CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Sodium peroxometaborate

EC Number: 231-556-4

CAS Number: 7632-04-4

Index Numbers: 005-017-00-7; 005-017-01-4

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0 BACKGROUND INFORMATION

The present proposal for harmonised classification and labelling concerns two existing entries (**Index no. 005-017-00-7 and 005-017-01-4**) in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation). The per(oxo)borate covered in this proposal has a harmonised classification as toxic to reproduction for both developmental effects and fertility effects, i.e. Repr. 1B (H360Df). It also has various specific concentration limits (SCLs) for adverse effects on sexual function and fertility and for adverse effects on the development of the offspring which were set based on the toxicity of the boron moiety (B) using an approach proposed by BauA (1998).

Later, this approach has been challenged and the Committee for Risk Assessment (RAC) has removed SCLs derived by it for a number of substances (see for example RAC opinions on NMP[1] and on N,N-dimethylacetamide[2]). Moreover, in 2019, the RAC removed the SCLs calculated based on the old method and concluded on the harmonisation of GCL 0.3% w/w for boric acid and six sodium borates[3] that have a harmonised classification as Repr. 1B.

The objective of the present CLH-proposal is to

- Harmonise the per(oxo)borates included in Annex VI of the CLP Regulation, i.e. by proposing classification in Category 1B for adverse effects on fertility based on read-across of data from boric acid and borate salts that already have a harmonised classification as Repr. 1B; H360FD;
- To revise SCL:s for reproductive toxicity in accordance with the Guidance on the application of CLP criteria (2017)
- Remove of the cut-off values for particle size used for the classification of acute inhalation toxicity, discussed and adopted by the Technical Committee for Classification and Labelling (TC C&L) in 2006 (ECBI/90/06 Rev. 8)
- Split sodium perborate (EC No. 239-172-9; CAS No. 15120-21-5) from sodium peroxometaborate (EC No. 231-556-4; CAS No. 7632-04-4), in Annex VI entries 005-017-00-7 and 005-017-01-4 to create a separate entry for sodium peroxometaborate (covered by this proposal) and to include sodium perborate in a new entry with perboric acid, sodium salt; perboric acid, sodium salt, monohydrate; perboric acid (HBO(O2)), sodium salt, monohydrate; sodium peroxoborate (covered in a separate proposal submitted in parallel with this).
- Remove sodium peroxoborate from the entry for sodium peroxometaborate
- Merge existing Annex VI entries **005-017-00-7** and **005-017-01-4**

The reason for submitting a separate CLH-dossier for sodium peroxometaborate is based on different substance identity (see Section 7) and different ATE values for acute oral and inhalation toxicity from the respective ATE values of sodium perborate (EC No. 239-172-9; CAS No. 15120-21-5), which is part of the same Annex VI entry. Moreover, in 2014, Denmark submitted separate SVHC identification proposals for sodium peroxometaborate[4] and for the hydrated forms of sodium per(oxo)borates[5], where it was explained that sodium peroxometaborate is not a well-defined substance, and that it differs from the dimeric cyclic structures of the other sodium per(oxo)borates.

[1] https://www.echa.europa.eu/documents/10162/355b86c1-5a0f-f104-0931-8ffdce4e1cbd

[2] https://www.echa.europa.eu/documents/10162/a435d3fc-a05f-b558-3f51-9aff166f2de0

[3] https://www.echa.europa.eu/documents/10162/584263da-199c-f86f-9b73-422a4f22f1c3

[4] https://www.echa.europa.eu/documents/10162/74778154-75a8-428e-adad-0516a1189da7

[5] https://www.echa.europa.eu/documents/10162/ffdb7fc4-0e71-4292-988a-3f6f46200c38

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of sodium peroxometaborate (EU RAR, 2007; Annex XV report on sodium peroxometaborate, 2014)

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Sodium peroxometaborate Perboric acid (HBO(O2)), sodium salt (1:1)
Other names (usual name, trade name, abbreviation)	Dehydrated sodium perborate Dexol Oxoborate
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	231-556-4
EC name (if available and appropriate)	Sodium peroxometaborate
CAS number (if available)	7632-04-4
Other identity code (if available)	-
Molecular formula	$NaBO_3$*
Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	81.81 g/mol*
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

* The molecular and structural information provided in this table are theoretical and the information in the literature indicates that the substance is not well-defined (Annex XV report on sodium peroxometaborate, 2014).

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Sodium peroxometaborate EC No. 231-556-4 CAS No. 7632-04-4	Unknown (substance not registered)	Annex VI Index No. 005-017-00-7 Ox. Sol. 2; H272 Repr. 1B; H360Df Acute Tox. 4*; H302 STOT SE 3; H335 Eye Dam. 1; H318 Repr. 1B; H360D: 6,5 % ≤ C < 9 % Repr. 1B; H360Df: C ≥ 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 % Annex VI Index No. 005-017-01-4 Ox. Sol. 2; H272 Repr. 1B; H360Df Acute Tox. 3*; H331 Acute Tox. 4*; H302 STOT SE 3; H335 Eye Dam. 1; H318 Repr. 1B; H360D: 6,5 % ≤ C < 9 % Repr. 1B; H360Df: C ≥ 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	Ox. Sol 3 Repr. 1B, H360 Acute Tox. 4; H302

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No data available				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No data available					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed harmonised classification according to the CLP criteria

