and office workers. (Çöl 2000, as summarised by EBA).

Chang et al. (2006) evaluated reproductive health in a cohort of boron mining and processing male workers (N=936) and a comparison group of males (N=251) in northeast China. The reproductive effects data were obtained by self-report of delays in pregnancy, pregnancy outcomes, total number of children, and gender of children. Exposure estimates for the boron workers was 31.3 mg boron/day and 1.40 mg B/day for the comparison group (Scialli et al. 2010). No statistically significant differences were observed in delay in pregnancy, multiple births, spontaneous miscarriage, induced abortion, stillbirth, tubal or ectopic pregnancy, and boy/girl ratio (Chang 2006, as summarised by EBA).

In a case control study from Hungary the difference in congenital abnormalities between mothers in the study group that received boric acid treatment during pregnancy for infectious diseases of the genital organs (vaginal tablets of 30 mg each daily for 7 days) compared to the control group was not statistically significant. Two out of 211 (0.9%) cases of congenital abnormalities affecting the skeletal system occurred in the offspring of mothers who were treated with boric acid during their entire pregnancy. There was a higher risk of neural tube defects when boric acid was used during the second and third months of pregnancy, but this finding was based on only two cases. There was a higher risk for congenital abnormalities after using boric acid in the second and third months. However, the difference in congenital abnormalities between mothers in the study group that received boric acid treatment the entire pregnancy compared to the control group was not statistically significant. (Acs 2006, as summarised by EBA).

4.11.3 Other relevant information

Boric acid is produces specific malformations in rodents at the level of the axial skeleton, more specifically fusions and homeotic transformation of the axial skeleton fragments. In embryos (from boric acid treated rats) collected on GD 13.5, a specific cranial shift of the cranial limit of expression of hoxc6 and hoxa6 was observed in the prevertebrae. Anteriorization of the expression domain of hoxc6 and hoxa6 is consistent with the posterior transformation of cervical vertebrae. This may explain the malformations observed in fetuses exposed to boric acid (Wery 2003).
Another mechanistic study with regard to the boric acid related teratogenicity was performed by Di Renzo et al. (2007). Pregnant mice were treated intraperitoneally with a teratogenic dose of boric acid (1000 mg/kg on GD8). No signs of maternal toxicity were observed. In boric acid treated fetuses, vertebral or rib fusions, changes in the typical number of segments in the different axial districts, homeotic respecifications were observed at term of gestation. Analysis of the embryos showed H4 hyperacetylation at the level of somites and a significant inhibition of histone deacetylases. Inhibition of histone deacetylases has been described as a key mechanism of teratogenesis, inducing alterations in gene expression and phenotype. The same mechanism for induction of rodent malformations is described for valproic acid (VPA). Boric acid and VPA cause similar malformations in rodents. VPA is a well known teratogenic in experimental animals as well as in humans (Di Renzo et al., 2007). This indicates that the described mechanism is likely to be also relevant for humans.

Due to the toxicological similarities of boron compounds classified as toxic to reproduction category 1B according to Annex VI of CLP, the following boron compounds have been included in the Candidate List following their identification as substances of very high concern (SVHC):

- **Boric acid** (CAS: 10043-35-3);
  covering also
  boric acid, crude natural (CAS: 11113-50-1)
- **Disodium tetraborate, anhydrous** (CAS: 1330-43-4);
  covering also
  disodium tetraborate pentahydrate (CAS: 12179-04-3),
  disodium tetraborate decahydrate (CAS: 1303-96-4) and
  tetraboron disodium heptaoxide, hydrate (CAS: 12267-73-1)
- **Tetraboron disodium heptaoxide, hydrate** (CAS: 12267-73-1);
  covering also
  disodium tetraborate, anhydrous (CAS: 1330-43-4),
  disodium tetraborate pentahydrate (CAS: 12179-04-3),
  disodium tetraborate decahydrate (CAS: 1303-96-4)
- Diborontrioxide (CAS: 1303-86-2)

4.11.4 Summary and discussion of reproductive toxicity

Sexual function/fertility

In a multigeneration reproduction toxicity study in the rat with boric acid severely impaired reproductive potency was observed at 336 mg/kg bw/day. At this dose also marked reductions (70%) in relative testes weights were observed. At lower doses no reproductive effects or effects on testes weight were observed. These findings suggest that a reduction in testes weight will result in an impaired fertility.Since this study was seriously flawed, no definitive conclusions on the effects of boron on fertility in the rat can be drawn (Weir 1966, Weir and Fisher 1972 as summarized in CAR 2006 and EHC, 1998).

A reproductive toxicity study in mice also indicates that boron significantly impairs fertility (NTP, 1987, as summarised in CAR, 2006). Other repeated dose studies in several animal species have consistently demonstrated that the testis is a primary target organ for boron. Based on the data from the 2 years feeding study with boric acid in rats, the overall NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day (Weir 1966, Weir and Fisher 1972 as summarised in CAR 2006 and EHC, 1998). This conclusion is supported by the study with disodium tetraborate decahydrate (Weir 1966b, as summarised in CAR 2006). It is considered unlikely that the effects on the testes (about 75% reduction in weight) at 58.5 mg B/kg bw/day are secondary to other toxicity, e.g. haematological effects (Hb levels reduced up to 19%, RBC cell volume reduced up to 18%).

Development

Developmental toxicity was studied in the mouse, rat and the rabbit. The most sensitive species for developmental effects appears to be the rat. The overall NOAEL for embryotoxic/teratogenic effects of boric acid in rats was 55 mg/kg bw/day (9.6 mg B/kg bw/day), based on a reduction in mean fetal body weight/litter and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day) (Price 1994/1996 as summarised in CAR 2006 and EHC 1998).

In a developmental toxicity study in rabbits with boric acid a highly increased incidence in major heart and/or great vessel malformations was observed at 250 mg/kg bw/day (44 mg B/kg bw/day). The NOAEL for maternal and embryotoxicity/teratogenicity was 125 mg/kg bw/day (22 mg B/kg bw/day) (Price 1991/1996, as summarised in CAR 2006 and EHC 1998).

In a study in mice skeletal malformations were observed at 79 mg B/kg bw/day (NOAEL was 43 mg B/kg bw/day) (Heindel 1992, as summarised in CAR 2006 and EHC 1998).

Mechanistic studies indicate that the teratogenicity is caused by an altered hox gene expression, caused by inhibition of histone deacetylases, a mechanism that is likely to be also relevant for humans (Wery, 2003; Di Renzo et al., 2007).