	Index No	International Chemical Identification	EC No.	CAS No.	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entries	005-017-00-7	sodium perborate; [1] sodium peroxometaborate; [2] sodium peroxoborate; [containing = 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 231-556-4 [2]	15120-21-5 [1] 7632-04-4 [2]	Ox. Sol. 2 Repr. 1B Acute Tox. 4* STOT SE 3 Eye Dam. 1	H272 H360Df H302 H335 H318	GHS03 GHS05 GHS08 GHS07 Dgr	H272 H360Df H302 H335 H318		Repr. 1B; H360D: 6,5 % ≤ C < 9 % Repr. 1B; H360Df: C ≥ 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	
	005-017-01-4	sodium perborate; [1] sodium peroxometaborate; [2] sodium peroxoborate; [containing < 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 231-556-4 [2]	15120-21-5 [1] 7632-04-4 [2]	Ox. Sol. 2 Repr. 1B Acute Tox. 3* Acute Tox. 4* STOT SE 3 Eye Dam. 1	H272 H360Df H331 H302 H335 H318	GHS03 GHS06 GHS05 GHS08 Dgr	H272 H360Df H331 H302 H335 H318		Repr. 1B; H360D: 6,5 % ≤ C < 9 % Repr. 1B; H360Df: C ≥ 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	
Dossier submitters proposal	**Merge:** 005-017-00-7 & 005-017-01-4	**Modify:** sodium peroxometaborate;; **Remove:** sodium perborate; sodium peroxoborate	**Retain:** 231-556-4 [2] **Remove:** 239-172-9 [1]	**Retain:** 7632-04-4 [2] **Remove:** 15120-21-5 [1]	**Modify:** Repr. 1B Acute Tox. 3 Acute Tox. 4	**Modify:** H360FD H331 H302	**Retain:** GHS06 GHS08 Dgr	**Modify:** H360FD H331 H302		**Remove:** Repr. 1B; H360D: 6,5 % ≤ C < 9 % Repr. 1B; H360Df: C ≥ 9 % **Add:**	

		[containing = 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm] [2] [containing < 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm] [2]								Inhalation: ATE = 0.62 mg/L Oral: ATE = 918 mg/kg bw/day	
Resulting Annex VI entry if agreed by RAC and COM	TBD	sodium peroxometaborate;	231-556-4	7632-04-4	Ox. Sol. 2 Repr. 1B Acute Tox. 3 Acute Tox. 4 STOT SE 3 Eye Dam. 1	H272 H360FD H331 H302 H335 H318	GHS03 GHS06 GHS05 GHS08 Dgr	H272 H360FD H331 H302 H335 H318		Inhalation: ATE = 0.62 mg/L Oral: ATE = 918 mg/kg bw/day Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 % §	#

§The generic concentration limit of 0.3% will apply for toxicity to reproduction.
#The inclusion of a specific note to apply additivity for boron compounds that exert their reproductive toxicity through the same toxic entity (boric acid/borate ion) should be considered: "Classification of mixtures is necessary if the sum of boron compounds that are classified as Repr. 1A/1B in the mixture as placed on the market is ≥ 0.3 %".

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	**Harmonised classification proposed**	**Yes**
Acute toxicity via dermal route	**Data conclusive but not sufficient for classification**	**Yes**
Acute toxicity via inhalation route	**Harmonised classification proposed**	**Yes**
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	**Harmonised classification proposed**	**Yes**
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard class not assessed in this dossier	No
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Harmonised classification for toxicity to reproduction

As detailed in the minutes of the TC C&L meeting, the classification according to the Dangerous Substances Directive (Dir. 67/548/EEC) for toxicity to reproduction for the sodium per(oxo)borate covered by the current CLH-proposal as Repr. Cat. 2; R61 and Repr. Cat. 3; R62 (equivalent to Repr. 1B; H360D and Repr. 2; H361f; CLP Regulation, EC No 1272/2008) was based on the recommendation of the Specialised Experts from 2004 (ECBI/60/05 Rev. 3).

A summary of the discussion from the Specialised Experts (SE) meeting is enclosed in the EU RAR (2007). The only study available for the assessment of effects on fertility was a 28-day repeated dose toxicity study with sodium per(oxo)borate tetrahydrate (PBS-4) (OECD TG 407; limit test). The Specialised Experts concluded that the results of this study are very limited and insufficient for the purpose of classification and evidence that boric acid is a degradation product of per(oxo)borates was considered. It was also pointed out that "*boric acid as a metabolite of sodium perborate will be systemically available and thus, the same effects are expected and the data on boric acid and borates have to be taken into consideration for read-across. Based only on read-across, the classification for boric acid/borates should also apply for sodium perborate*". In 2005, the recommended classification for boric acid was as Repr. Cat. 2; R60 (equivalent to Repr. 1B; H360F). It is not clear to the dossier submitter why the resulting classification of per(oxo)borates was Repr, 2; H361f and not category 1B similar to boric acid based on read-across.

A prenatal developmental toxicity study (PNDT) performed according to OECD TG 414 with PBS-4 was available for evaluation. Based on the results of this study, the Specialised Experts concluded that PBS-4 is a developmental toxicant due to the release of boron, as the malformations seen at the highest dose level are similar to those induced by boric acid and borates. Regarding the observed differences in malformations, it was further discussed that these could be explained by different kinetics due to different routes of administration (feed, oral gavage). Thus, it was concluded that "*the developmental effects of PBS-4 seen in one rat study, which are not a consequence of general systemic toxicity, warrant classification as Repr. Cat. 2; R62*".

The issue of concentration limits for reproductive toxicity was discussed at a later TC C&L meeting (ECBI/90/06 Rev. 8). Different specific concentration limits (SCLs) for fertility and developmental toxicity were set using the approach proposed by BAuA (1998) where the molecular weights of the different per(oxo)borates were used to calculate the contribution of their boron contents to the overall hazard.

The existing SCLs for effects on development for the per(oxo)borates included in Annex VI of CLP were derived based on the limit dose of 1000 mg/kg bw/day as described in the OECD TG 414 performed with PBS-4 and using the NOAEL for embryotoxic/teratogenic effects of 100 mg PBS-4/kg bw/day, (based on increased post-implantation loss, increased number of resorptions, decreased number of live foetuses, decreased foetal weight). The corresponding SCL for sodium per(oxo)borate monohydrate (PBS-1) was calculated from the SCL of PBS-4, using the molecular weight of PBS-1 and PBS-4. The SCLs for fertility effects were derived based on the SCLs for boric acid that were also set using the old approach proposed by BAuA, and corrected for the differences in boron content (ECBI/38/03 Add.17).

Already in 2006, some MS signalled their concern about using the approach proposed by BauA (1998) to derive SCLs as it would imply an unreasonably high degree of scientific certainty and that it did not adequately distinguish between different categories of reproductive effects (ECBI/90/06 Rev. 8).

Harmonised classification for acute inhalation toxicity

In 2006, the TC C&L agreed upon the introduction of a "thoracic fraction" concept in the case of sodium per(oxo)borates, based on earlier discussions at the level of the Aerosols Working Group. Thus, split entries with a 50 µm particle diameter size cut-off point were proposed. This led to classifying only the thoracic fraction with T; R23 (Acute Tox. 3; H331) for PBS-1 and with Xn; R20 (Acute Tox. 4; H332) for PBS-4, while the non-thoracic fractions were not classified for inhalation toxicity (ECBI/90/06 Rev. 8).

In earlier discussions on this topic (TC C&L and Aerosol Working Group), it was highlighted that the thoracic fraction is a conservative approach that leads to differences in classification for inhalation of individual substances, and that deposition also occurs in the upper airways and can contribute to the lethality

of a substance. Another issue that was brought forward was the difficulty in requesting various tests with different particle sizes to investigate if a substance could cause irritancy (bigger particles) or systemic effects (smaller particles) in different parts of the respiratory system (ECBI/55/05).

The "thoracic fraction" concept is an old approach no longer in practice. As it is difficult to predict the most responsive region of the respiratory tract or the most harmful particle size, the revised OECD TGs for acute inhalation toxicity recommend that the particle size distribution of dusts and aerosols should be such that exposure of all regions of the tract can be achieved. An aerosol with a mass median aerodynamic diameter (MMAD) ≤4 μ m and a geometric standard deviation (GSD) in the range of 1.0 to 3.0 is recommended to ensure that comprehensive respiratory tract exposure occurs (OECD TG 403; OECD TG 433).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

- Change in existing entry due to changes in the criteria for acute toxicity

The justification for modification of the harmonised classification Acute Tox. 3* H331 and Acute Tox. 4* H302 is that these are minimum classifications, and it is concluded that removal of the asterisks is warranted. Moreover, ATE:s have been set.

- Change in existing entry due to new data and new evaluation of existing data for reproductive toxicity.

Since the per(oxo)borate covered by the present proposal was subject to harmonised classification, new recommendations on how to derive concentration limits for reproductive toxicity have been agreed upon (CLP Guidance, 2017). Revising the SCLs for the per(oxo)borates included in Annex VI of the CLP Regulation will ensure that all per(oxo)borates are assessed similarly and according to the new guidance. It will result in a level playing field in between the per(oxo)borates as well as in relation to other classified substances. Moreover, it is also considered appropriate to read-across data from boric acid to revise the current classification for adverse effects on sexual function and fertility.

5 IDENTIFIED USES

Sodium per(oxo)borates mono- and tetrahydrates are used as oxidising and bleaching agents mainly in detergents (household detergents as well as detergents for institutional uses) and in cleaning products (stain removers in form of bleach booster tablets and dishwashing tablets). Per(oxo)borates are used in both regular and compact heavy-duty laundry powders.

Per(oxo)borates were also used in cosmetic products such as hair dyes, teeth whitening or bleaching products and nail hardening products. Due to their harmonised classification as Repr. 1B, per(oxo)borates are restricted in cosmetic products according to the EU Cosmetics Regulation (1223/2009/EC) since December 2010.

6 DATA SOURCES

Experimental data and information included in this CLH-report mainly come from the publicly disseminated REACH Registration dossier of "perboric acid, sodium salt" EC No. 234-390-0 (CAS No. 11138-47-9). These numerical identifiers have been used as "collective" identifiers in order to describe sodium per(oxo)borates having a dimeric cyclic structure in various hydrated forms. Assessment reports such as EU RAR (2007; 2003), Annex XV identification proposals (2014), SCCS Opinion (2010), ATSDR (2010) and RAC Opinions (2014; 2019;2020) on sodium per(oxo)borates, boron compounds and hydrogen peroxide as well as relevant studies available in the scientific literature have also been included.

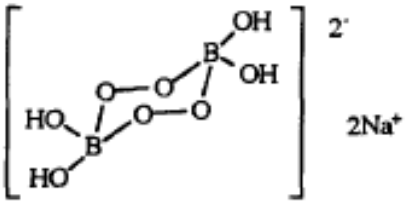
7 PHYSICOCHEMICAL PROPERTIES

Sodium peroxometaborate is not registered under REACH. The information on physicochemical properties on sodium per(oxo)borates presented below comes from the EU RAR (2007), Annex XV report on sodium peroxometaborate (2014) and scientific literature.