4.11.5 Comparison with criteria

Sexual function/fertility

Studies of reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that boron impairs fertility through an effect on the testes. The effects observed in the different species are similar in nature. Based on the data from the 2 years feeding study with boric acid in rats, the overall NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. This conclusion is supported by the study with disodium tetraborate decahydrate. There are no indications that the impaired fertility is secondary to other toxic effects.

The similarities in the toxicokinetics and toxicodynamics of boron in animals indicate that the effects of boron on fertility and development in animals are relevant for humans. Epidemiological studies in humans exposed to relatively high boron levels do not report impaired fertility. It is noted that in these human studies the estimated exposure levels are lower than the overall NOAEL for testes effects in rats (Bolt et al, 2012). The human data does not contradict the animal data. Therefore, there is no evidence that the effects observed in animals are not relevant to humans.

Development

Developmental toxicity (malformations) was clearly observed in studies in mice, rats and rabbits, the rat being the most sensitive species, with an overall NOAEL of 9.6 mg B/kg bw/day.

There are no indications that the developmental effects are secondary to other toxic effects. In addition, the teratogenicity is probably caused by an altered hox gene expression, caused by inhibition of histone deacetylases, a mechanism that is likely to be also relevant for humans.

Lactation
There are no indications that boron exposure through lactation has adverse effects.

4.11.6 Conclusions on classification and labelling

No information is available for disodium octaborate anhydrate. Considering the fact that borates (including disodium octaborate anhydrate) will predominantly exist as undissociated boric acid in physiological conditions, the toxicological properties of borates are expected to be similar. Therefore, read across to disodium octaborate anhydrate is applied.

Based on the clear adverse developmental and fertility effects of borates in toxicological studies in several animal species it is proposed to classify disodium octaborate anhydrate with reproduction category 2 and assign risk phrases R60-61 according to Directive 67/548/EEC.

Based on the adverse developmental and fertility effects of borates in rats and rabbits, disodium octaborate anhydrate should be classified with Repr. 1B, H360FD May damage fertility. May damage the unborn child according to Regulation EC 1272/2008.

This is in line with the proposal of the EU commission working group of specialized experts in the field of reprotoxicity (see Annex I, Summary record ECBI/132/04 Rev 2, 2004) and the harmonised classification of several other borates.

In the EU SCLs have been determined for several borates according to Commission Regulation 790/2009, based on the effects of boron in toxicity studies on reproduction, using the German method (BAuA, 1998). The SCL for boron is based on the overall NOAEL for reproductive effects, i.e. 9.6 mg B/kg bw/day, observed in a developmental toxicity study in the rat (see above). For boron the calculated limit is: 9.6 / 1000 * 100 = 0.96% = 1%, and for instance for boric acid the SCL is 5.5%. Disodium octaborate anhydrate contains 25.7% (w/w) boron. Correcting for the percentage of boron the SCL for disodium octaborate anhydrate is 3.7%, according to the German method.

SCLs for disodium octaborate anhydrate can also be determined according to the guidance for the setting of specific concentration limits of the EU expert group (adopted in October 2012). According to the guidance the SCL should be based on the lowest ED10 for the reproductive effect. For borates the most sensitive reproductive effect was the increased incidence of short rib XIII in a developmental toxicity study in rats (see above). The fetal incidence of this malformation was 1.2 and 1.5% at the LOAEL (13.3 mg B/kg bw/day and the highest dose (25 mg B/kg bw/day) respectively. As the incidences are low, it is not possible to derive an ED10. In this instance the LOAEL should be used for setting the SCL, according to the guidance. Correcting for the percentage of boron (w/w), the LOAEL of 13.3 mg B/kg bw/day corresponds to a LOAEL of 52 mg/kg bw/day for disodium octaborate anhydrate. According to the guidance disodium octaborate anhydrate belongs to the medium potency groups (4 mg/kg bw/day < ED10 (LOAEL) < 400 mg/kg bw/day). None of the modifying factors apply. As borates are classified in category 1B according to the guidance for disodium octaborate anhydrate the GCL of 0.3% would apply.

Nevertheless, it is proposed to set an SCL of 3.7% for disodium octaborate anhydrate, as determined according to the German method (ECBI/19/95 add), because in this way the SCL of this borate is in line with the other borates with a harmonized classification.

Since there are no indications that boron exposure through lactation has adverse effects it is not necessary to classify disodium octaborate anhydrate for effects on or via lactation.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

No neurotoxic studies were available for the biocide evaluation. CNS depression was observed in poisoning cases. Apart from the CNS effects that occur at these very high doses there are no indications that boric acid or other borates have neurotoxic properties.

4.12.1.2 Immunotoxicity

No immunotoxic studies were available for the biocide evaluation. There are no indications from acute and repeated dose studies that borates have immunotoxic properties.

4.12.1.3 Specific investigations: other studies

No data available

4.12.1.4 Human information

Human Data from Poison Control Centres and Literature Cases
Apart from the effects of borates in humans that are described paragraphs 4.1-4.11 no other toxic effects in humans were identified.

4.12.2 Summary and discussion

Apart from the effects described in paragraphs 4.1-4.11 no other toxic effects of borates were identified.

4.12.3 Comparison with criteria

Apart from the effects described in paragraphs 4.1-4.11 no other toxic effects of borates were identified.

4.12.4 Conclusions on classification and labelling

It is not necessary to classify disodium octaborate anhydrate for toxic effects other than those described in the paragraphs above.

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental hazard properties assessment for disodium octaborate anhydrate is based on the Competent Authority Report (CAR, 2006) for disodium octaborate tetrahydrate (document IIA). The CAR was prepared in the context of the possible inclusion of disodium octaborate tetrahydrate in Annex I of Council Directive 91/414/EEC (June 2006), RMS The Netherlands), on the inclusion of disodium octaborate tetrahydrate in Annex I to Directive 98/8/EC concerning the placing biocidal products on the market. Only

studies indicated in the CAR as being reliable have been included in this CLH report. Additional good quality aquatic toxicity studies (equivalent to Klimisch score 1 and 2) carried out in line with recognised guidelines and reported in the EU RAR and the REACH registration dossier were included if the results obtained in these studies were lower than those reported in the CAR. If a study is cited in a number of sources, then the study is referenced according to the non-confidential source.

All tables in the present assessment are copied from the final CAR with information from the other sources used added. The tables are renumbered in accordance with the paragraph numbers.

Disodium octaborate anhydrate undergoes rapid dissolution in water to form other species. The mode of dissolution is complex and depends on the conditions (pH, temperature and concentration). In dilute aqueous solutions at pH<7, boric acid is the predominant form, whereas at pH>11 the metaborate ion [$B(OH)_4$] becomes the main species in solution. At pH values between 7 and 11, both species are present. The estimated pKa value for this equilibrium is 9.0. Boric acid is the most common form present under most environmentally and physiologically relevant conditions. According to the CAR, it is assumed that of all the possible forms of borate in the environment, the boron ion is the potentially toxic compound.

5.1 Degradation

Mode of dissolution of borates in water[3]

Most of the simple inorganic borates (for example, boric acid, boric oxide, sodium metaborates, tetraborates and octaborates) are highly water-soluble. The mode of dissolution of borate compounds as well as of boric acid is complex and depends very much on the conditions (pH, temperature and concentration).

Boron concentrations ≤ 0.025 M

At lower concentrations of boron (B ≤ 0.025 M; 270 mg/L), the following equilibrium is found between boric acid and metaborate.

$B(OH)_3 + 2H_2O \leftrightarrow [B(OH)_4]^- + H3O^+$ pKa = 9.0 at 25 °C

In dilute aqueous solutions (B ≤ 0.025 M), boric acid remains un-dissociated at pH < 7, whereas at pH > 11 the metaborate ion $[B(OH)_4]^-$ becomes the main species in solution. At pH values between 7 and 11, both species are present.

Boron concentrations > 0.025 M

At higher boron concentrations (B > 0.025 M) an equilibrium is formed between $B(OH)_3$, polynuclear complexes of $B_3O_3(OH)_4^-$, $B_4O_5(OH)_4^{2-}$, $B_3O_3(OH)_5^{2-}$, $B_5O_6(OH)_4^-$ and $B(OH)_4^-$.
In short: $B(OH)_3 \leftrightarrow$ polynuclear anions $\leftrightarrow B(OH)_4^-$. In acid solution at pH < 5, boron is mainly present as $B(OH)_3$ and in alkaline solution at pH > 12.5, boron is mainly present as $B(OH)_4^-$. At pH values (pH 5-12) polynuclear anions are found as well as $B(OH)_3$ and $B(OH)_4^-$.

The dissociation constants depend upon temperature, ionic strength and presence of group I metal ions (Na, K, Cs).

The dissolution to un-dissociated boric acid by all the borates was confirmed in the study by De Vette et al., 2001 (CAR:Doc IIIa-7.1.1.1.1), who identified and compared the dissociation products of sodium borates (disodium tetraborate decahydrate and disodium octaborate tetrahydrate) and boric acid in dilute aqueous solutions. The data showed through Raman spectra that the predominant species present was un-dissociated boric acid.

[3] Information copied from CAR IIA-4.1 (June 2006).

From the above it is clear that speciation is important. It is assumed that boric acid will be the predominant species. Most of the toxicity tests were performed in the range where it is mainly present, as is the case in natural water (WHO, 1998).

5.1.1 Stability

Stability in water

Disodium octaborate tetrahydrate is an inorganic compound that dissociates in water but does not have any chemical bonds prone to hydrolysis. Hence, hydrolysis is considered not a relevant degradation pathway.

Photolysis in water

Disodium octaborate anhydrate and the species it forms in water are inorganic compounds without any light absorption characteristics. It is therefore unlikely that the concentration of boric acid in water is influenced by light. Disodium octaborate anhydrate is consequently considered to be resistant to photochemical degradation.

5.1.2 Biodegradation

Disodium octaborate anhydrate is an inorganic substance. According to CLP Annex I section 4.1.2.10.1, for metals and inorganic compounds, the concept of degradability as applied to organic compounds has limited or no meaning. Methods for the determination of biodegradability are not applicable on inorganic substances. Therefore biodegradation is not considered as a relevant pathway.

5.1.3 Summary and discussion of persistence

Disodium octaborate anhydrate is an inorganic substance that undergoes rapid dissolution in water to form boric acid as the predominant species at environmentally relevant pH values. Other borate compounds may also be formed depending on factors such as concentration and pH. Boric acid has good water solubility. Disodium octaborate anhydrate does not hydrolyse, and is considered resistant to photochemical degradation. As disodium octaborate is an inorganic compound, the term biodegradation has no meaning.

Based on the available information, disodium octaborate anhydrate dissociate rapidly to form boric acid. However, boric acid and the boron ion, the potentially toxic compound, do not rapidly degrade. Therefore, disodium octaborate anhydrate must be considered not readily or rapidly degradable.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Not relevant for this dossier.

5.2.2 Volatilisation

Not relevant for this dossier.

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

No data available

5.3.1.1 Bioaccumulation estimation

No data available

5.3.1.2 Measured bioaccumulation data

Disodium octaborate anhydrate is an inorganic compound that undergoes rapid dissolution in water to form boric acid as the predominant species. The bioaccumulation potential of boric acid is considered negligible. Furthermore, laboratory data suggest low Bioconcentration Factors (BCF) for boron in oysters and salmon, although the tests pre-date current protocols. Maximum BCF-values in the range of 1-1.5 L/kg for Pacific oysters (*Crassostrea gigas*) have been reported. Furthermore**,** boron levels in tissue of sockeye salmon (*Oncorhynchus nerka*) were not significantly different from test water concentrations. Another study reported a bioconcentration factor of 0.3 L/kg for fathead minnow (*Pimephales promelas*) and green sunfish (*Lepomis cyanella*), when exposed to components of coal fly ash extract containing boron at concentrations ranging from 1.23 to 91.7 mg/L.
Given the available data and the physical form of disodium octaborate anhydrate in water, its bioconcentration and bioaccumulation potential is considered low.

5.3.2 Summary and discussion of aquatic bioaccumulation

Disodium octaborate anhydrate is considered to have a low bioaccumulating potential.

5.3.3 Estimations on terrestrial bioconcentration

Not relevant for this dossier.