Sodium per(oxo)borates are white, odourless, crystalline, water-soluble powders. Their molecular crystalline structure consists of dimeric $[(HO)_2(BOO)]^-$ units which form symmetric cyclic hexagonal anions with two peroxy bridges each. This dimeric structure was confirmed by X-ray crystallography, infra-red and Raman spectroscopies (Carrondo et al. 1978 and Flanagan et al. 1979, as cited by Grootveld et al. 2020).

Therefore, owing to the dimeric structure of the peroxoboron anions, it means that in reality there are only two types of sodium per(oxo)borates:

- The dimeric cyclic structure with two peroxy bridges, which has been historically referred to as "*sodium perborate monohydrate*" (empirical formula $NaBO_3.H_2O$). These old name and formula do not take into account the dimeric cyclic nature of the substance. The same structure may also have been wrongly represented by the empirical formula $NaBO_2.H_2O_2$. In reality, there would not be any crystalline water in "sodium perborate monohydrate".



  - Hydrates of the dimeric structure also exist. What was historically known as "*sodium perborate tetrahydrate*" (empirical formula $NaBO_3.4H_2O$) is in fact the hexahydrate of the sodium salt with the dimeric structure shown above.

- The "dehydrated" form which is obtained from the "*sodium perborate monohydrate*" (which is not a true hydrated form as explained above) with the empirical formula $NaBO_3$; it is supposed to consist of sodium borate and boron oxygen radical and is also known as "oxoborate" or "dexol". This structure is presented in the literature as an anhydrous perboric acid species, which can be produced by the "dehydration" of the dimeric salts commonly referred to as the sodium perborate monohydrate or tetrahydrate, but this reference to "dehydration" may be confusing as chemical transformations other than crystalline water removal are involved (Ullmann's, Peroxo Compounds, inorganic as cited in Annex XV report on sodium peroxometaborate, 2014).
  - As detailed in a clarification document regarding the entries of sodium perborates into Annex I of Directive 67/548/EEC, brought forward at the TC C&L meeting in 2006, the substance with EINECS No. 231-556-4, CAS No. 7632-04-4 also known as oxoborate, does not have a dimeric cyclic structure as the hexahydrate (ECBI/38/03 Add. 15).

Furthermore, it is detailed in the EU RAR (2007) that "sodium peroxoborate trihydrate" (correct term should be "sodium perborate tetrahydrate") has also been described in the literature but is not of commercial importance.

Since it is still customary to use the "old" formulas and nomenclature, even if they disregard the dimeric structure of the molecules, the terms "sodium perborate monohydrate" or PBS-1 and "sodium perborate tetrahydrate" or PBS-4 are used throughout this CLH-proposal. The current CLH-proposal focuses on sodium peroxometaborate. In addition, the term "sodium per(oxo)borates" instead of sodium perborates will be used throughout the current report in order to better reflect the nature of these compounds.

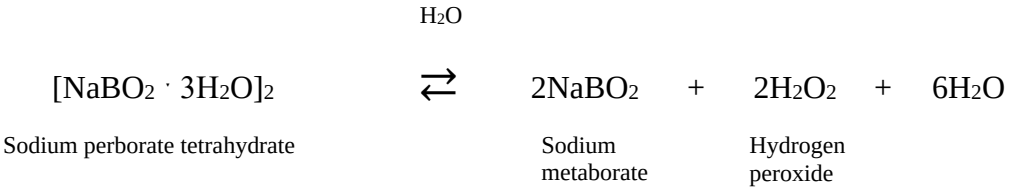
8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this CLH-proposal.

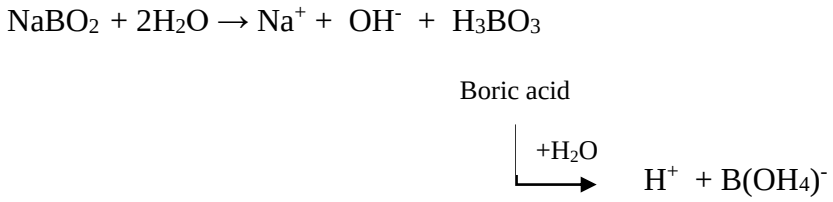
9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Properties of aqueous solutions of per(oxo)borates

Sodium per(oxo)borates are water-soluble compounds that in aqueous conditions release hydrogen peroxide with the formation of boric acid. The main species present in aqueous solutions of per(oxo)borates at physiological and acidic pH is boric acid, while hydrogen peroxide will rapidly decompose to water and oxygen in vivo. At room temperature, an equilibrium between sodium per(oxo)borates and their degradation products instantly establishes (EU RAR 2007). The equilibrium will largely shift towards the side of the degradation products at environmentally relevant concentration ranges and at low concentrations (i.e. ≤ 2 g/L), whereas at higher concentrations (i.e. ≥ 12 g/L), the undissociated molecule of sodium per(oxo)borate will mostly be present in the aqueous solution. The equilibrium is shifted irreversibly towards the degradation products by hydrogen peroxide removal, either catalyzed by metal ions or by catalase and peroxidase enzymes in blood (Urschel 1967).