5.4 Aquatic toxicity

Disodium octaborate anhydrate undergoes rapid dissolution in water to form other species. Boric acid is the most common form present under most environmentally and physiologically relevant conditions. According to the CAR, it is assumed that of all the possible forms of borate in the environment, the boron ion is the potentially toxic compound. The available studies on the ecotoxicity of boron have been performed with boric acid (H_3BO_3), anhydrous sodium tetraborate ($Na_2B_4O_7$), and hydrated sodium tetraborates ($Na_2B_4O_7.xH_2O$). For the purpose of classification and labelling, the results from the available studies have been converted to the concentrations of elemental boron (B) using the relative molar mass according to the table in section 4, and subsequently, the concentrations corresponding to the substance being classified have been calculated and compared with the classification criteria.

The table below shows the lowest available toxicity values for the three aquatic trophic levels fish, invertebrates and algae, normalised to boron and calculated for disodium octaborate anhydrate.

Table 22: Summary of relevant information on aquatic toxicity

Method	**Test substance, test conditions and reliability**	**Results [mg B/L]**	**Result [mg$Na_2B_8O_{13}$/L]**	**Reference**
Acute fish: *Limnanda limanda*	Sodium tetraborate (anhydrous) , seawater, reliable with restriction.	96-hours LC_{50} = 74	291	Taylor et al (1985) [c]
Chronic fish: *Oncorhynchus mykiss* (embryo and sac-fry stage)	Boric acid, peer-reviewd study, fresh water, 188 mg/L hardness, reliable without restriction.	28 days LC10 for mortality = 0.7	2.7	Dyer, 2001 [a] [c]
Acute invertebrate: *Litopenaeus vannamei*	Boric acid, comparable to guideline study, fresh water, 170 mg/L hardness, reliable without restriction.	96-hours EC_{50} = 25.05	98.7	Li et al. 2007[b]
Chronic invertebrate: *Daphnia magna*,	Boric acid, comparable to guideline study, fresh water, 170 mg/L hardness, reliable without restriction	21 days NOEC for reproduction = 6	24	Lewis and Valentine, 1981 [c]
Algae (acute) *Selenastrum capricornutum* *Algae (chronic)* *Emiliania huxleyi*	Boric acid, guideline study, fresh water, reliable without restriction.	3-days E_rC_{50} = 44.6 NOE_rC = 5	E_rC_{50} : 176 NOE_rC: 20	Anita and Cheng (1975) [c]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the REACH registration for disodium octaborate, accessed on October 25, 2012
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Table 23: Acute toxicity values for fish normalised to boron and calculated for disodium octaborate anhydrous.

Species	**Substance tested**	**Exposure duration**	**Criterion**	**Value [mg B/L]**	**Value expressed as [mg$Na_2B_8O_{13}$/L]**	**Reference**

Oncorhynchus kisutch	H_3BO_3	96 h	LC50	447	1761	Hamilton and Buhl (1990)[a]
Onchorhynchus tshawtscha	H_3BO_3	96 h	LC50	600	2364	Hamilton and Buhl (1990) [a]
Catostomus latipinnis	H_3BO_3	96 h	LC50	125	492	Hamilton and Buhl (1997) [a]
Pimephales promela	H_3BO_3	96 h	LC50	79.7	314	Study report.005 (2010) [b]
Limanda limanda	$Na_2B_4O_7$	96 h	LC50	74	291	Taylor et al (1985) [c]
Oncorhynchus kisutch	$Na_2B_4O_7$	283 h	LC50	113	445	Thompson et al (1976) [c] Raymond & Butterwick (1992) [c]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the REACH registration for disodium octaborate, accessed on October 25, 2012
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

5.4.1.2 Long-term toxicity to fish

Table 24: Freshwater chronic toxicity data for fish normalised to boron and calculated for disodium octaborate anhydrous.

Species	Life stage	Substance tested	Exposure time [days]	Effect	Criterion	Value [mg B/L]	Value expressed as [mg$Na_2B_8O_{13}$/L]	Reference
Carassius auratus	Embryo-larval	H_3BO_3	7	Mortality	LC10	15	59	Dyer, 2001 [a c]
Ictalusrus punctatus	Embryo-larval	H_3BO_3	9	Mortality	LC10	5	18	Dyer, 2001 [a c]
Oncorhynchus mykiss	Embryo-larval	H_3BO_3	28	Mortality	NOEC	2	8	Dyer, 2001 [a c]
Pimephales promelas	Egg and fry	H_3BO_3	30	Growth	NOEC	14	55	Dyer, 2001 [a c]
Brachydanio rerio	ELS test	H_3BO_3	34	Mortality	NOEC	5.6	22	Dyer, 2001 [a c]
Micropterus salmoides	Embryo and sac fry	H_3BO_3	32	Mortality	NOEC	1.39	5.4	Black et al (1993) [c] Dyer, 2001 [a]
Oncorhynchus mykiss	Embryo and sac fry	H_3BO_3	28	Mortality	LC10	0.7	2.7	Dyer, 2001 [a c]
Oncorhynchus mykiss	Embryo and sac fry	H_3BO_3	32-87	Mortality	NOEC	1.0	3.9	Black et al (1993) [c] Dyer, 2001 [a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the REACH registration for disodium octaborate, accessed on October 25, 2012
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

In many studies, more than one test conditions (pH, water hardness or exposure time) were used. Only the lowest value obtained in such a test series is reported.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Table 25: Freshwater acute toxicity data for invertebrates normalised to boron and calculated disodium octaborate anhydrous.

Species	Substance tested	Exposure duration	Criterion	Value (mg B/L)	Value expressed as [mg$Na_2B_8O_{13}$/L]	References
Daphnia magna	$Na_2B_4O_7$	48-h	LC50	141	555	Maier and Knight, 1991 [a]
Daphnia magna	H_3BO_3	48-h	LC50	133	524	Gersich, FM 1984 [a]
Daphnia magna	H_3BO_3	48-h	LC50	226	890	Lewis and Valentine, 1981 [a]
Hyalella azteca	H_3BO_3	48-h	LC50	64	252	Study report.014, 2010[b]
Ceriodaphnia dubia	H_3BO_3	48-h	LC50	91	358	Study report.013, 2010[b]
Litopenaeus vannamei	H_3BO_3	96-h	LC50	25.05 (3‰ salinity) 80.06 (20‰ salinity)	98.7 315.4	Li et al. (2007)[b] Reliability statement: 2 (reliable with restrictions)

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b]As summarised in the REACH registration for disodium octaborate, accessed on October 25, 2012

In many studies, more than one test conditions (e.g. pH, water hardness or salinity) were used. Only the lowest value obtained in such a test series is reported

Key Study
Litopenaeus vannamei were exposed to boric acid (special grade) for 96 hours under semi-static conditions. Information on test guideline is not provided. Test solutions were renewed every 24-hours and were continuously aerated. Twenty shrimp in triplicate were used in each vessel. Six concentrations were tested at different salinities 3‰ (20 – 640 mg/L boric acid) and 20‰ (30 – 960 mg/L boric acid). Test concentrations were analytically monitored. Actual concentrations of boron in test solutions were concordant with nominal concentrations. At 3‰ salinity, the LC50 was 25.05 mg B/L equivalent to 98.9 mg disodium octaborate anhydrate/L, based on nominal concentrations

5.4.2.2 Long-term toxicity to aquatic invertebrates

Table 26: Freshwater chronic toxicity data for invertebrates normalised to boron and calculated for disodium octaborate anhydrous.