One of the degradation products, sodium metaborate, is the salt of a strong base (sodium hydroxide) and of a weak acid (boric acid), and it is expected to be present in aqueous solutions at environmental temperature and pH, as the weakly dissociated boric acid (EU RAR, 2007):



9.2 Toxicokinetic data on per(oxo)borates

No studies according to validated and/or internationally accepted test guidelines on the toxicokinetics of per(oxo)borates in experimental animals were available. The following data are gathered from what is available in the open scientific literature and published assessment reports (ATSDR Report, 2010; EU RAR, 2003; 2007; HERA Report, 2002;2005).

Absorption

Oral

Based upon the below-described studies, per(oxo)borates are 100% absorbed from the gastrointestinal (GI) tract after oral exposure, while oral mucosa absorption is considered negligible.

The oral absorption of sodium perborate monohydrate by the oral mucosa or the GI tract was investigated in studies with volunteers using Bocosept as mouthwash solution (Edwall et al. 1979). In order to obtain a

mouthwash solution, one Bocosept package (containing 1.2 g sodium perborate monohydrate and 0.5 g sodium bitartrate) was dissolved in a small volume of water, which was circulated in the mouth for approximately 3 minutes and then spat out. Blood boron levels were measured after a single administration of Bocosept to two healthy volunteers and two gingivitis patients, with a mean blood boron concentration of 0.04 µg/mL measured prior to the experiment. The blood boron concentration increased gradually, measuring 0.06 µg/mL after 2 minutes and 0.14 µg/mL after 2 hours since the mouthwash administration. The mean blood boron concentration after 24 hours was 0.07 µg/mL, and no differences between healthy volunteers and gingivitis patients were found. The authors calculated that 97% of the administered mouthwash dose was spat out. The remaining 3% that was available for absorption corresponds to 36 mg sodium perborate monohydrate. Based on the results of the study the authors concluded that the oral mucosal absorption was negligible and thus, the GI tract was the main route of absorption, following ingestion of residual amounts left in the mouth after the treatment.

In another study, volunteers used Bocosept as mouthwash solution twice a day, for seven consecutive days (Dill et al. 1977). During the experiment, the mean blood boron concentration was between 0.15 – 0.20 µg/mL, whereas the mean blood boron concentration measured before administering Bocosept was 0.07 µg/mL. Two and four days after the cessation of the treatment, the blood and urine boron concentrations, respectively, returned to the background levels. The mean total amount of boron excreted in the urine for four days after the end of the treatment was approx. 2.8% of the total administered sodium perborate monohydrate amount. Since 3% is the amount equivalent to that which is not spat out (as shown by Edwall et al. 1979), and approximately the same amount was found in the urine, a 100% absorption rate from the GI tract is thus assumed.

Peak human plasma levels of boron after oral ingestion of sodium per(oxo)borates are presumed to be reached after 2h, with the half-life in plasma of 6 – 10 h.

Inhalation
No information was found on the absorption rate via inhalation for sodium per(oxo)borates.

Dermal
No information on the dermal absorption of sodium per(oxo)borates was available.

Distribution
No information on the distribution of sodium per(oxo)borates was available. Based upon the data on degradation of per(oxo)borates, boron will primarily exist in the body as boric acid.

Metabolism
No information on the metabolism of sodium per(oxo)borates was found. Based upon the data on degradation of per(oxo)borates, boron will primarily exist in the body as boric acid. Boric acid is not metabolised further in the body.

Excretion and elimination
According to the above-described studies performed with human volunteers, boron will be primarily eliminated as boric acid.

9.3 Toxicokinetic data on boric acid and borate salts

No studies according to validated and/or internationally accepted test guidelines on the toxicokinetics of boric acid or borate salts are available. The data described below are mainly represented by what is available in the open scientific literature as experimental (animal data) and occupational studies, and literature reviews (ATSDR Report, 2010).

Absorption
Oral

Humans and animals (rats, rabbits, sheep and cattle) absorb orally administered boric acid in a similar way, readily and completely from the gastrointestinal tract, with 92 – 95% of the dose being recovered in the urine.

Inhalation
After boric acid exposure via inhalation, boron is systemically distributed through absorption across pulmonary tissues and into the bloodstream.

Dermal
The available studies show that there is minimal dermal absorption (i.e. 0.5%) of boric acid through intact skin for both animals and humans. Absorption through non-intact skin varies with the used vehicle: as opposed to oil-based vehicle, aqueous-based ones lead to a greater dermal absorption of boric acid.

Distribution
After administration of boric acid, boron has a similar distribution for both humans and animals with the following common aspects:

- Boron is rapidly distributed throughout body fluids;
- Boron does not accumulate in soft tissue;
- Boron accumulates in the bone, reaching 2 – 3 times higher levels than in plasma.

Furthermore, the plasma and soft tissue concentrations of boron are equivalent for humans, while in rats, the adipose tissue levels of boron represent only 20% of the plasma ones. The testis levels of boron in male rats were almost equal to the ones measured in plasma. Moreover, in male rats, a close correlation between testicular and blood levels of boron was found, with testicular concentrations of 5.6 µg B/g (equivalent to 26 mg B/kg bw) and 11.9 µg B/g (equivalent to 52 mg B/kg bw) being associated with inhibited spermiation and testicular atrophy, respectively (Murray et al. 1998).

Metabolism
Boric acid is not metabolised in either humans or animals, boron being a trace element which exists in the body as boric acid (the only form of boron recovered in the urine).