Species	Exposure time [days]	Effect	Criterion	Value [mg B/L]	Value expressed as [mg$Na_2B_8O_{13}$/L]	Reference
Ceriodaphnia dubia	14	Reproduction	NOEC	10	39	Hickey CW, 1989 [a c]
Daphnia magna	21	Reproduction	NOEC	10	39	Hooftman et al 2000 [c]
Daphnia magna	21	Reproduction	NOEC	6	24	Lewis and Valentine, 1981 [c]
Hyalella azteca	42	Reproduction	NOEC	6.6	26	Study report.003 (2010) [b]
Daphnia magna	21	Reproduction	NOEC	6.4	25	Gerisch, FR (1984) [c]
Daphnia magna	14d	Growth Reproduction	NOEC NOEC	13.8 14.3	54-56	Gerisch and Milazzo (1990) [c]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[b] As summarised in the REACH registration for disodium octaborate, accessed on October 25, 2012
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

5.4.3 Algae and aquatic plants

Table 27: Freshwater toxicity data for green algae normalised to boron and calculated for disodium octaborate anhydrous.

Species	Substance tested	Exposure duration	Criterion	Value [mg B/L]	Value expressed as [mg$Na_2B_8O_{13}$/L]	Reference
Selenastrum capricornutum	H_3BO_3	74.5 h	EC50	44.6	176	Hanstveit and Oldersma (2000) [a]
Selenastrum capricornutum	H_3BO_3	74.5 h	NOEC	17.5	69	Hanstveit and Oldersma (2000) [a]
Spirodella polyrrhiza (duckweed)	H_3BO_3	10 d	NOEC	6.1	24	Davis et al (2002) [c]
Amphidinium carteri Chroomonas Salina Cyckitekka cryptica Isochrysis galbana Monallantus salina Monochrysis Lutheri Nannochloris oculata Phaeodactylum tricornutum Rhodomonas lens Skeletonema costatum Tetraselmis maculate	H_3BO_3	10 d	NOEC	10	39	Anita and Cheng (1975) [c]
Emiliania huxleyi	H_3BO_3	10 d	NOEC	5	20	Anita and Cheng (1975) [c]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

5.4.4 Other aquatic organisms (including sediment)

Toxicity data of disodium octaborate anhydrous to other aquatic organisms is summarised in Table 28.

Table 28: Toxicity data for other aquatic organisms (including sediment)

Species	Substance tested	Exposure duration	Effect	Criterion	Value [mg B/L]	Value expressed as [mg$Na_2B_8O_{13}$/L	Reference
Chilomonas paramaecium	$Na_2B_4O_7$	48 h	growth	NOEC	10.6	42	Bringmann and Kühn, 1980a [a]
Uronema pardaczi	$Na_2B_4O_7$	20 h	growth	NOEC	30	118	Bringmann and Kühn, 1980b [a]
Pseudomonas putida	$Na_2B_4O_7$	16 h		NOEC	7.6	30	Schoberl and Huber, 1989 [a]
Microcystis aeruginosa	$Na_2B_4O_7$	8 d	growth	NOEC	20	79	Bringmann and Kühn, 1978ab [a]
Chironomus decorus (4th instar)	$Na_2B_4O_7$	96 h	growth	NOEC	10	39	Maier and Knight, 1991 [a]
Bufo fowleri (embryo-larval)	H_3BO_3	7 d	mortality	NOEC	30	118	Raymond and Butterwick, 1992 [a]
Rana pipiens (embryo larval)	$Na_2B_4O_7$	7 d	mortality	NOEC	15	59	Raymond and Butterwick, 1992 [a]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

CLP- Acute aquatic hazards

The lowest L(E)C_{50} obtained in acute aquatic toxicity studies is 25.05 mg B/L, equivalent to 98.7 mg/L disodium octaborate anhydrate, in the invertebrate *Litopenaeus vannamei*. This value is above the classification threshold value of 1 mg/L. Disodium octaborate anhydrate does therefore not fulfil the criteria for classification as acute hazard to the aquatic environment.

CLP- Chronic aquatic hazards

Disodium octaborate anhydrate is considered not rapidly degradable in the environment. Chronic aquatic toxicity information is available for all trophic levels. The lowest NOEC available is 0.7 mg B/L, equivalent to 2.6 mg/L disodium octaborate anhydrate, obtained in fish. This value is above the classification threshold value of 1 mg/L. Disodium octaborate anhydrate does therefore not fulfil the criteria for classification as a chronic hazard to the aquatic environment.

Directive 67/548/EEC

Disodium octaborate anhydrate is considered not readily degradable in the environment. Experimental BCF-values are low (up to 1.5 L/kg based on boron). Taking into account the available data and the physical form of disodium octaborate anhydrate, the bioconcentration and bioaccumulation potential is considered low. The lowest L(E)C50 obtained in acute aquatic toxicity studies is 25.05 mg B/L, equivalent to 98.7 mg/L disodium octaborate anhydrate, in the invertebrate *Litopenaeus vannamei*. This value falls in the range of 10 mg/L < L(E)C50 ≤ 100 mg/L . Disodium octaborate anhydrate therefore fulfils the criteria for classification with R52/R53.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Substance	Directive 67/548/EEC		CLP Regulation	
	Classification	SCL	Classification	M factor
Disodium octaborate anhydrate	R52/53	-	Does not need to be classified	-

No classification for the environment under CLP for aquatic acute and chronic hazards is needed.

However under Directive 67/548/EEC, disodium octaborate anhydrate fulfills the criteria for classification with R52/R53. This is based on data from a valid and acceptable study on the invertebrate, *Litopenaeus vannamei* and data that indicate that the substance does not rapidly degrade.

Please note that we conclude different CLP and DSD classifications for the environment based on the same dataset because of the 2nd ATP changes in the CLP criteria for classification of substances and mixtures for environmental hazard. There is a full data set available for disodium octaborate anhydrate, acute and chronic, for all trophic levels. There is no acute toxicity under 1 mg/L, there is one acute toxicity value under 100 mg/L and all chronic values are above 1 mg/L. The substance is not rapidly or readily degradable. Hence, no CLP classification but a DSD classification is fulfilled.

6 OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of disodium octaborate tetrahydrate according to Directive 98/8/EEC. The summaries included in this proposal are partly copied for the CAR and CAR document IIA. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the CAR and its document IIA.

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8 ANNEXES

Annex I

ECBI/132/04 Rev. 2

Ispra, November 22, 2004

SUMMARY RECORD

Commission Working Group of Specialised Experts in the fields of Reprotoxicity

1. Ispra, October 5-6, 2004

1.a Boric acid and Borates

The following substances/Annex I entries are covered by the discussion:

I. boric acid (EC: 233-139-2)
boric acid, crude natural, containing not more than 85 per cent of H_3BO_3 calculated on the dry weight (EC: 234-343-4)

ANNEX I NO: 005-007-00-2

II. diboron trioxide, boric oxide (EC: 215-125-8)
Annex I: 005-008-00-8

III. disodium tetraborate, anhydrous boric acid, disodium salt (EC: 215-540-4); tetraboron disodium heptaoxide hydrate (EC: 235-541-3)
orthoboric acid, sodium salt (EC: 237-560-2)
Annex I: 005-009-01-0

IV. disodium tetraborate decahydrate, borax decahydrate (EC: 215-540-4)
Annex I: 005-009-02-8

V. disodium tetraborate pentahydrate, borax pentahydrate (EC: 215-540-4)
Annex I: 005-009-03-5

Elisabet Berggren (ECB) the chair of the meeting welcomed the participants and explained the procedure of the discussions. She pointed out that industry (ind) had the possibility to give a presentation before the usual closed session with the specialised experts (further referred to as se) nominated by the competent authorities

of the member states. Further she explained that the conclusions of the discussions of each substance or group of substances would be drafted together with the experts after each discussion and adopted by the experts before the end of the meeting.

Sue Hubbard (IND) gave a presentation. She said that generally people did not know a lot about all different uses of borates. She stressed that the issues discussed at the Special Experts meeting were very critical to the borate industry and added further that IND was of the opinion that borates should not be classified for reprotoxic effects.

Two of the main sources of borates for industry were a mine in California (this is the Borax facility) and in Turkey. But there were also mining facilities in South America, Russia, India and China. Different ores of borates existed and the major borate products were the sodium borates. The product Borax was disodium tetraborate decahydrate but there were also other borates. At the meeting the simple borates and boric acid were to be discussed. There are large amounts of boron in seawater (5 ppm) and variable amounts in soil and there are areas where there is boron deficiency in the soil. . There were about 150 different uses of borates. Just to give an idea about how widely they were used she reported that they were used for instance for chemical buffering, nuclear shields, medical uses, flame retardants, preservatives, antifreeze agents, paints, insect-killers, wood preservatives, detergents and many other uses. Since the 1920s it was known that boron was an essential element in plants. It was nutritionally important for humans and there were recent publications about boron dependent enzymes.

Boron was nutritionally beneficial. In Europe the major boron source in diet was wine whereas in the US it was coffee (not because of the high levels of boron, but due to the large volumes of coffee consumed). The risk assessments made within the EU differed from those in the US since different safety factors were applied.
She further continued to say that the simple inorganic borates dissociated to boric acid. There was no metabolism beyond that. Once the acute phase was passed all toxicological properties were related to boric acid. Regarding toxicokinetics she said that borates were readily absorbed orally but not through intact skin. She added that there were human data existing to support the lack of dermal absorption.

There was generally no accumulation except in the bones. Boric acid was excreted almost exclusively with the urine within 24 h. It was not a skin irritant but some borates were mild eye irritants. That property was due to the crystal shape and was physical rather than chemically driven. Boric acid was not mutagenic, not skin sensitising and not carcinogenic.

There were however reprotoxic properties that were not disputed. But these properties did not merit classification. She referred to a dog study of very poor quality that was done in the 1960s and to studies carried out in rats and mice. Indeed at high doses testicular atrophy was observed and also a decrease in ovulation rates. But that was due to maternal toxicity. She said that several different scientific boards agreed that the data from the dog studies were not adequate for a risk assessment or to set a NOAEL.

There were developmental effects seen in rats, mice and rabbits. But it was not clear whether those effects were malformations or just variations. The effects in mice and rabbits occurred at doses when there was already maternal toxicity observed.

Boron intake in rats, which eat plant food, was higher than in humans. Fruits and vegetables in human diet were also the main source of boron. In mine workers who were exposed to high boron concentrations (possibly the highest exposure in workers known), their blood boron levels reached a peak and the levels decreased very rapidly over the weekend when they were not working. The increased boron blood levels in humans were still within the range of the background levels from rats. In a human intervention study with 5 males given high doses of boron the human boron levels were still within the range of boron blood levels of rats.

In another human study conducted in California no effects on reproduction were seen in a population exposed to the equivalent of 162 mg boric acid per day. In a similar study conducted in Turkey also no effects on reproduction were observed.

Human dermal absorption data showed that absorption via the skin was less than 0.3 %. Renal clearance studies showed further that in rats, borates were voided three times faster from the body than in humans on a bodyweight basis but not when compared to body surface when humans cleared boric acid 2 times faster than rats. Humans have severe diarrhoea and vomited already at doses of 2 grams or more, while a single dose of 30 grams can be fatal.

She concluded the presentation saying that the classification of boric acid and borates was challenged because reproductive effects have a threshold value below which effects would not occur and substances should only be classified if the exposures are relevant for humans during normal handling and use and the effects are relevant for humans. The most relevant exposure routes for humans were dermal and inhalation exposure, but all animal studies had been performed by the oral route. Furthermore rats could not vomit. Continuous exposure of humans to such high levels would be unlikely because of the nausea and vomiting in humans. Therefore the effects seen in rats would not occur and under normal handling and use where humans would only be exposed by dermal route or by inhalation. Oral intake of the substance would be abuse and would not be covered by the classification criteria. Exposure to >300 mg/m^3 respirable dust would be necessary to achieve a dose close to that which caused an effect in rats. Several video clips were shown that showed the atmosphere that is seen at various dust levels. At 70 mg/m^3 the level of dust was so high that no worker could remain in such an environment for a time period long enough to obtain blood levels high enough to lead to reproductive effects.