Excretion and elimination
Independently of the route of exposure, boric acid is primarily excreted through renal elimination and has a half-life less than 24h for both humans and animals. Based on literature data, eliminated fractions of absorbed boron were estimated to be 67 – 98% for humans and 99% for rats (ATSDR 2010), and the calculated clearance values were 40 mg/kg/hour in humans and 163 mg/kg/hour in rats, respectively. In addition, the glomerular filtration rate appears to be the determining factor in the renal elimination of boron.

9.4 Toxicokinetic data on hydrogen peroxide

No studies according to validated and/or internationally accepted test guidelines on the toxicokinetics of hydrogen peroxide are available. The following data are gathered from what is available in the open scientific literature as experimental studies, case reports and published assessment reports (EU RAR, 2003; HERA Report, 2005).

Absorption
It is expected that hydrogen peroxide is readily taken up by the cells at the absorption surfaces due to the high permeability of the biological membranes to H_2O_2. The permeability constants for peroxisomal membranes (0.2 cm/min) and for erythrocyte plasma membranes (0.04 cm/min) are comparable to those for water for several types of cell membranes, ranging between 0.02 – 0.42 cm/min (Chance et al. 1979).

Oral
Hydrogen peroxide is readily absorbed after oral exposure. It may be demonstrated by effects such as tachycardia, lethargy, coma, convulsions, apnoea, cyanosis and cardiorespiratory arrest were reported in humans within minutes of ingestion, as a result of oxygen embolism (Watt et al. 2004).

Inhalation
Hydrogen peroxide is readily absorbed after exposure via inhalation in rabbits. Hydrogen peroxide as 1 – 6% aerosol was administered via a ventilation apparatus to anesthetised rabbits (Urschel 1967). The blood collected from the left atrium was found to be suprasaturated with oxygen at a level equivalent to oxygen administration at 3 atm. The 1% aerosol provided the same level of oxygen as the other higher H_2O_2 > 1% concentrations.

Dermal
In rats, trace amounts of 5 – 30% hydrogen peroxide solutions were found to penetrate the skin, by being localised in the excised epidermis a few minutes after application. In *in vitro* tests with human cadaver skin show that H_2O_2 was found in the dermis only after the application of high concentrations or after the treatment with hydroxylamine that acts as a catalase inhibitor. The performed histochemical analysis showed that the passage was trans-epidermal and that H_2O_2 was not metabolised in the epidermis (EU RAR 2003). This is in line with the findings of Riihimaki et al. 2002 who observed that unintentional dermal contact to concentrated H_2O_2 solutions led to the appearance of white spots, due to oxygen microbubble formation, which disappeared with time.

Distribution
According to available animal and human data, H_2O_2 is distributed to a variety of tissues (i.e. brain, myocardium, intestines, lungs, spleen and kidneys) as oxygen microbubbles, which lead to gas embolism (EU RAR 2003).

Metabolism
Hydrogen peroxide is rapidly metabolised by two main enzymes, catalase and glutathione (GSH) peroxidase, which maintain H_2O_2 concentration at certain levels in different parts of the cells. At levels lower than 10 µM, 80 – 90% H_2O_2 is decomposed by GSH peroxidase while catalase deals with larger amounts of H_2O_2 that may be generated in peroxisomes, the contribution of catalase increasing with the increase in H_2O_2 concentration (Makino et al. 1994). H_2O_2 does not bio-accumulate.

It should be noted that both catalase and GSH peroxidase activity is unevenly distributed in different tissues for different species. In general, the brain and the heart have low catalase activity, while GSH peroxidase is lacking in the muscle tissue (Chance et al. 1979).

Excretion and elimination
The excretion of hydrogen peroxide in urine was assessed through a radioactive method (based on the decarboxylation of alfa-ketoglutaric acid by H_2O_2) from samples of healthy volunteers aged 20 – 35 years. The average concentration of H_2O_2 in the urine of male subjects was 106 µM, while for the female volunteers was 89 µM (Varma and Demanoharan 1989).

9.5 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

As described in Section 9.1, the main species present in physiological solutions of per(oxo)borates at neutral and acidic pH is boric acid, while hydrogen peroxide will rapidly decompose to water and oxygen *in vivo*. Hydrogen peroxide is therefore not considered to contribute significantly to repeated dose toxicity. The view that boric acid is a degradation product of per(oxo)borates at physiological conditions and expected to have the same toxicological effects, was already expressed in 2005 at the TC C&L meeting (ECBI/60/05 Rev. 3).

Available toxicokinetic data show that per(oxo)borates/boric acid are readily absorbed after oral exposure (100 and 92-95 % respectively). Boric acid is also rapidly absorbed after inhalation exposure whereas it is minimal via skin (0.5%). Boric acid is distributed throughout the body and is eliminated as such from the body via urine. A close correlation between blood boron levels, testicular levels of boron and effects such as inhibited spermiation and testicular atrophy has been found.

9.5.1 Justification for read-across

From data on boric acid and borates

In aqueous solutions at room temperature, an equilibrium between per(oxo)borates and their degradation products will be established (see Section 9.1). Sodium metaborate, i.e. one such degradation product, is expected to be present in aqueous solutions (at environmental temperature, physiological and acidic pH) mainly as weakly dissociated boric acid (pK_a = 9.25) (SCCS Opinion, 2010). As also discussed at the Specialised Experts Meeting (in Ispra, 2004), boric acid as a degradation product of sodium per(oxo)borate will be systemically available and the same effects are expected, and thus, the data on boric acid and borates have to be taken into account for read-across (EU RAR, 2007). Furthermore, the report on boron performed in 1998 by the International Programme on Chemical Safety (IPCS)[6] stated that the chemical and toxicological effects of boric acid and other borates are similar on a mol boron/litre equivalent basis, when dissolved in water or in biological fluids at low concentration and at the same pH.