One expert wondered why only oral tests had been performed while exposure could only happen via dermal and inhalation route. Furthermore he questioned why industry referred to the renal clearance on a body weight basis when the surface area basis was more favourable.

Sue Hubbard (IND) replied that this was historical and that typically toxicological tests are performed to maximise the dose that is applied. It is the normal convention for toxicological studies. Referring to the second question of the expert she answered that the use of body weight as a reference was based on convention and the usual way that risk assessment is carried out. To use surface area would mean that all the data (doses applied in the studies and NOAELs) would need to be redone on a body surface area basis. She saw no indications for big differences in susceptibility between rats and humans and therefore there was no need for the application of a huge safety factor.

The expert further asked whether there were dermal or inhalation studies going on at the moment.

Sue Hubbard replied that she was not aware of such studies. Maybe concerns for animal welfare were the reason for not conducting such studies.

An expert pointed out that it was difficult to apply safety factors. 200 mg/kg in rats might be equivalent to 2 mg/kg in humans. He added that there were lethal poisoning cases in children also and due to the poor quality of the negative human data conclusions could not be drawn.

Sue Hubbard said that only through poisoning enough substance could be taken up. The babies who had died did so before their renal functions were working properly and it was also accidental poisoning. If the babies had been older than six months they probably would have survived. Referring to the negative human study mentioned by the expert she said that it was a birth ratio-study on mine workers living in the desert. The birth rate was higher from this study related to the number of vasectomies. There was nothing wrong with that study. Conclusions could be drawn even though no sperm counts were made.

An expert asked further whether the study design of the investigation carried out in Turkey was the same. Only the number of children born was recorded over a time period of 15 years, which was not long enough.

Even with a fertility reduced to 8 %, one could have one child in twelve months. The really interesting information from such a study would be the time to pregnancy. He also asked whether the results from an ongoing study by NIOSH were available.

Sue Hubbard answered that concerning the NIOSH study the data collection was currently being completed and the analysis started. However she did not know anything about confounding factors. They were also looking at women in terms of beneficial effects like bone strength. She added that she was, however, in contact with them.

One expert agreed that in regard to the human studies time to pregnancy would be a much better endpoint than just the number of born children within a certain time period and he further asked whether sperm quality would be checked in that on-going study.

Sue Hubbard said that it was generally difficult in the United States to obtain consent from the Labour Unions for human studies and in particular for such investigations. First they would look at the NIOSH study and based on that decide whether to go on with further investigations.

One expert noted that not all humans vomited at the same dose levels and was of the opinion that high blood levels could be reached in humans.

Sue Hubbard answered that there were old studies from the time when borates were used in the treatment of epilepsy with a total uptake of 2 grams per day. The recommended dose was reduced due to vomiting. In the literature, such as from poison centres, sometimes vomiting was indeed not reported. That was due to the fact that sometimes vomiting was not considered as a sign of poisoning. She would think that on balance everybody would vomit, despite the unknowns in this regard.

The Chair thanked Industry and especially Sue Hubbard for the collaboration and informed that the further discussion would take place between the experts in a closed session.

Industry left the room.

The Chair invited participants to introduce themselves and stressed further that they were at this meeting consulted as individual experts and not as representatives of their Member States. No individual expert would be named in the Summary Record of the meeting so that the meeting would create a space to think where individual opinions were protected. The participant from DG Environment also emphasised that SE were asked to provide their expert views as individuals.

One expert presented the original Danish proposal for classification from 1999 based only on animal data. There were clear effects in three different animal species for fertility and development; therefore as a default proposal boron compounds should be classified for both endpoints in Rep. Cat. 2. However, he thought that first of all the relevance of the animal and the human data should be discussed. One question was whether there was sufficient proof that the reproductive effects seen in animals were irrelevant for humans to disregard the proposed classification based on animal data? Did marked differences exist between humans and animals in the toxicokinetics and toxicodynamics of boric acid and borax? Of other issues to discuss was the relevance of route of administration in the animal studies and maternal toxicity. Another question was the dose i.e. are the data sufficient to show that the chance to achieve a sufficient dose in man to cause adverse effect is negligible? Virtually no accumulation of the boron compounds in the organism had been shown, and data for acute doses did not indicate an impact on fertility and development. However, irrespective of the dose considerations the expert emphasised that the SE should consider the evidence for hazards and not possible risks.

The Chair added that a document including some detailed questions was submitted by DK very late before this meeting and had therefore not been forwarded to the other experts. The questions could have been considered as further guidance to the experts but should have been made available together with the dossier itself.

The Chair then suggested to start with discussing the animal data and then to discuss the relevance for humans. First fertility and then development should be discussed.

2. Fertility

One expert said that there were clear effects on fertility in three different species and that effects in one species would already be a sufficient basis for classification. In the criteria it was clearly written that human data should normally not be used to negate animal data. Regarding the epidemiological studies the number of children born was not an adequate endpoint, as effects on fertility could still remain undetected. PSA (Prostate Specific Antigen) was also reduced by boric acid. That was an additional effect observed, which was related to human fertility. The data warranted a clear-cut classification with Repr. Cat. 2 for fertility.

All SE agreed to recommend classification of borates with Repr. Cat. 2; R60 on the basis of evidence in animal studies and the discussion on relevance to humans would continue after looking at the animal studies available for developmental effects.

3. Development

One expert said that there were similar malformations seen in rats, mice and rabbits not paralleled by severe maternal toxicity. That was a clear case for classification for developmental effects.

Other experts agreed that when looking at animal data it was a clear case for classification as Repr. Cat. 2 for developmental effects.

All SE agreed to classify the borates with Repr. Cat. 2; R61 on the basis of evidence in animal studies and the discussion on relevance to human would then follow.

4. Human relevance

One expert said that there was a clear temptation to go into a discussion of risk assessment in this case since a pure hazard discussion was just black and white. However much better data would be needed to disregard the current evidence observed in animal studies. The data on humans were indeed not good and could not negate the positive animal studies. One would need about 5,000 exposed pregnancies to draw conclusions from birth rates alone.

Another expert added that such studies were difficult to conduct and that it would be better to carry out mechanistic studies.

A further expert showed a slide with extrapolation factors pointing out that there was no need to discuss which extrapolation factor should be used. The question was whether to use an extrapolation factor at all.

The expert further said that the extrapolation factors should be used because the representative from IND had said that human exposure could not occur because of an immediate vomiting reflex. That statement was, however, not justified, as there was no reason to assume a one to one relation between animal and human effect levels. In addition there was no information available on the internal exposure levels.

Another expert replied that such an extrapolation factor was needed since there was no data on sensitivity in humans.

One expert said that this was very much related to the question about normal handling and use. Would accidental exposure also be considered? He thought that this should be the case and then the safety margin at the workplace was not sufficient. Accidents both at the workplace and in the household must be covered by the hazard assessment.

Another expert repeated that human data was not sufficient to dismiss the animal data.

One expert wanted to ask the whole group whether they considered accidental ingestion as normal handling and use. He was of the opinion that this was not the case and he would like to hear the opinions of the other experts.

One expert replied that he had discussed that question with his ministry and that the outcome was that they said that the label was there exactly for such cases. The label should also give information in the case of accidents. In particular occupational exposures might occur under special circumstances that would be well beyond the safety limits. Accidental exposures could for example occur when there was contact with wounded skin.

The expert who had put the question to the group was not convinced whether in consumer products these substances were contained in sufficient concentrations to lead to exposure. Should people really be warned of reproductive hazards if they were accidentally empoisoned?

One expert pointed out that the legislation was based on hazard and not on risk. What if children swallowed these products? If the last statement would be taken into account a completely different legislation would be needed.

Another expert agreed to that adding that the SE had to stick to the current classification system. Risk assessment was something completely different.

A further expert noted that this forum had to judge about danger and not about risk. A further expert agreed to that and noted that the group could only give a recommendation for classification. That could not be changed because of any expected implications on the downstream legislation. He advised the group to stick to hazard considerations.

One expert disagreed adding that there was a way to take account of the risk; the criteria mentioned both hazard and risk.

One expert referred to the accidental exposure and the respective labelling. For example if there was a man accidentally heavily exposed and then sperm would be collected one would expect to see and adverse effect.

Another expert agreed to this and added further that there were not enough human data to disregard the results from the animal experiments.

Another expert preferred to discuss the question of relevance for humans. He criticised the rationale explained by IND. There were only oral studies. IND said that the dermal exposure was negligible. But why were no dermal studies available? Also systemic uptake of boron by inhalation was plausible. These were the two realistic scenarios at the workplace.

One expert did not understand this point. He had made some calculations confirming that the dose that can be applied orally could hardly be reached by inhalation.

Another expert pointed out that nobody knew about the dose effective in man and that this lead to the big uncertainty.

One expert had carried out calculations and said that that uncertainty should be covered by the uncertainty factor of about 30. That should be enough to be on the safe side.

Another expert summarised that for development and fertility similar effects in three different species were found. That was not often the case with other substances. It was also very plausible that in humans the same effects would occur, as it could not be expected that they would react differently.

One expert noted that the safety margins provided by IND were too small. Nothing was known about blood plasma concentrations.

An expert made further calculations and said that an assumed inhalation exposure of 10 mg/m^3 for 8 hours would correspond to a potential intake of about 100 mg boric acid, which would correspond to about 2 mg/kg bodyweight of boric acid or 0,35 mg/kg bodyweight of boron. This value is only a factor of about 30 below the NOAEL for developmental toxicity in animal experiments conducted by the oral route. Thus, exposure to 10 mg/m^3 would represent the highest concentration for an 8-hour exposure period that would not be of concern, when uncertainties relating to interspecies and intraspecies differences in sensitivity are taken into account. All experts agreed that the extrapolation from inhalation exposure was relevant. Therefore the SE could not accept the IND opinion that a person needed to be exposed to unfeasibly high concentrations of dust, in excess of 300 mg/m^3 for 8 h, to achieve an intake of concern

Another expert pointed out that the effect on PSA must also be considered. Boron was a physiologically active compound. Humans should have the same sensitivity as the tested species. The doses in man without leading to vomiting are only a factor of 5 lower than those used in the animals. That should be written down in the recommendations.

Other experts supported that statement. There was no threshold dose identified in humans.

One expert asked what the significance of reduced PSA levels in humans was.

Another expert explained that PSA is an enzyme originally identified as a prostate specific antigen. It was used as a marker for leakage from the prostate and as such a marker for prostate cancer. That means that boron interacts with an androgen dependent function of the human prostate, which would be of concern for human fertility. However, the dose was not known.

One expert said that the arguments from IND regarding dermal absorption should be addressed also. In case that there was abraded skin there would be increased absorption.

One expert said that that happened in the baby empoisoning case, when borates had been used in the powder put on the red and irritated skin under the nappies.

Another expert pointed out that it should be noted that many people have eczemas, which then could also lead to enhanced absorption.

The SE added that given the wide variety of applications and uses of boron-containing preparations, they recommended that any risk management decisions, concerning the final uses of those preparations should depend on risk assessments conducted on a case by case basis.

Conclusion: Boric acid and Borates

The evidence from different animal species shows that boric acid and the borates have an adverse effect on fertility (rat, mouse, dog) and development (rat, mouse, rabbit), which is not a consequence of general systemic toxicity. The effects observed across species were very similar, both in nature and effective doses (mg boron per kg bodyweight per day).

The epidemiological studies in humans are insufficient to demonstrate the absence of an adverse effect on fertility.

Regarding the relevance of the animal data to humans the Specialised Experts considered kinetic and dynamic aspects in relation to exposure levels that could potentially be experienced by humans.

The available data on kinetics do not indicate major differences between laboratory animals and humans. It is not known whether there are significant differences in the dynamics between humans and laboratory animal models and in the absence of such knowledge it must be assumed that the effects seen in animals could occur in humans. On the basis of kinetic and dynamic considerations it is assumed that the animal data are relevant to humans.

Potential human exposure levels via inhalation and oral routes could be within one order of magnitude of the NOELs for reproductive toxicity found in animal studies. The threshold level for effects in humans is not known but it cannot be excluded that it could be below the level causing vomiting in humans.

Given the clear effects on fertility and development seen in animal models that are considered as relevant to humans the Specialised Experts recommend to classify boric acid and the borates with Repr. Cat. 2; R60-61.