Reproductive toxicity

Moreover, as stated in the CLH-reports of disodium octaborate, anhydrate and disodium octaborate tetrahydrate (2013) and in the CLH-proposal on revising the SCLs for boric acid and borate salts (2019), read-across from boric acid to other borates and between borates has long been accepted in a regulatory context. Experts from the CL Working Group, the TC C&L and the ATP Committee agreed that borates have similar properties and therefore that read-across between substances can be applied.

Limited toxicity data are available for the hazard assessment of fertility of per(oxo)borates. Therefore, classification for sexual function and fertility following oral exposure in Category 1B (H360F) is supported using a read-across approach based on boron equivalents, from tested borates (borax or disodium tetraborate decahydrate, disodium octaborate anhydrate, disodium octaborate tetrahydrate) and boric acid, justified on the basis of hydrolytic and toxicokinetic behaviour, and toxicological data. A comparable toxicity profile is demonstrated in teratogenicity studies with boric acid and sodium borates, and sodium per(oxo)borates. Moreover, according to the minutes of the TC C&L (2005 – 2006) where the classification of the sodium per(oxo)borates was discussed and adopted, the SCLs currently included in the Annex VI of CLP for effects on fertility were indeed derived on a boron-equivalent basis, using the SCL of boric acid of that time[7] as a starting point. It can, therefore, be assumed that a similar read-across may be used in the derivation of new concentration limits for effects on fertility, based upon the method described in the ECHA Guidance on the application of the CLP criteria (2017).

Read-across of experimental data from boric acid and borates is not applied for the assessment of adverse effects of sodium per(oxo)borates on the development of the offspring. The sodium per(oxo)borates included in Annex VI of CLP have a harmonised classification as Repr. 1B; H360D based on a PNDT (OECD TG 414) study conducted with PBS-4. However, since no data on the effect of sodium per(oxo)borates on human fertility, development and lactation are available, read-across of data from epidemiological studies of boric acid and borates is used.

Acute toxicity

Read-across from boric acid and borates is not considered appropriate for the assessment of acute toxicity since per(oxo)borates and boric acid/borates have an uncommon degradation product: hydrogen peroxide. The available studies show that the higher acute oral toxicity of sodium per(oxo)borates as compared to

[6] http://www.inchem.org/documents/ehc/ehc/ehc204.htm#PartNumber:6

[7] The SCL of 5.5% for boric acid was calculated based on the approach proposed by BauA (2005-2006). In 2019, the RAC has removed the SCLs calculated through this old approach and concluded on the harmonisation of GCL values to 0.3% w/w for boric acid and six sodium borates that have a harmonised classification as Repr. 1B.

borates is due to the in vivo formation of hydrogen peroxide (which leads to local irritation and oxygen accumulation) and not to boron-exposure.

From data on sodium perborate tetrahydrate (PBS-4) and sodium perborate monohydrate (PBS-1)

In addition to sodium metaborate and hydrogen peroxide, other per(oxo)borate species such as anhydrous perboric acid (HBO_3) will also be present in aqueous solutions of sodium per(oxo)borates, at environmental temperatures and pH (Grootveld et al. 2020). Sodium peroxometaborate ($NaBO_3$) is described as the sodium salt of anhydrous perboric acid. Similarly to PBS-1 and PBS-4, it degrades to hydrogen peroxide and sodium metaborate ($NaBO_2$), the latter being systemically available as boric acid, and thus the same systemic effects are expected for sodium peroxometaborate, PBS-1 and PBS-4. As detailed above, PBS-1 and PBS-4 are sodium salts of the peroxoboron anions, differing in water content.

No studies conducted with sodium peroxometaborate are available. The same read-across approach which led to the harmonised classification of sodium per(oxo)borates as Acute Tox. 4; H302, Acute Tox. 3; H331 and Repr. 1B; H360D as adopted by the TC C&L in 2005-2006, is also employed in this CLH-proposal.

Acute toxicity
Read-across approach of data from studies conducted with PBS-1 and PBS-4 is considered appropriate to use for the proposed harmonised classification of sodium peroxometaborate for acute oral, dermal and inhalation toxicity justified on the basis of water dissolution behaviour and toxicological data.

Reproductive toxicity
Read-across of data from studies conducted with PBS-4 is considered appropriate to use in order to support the proposed ED10 derivation for developmental toxicity (on a boron-equivalent basis), justified on the basis of water dissolution behaviour and toxicological data.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 7: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any[8]	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Sodium perborate monohydrate (PBS-1)					
EPA OPP 81-1, GLP (Acute Oral Toxicity)	Rat, Sprague-Dawley Male/female n = 5/sex/dose group	Sodium perborate monohydrate (grade A) Purity: unknown	500, 1000 and 2000 mg/kg bw 14 days post-	Male: 1300 mg/kg bw Female: 890 mg/kg bw Male/female: 1120 mg/kg bw **Dose (mg/kg) / Lethality M / Lethality F**	REACH registration (ECHA dissemination, [2020])

[8] Where applicable and unless stated otherwise, the reliability scores of the studies presented in Table 7 are according to the publicly disseminated REACH Registration dossier for EC no. 234-390-0, available at https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/3/2

<table>
<tr><th>Method, guideline, deviations if any[8]</th><th>Species, strain, sex, no/group</th><th>Test substance</th><th>Dose levels, duration of exposure</th><th>Value LD_{50}</th><th>Reference</th></tr>
<tr><td>Reliability: 1</td><td></td><td>Vehicle: water

Oral gavage</td><td>exposure observation period</td><td><table><tr><td>500</td><td>0/5</td><td>0/5</td></tr><tr><td>1000</td><td>1/5 (on day 1)</td><td>3/5 (1/5 on day 1 and 2/5 on day 2)</td></tr><tr><td>2000</td><td>5/5 (3/5 on day 0 and 2/5 on day 1)</td><td>5/5 (on day 0)</td></tr></table></td><td>Study Report, 1988</td></tr>
<tr><td>EPA OPP 81-1, GLP

(Acute Oral Toxicity)

Reliability: 1</td><td>Rat, Wistar

Male/female

n = 5/sex/dose group</td><td>Sodium perborate monohydrate

Purity: unknown

Vehicle: water

Oral gavage</td><td>1200, 1500, 1900, 2500 and 5000 mg/kg bw

14 days post-exposure observation period</td><td>Male: 2100 mg/kg bw

Female: 1700 mg/kg bw

Male/female: 1800 mg/kg bw

<table><tr><th>Dose (mg/kg)</th><th>Lethality M</th><th>Lethality F</th></tr><tr><td>1200</td><td>0/5</td><td>0/5</td></tr><tr><td>1500</td><td>0/5</td><td>1/5 (on day 1)</td></tr><tr><td>1900</td><td>3/5 (2/5 on day 1 and 1/5 on day 2)</td><td>4/5 (1/5 on day 0 and 3/5 on day 1)</td></tr><tr><td>2500</td><td>4/5 (2/5 on day 0 and 2/5 on day 1)</td><td>5/5 (2/5 on day 0 and 3/5 on day 1)</td></tr><tr><td>5000</td><td>5/5 (on day 0)</td><td>5/5 (on day 0)</td></tr></table></td><td>REACH registration (ECHA dissemination, [2020])

Study Report, 1987a</td></tr>
<tr><td>Non-guideline, non-GLP, acute oral toxicity test(publication)

Reliability: 2</td><td>Rat, strain not specified

Sex not specified

n = 10 – 33 /dose group</td><td>Sodium perborate monohydrate

Purity: unknown

Vehicle: presumably water

Oral gavage</td><td>130 – 650 mg/kg bw</td><td>Male/female: > 650 mg/kg bw</td><td>REACH registration (ECHA dissemination, [2020])

Mulinos et al. 1952</td></tr>
<tr><td colspan="6">Sodium perborate tetrahydrate (PBS-4)</td></tr>
<tr><td>OECD TG 401 (Acute Oral Toxicity), non-GLP

Reliability: 1</td><td>Rat, Wistar

Male/female

n = 3/sex/dose</td><td>Sodium perborate tetrahydrate

Purity: unknown</td><td>2150, 2610 and 3160 mg/kg bw

14 days post-exposure</td><td>Male: 2670 mg/kg bw

Female: 2360 mg/kg bw

Male/female: 2567 mg/kg bw

<table><tr><th>Dose (mg/kg)</th><th>Lethality M</th><th>Lethality F</th></tr></table></td><td>REACH registration (ECHA dissemination, [2020])

Study Report,</td></tr>
</table>

Method, guideline, deviations if any[8]	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
	group	Vehicle: 1% aqueous Tragant suspension Oral gavage	observation period	2150 0/3 0/3 2610 1/3 (on day 1) 3/3 (2/3 on day 0 and 1/3 on day 1) 3160 3/3 (on day 0) 3/3 (on day 0)	1987b
Non-guideline, non-GLP, acute oral toxicity test Reliability: 2	Mouse, strain not specified Sex not specified n = 3/sex/dose group	Sodium perborate tetrahydrate Purity: unknown Vehicle: water Oral gavage	1330, 2000, 3000 and 4500 mg/kg bw 21 days post-exposure observation period	Male/female: 2800 mg/kg bw	REACH registration (ECHA dissemination, [2020]) Study Report,1966a
Non-guideline, non-GLP, acute oral toxicity test Limited reporting of methods and results Reliability: 4	Mouse, strain not specified Sex not specified Number of animals/dose group not specified	Sodium perborate tetrahydrate Purity: unknown Vehicle: unknown Oral	2730 mg/kg bw 48h post-exposure observation period	Male/female: > 2730 mg/kg bw	REACH registration (ECHA dissemination, [2020]) Study Report,1966b
Non-guideline, non-GLP, acute oral toxicity test Limited reporting of methods and results Reliability: 4	Rat, strain not specified Sex not specified Number of animals/dose group not specified	Sodium perborate tetrahydrate Purity: unknown Vehicle: unknown Oral	2440 mg/kg bw 48h post-exposure observation period	Male/female: > 2440 mg/kg bw	REACH registration (ECHA dissemination, [2020]) Study Report,1966c
Non-guideline, non-GLP, acute oral toxicity test	Rat, strain not specified Sex not specified	Sodium perborate tetrahydrate Purity:	1200 and 1600 mg/kg bw	1600 mg/kg (20 % aq. sol.) Or 1200 mg/kg (50 % aq. sol.)	REACH registration (ECHA dissemination, [2020])

Method, guideline, deviations if any[8]	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure	Value LD_{50}	Reference
Limited reporting of methods and results Reliability: 4	Number of animals/dose group not specified	unknown Vehicle: unknown Oral			Study Report,1965
Sodium perborate (hydration degree unknown)					
Non-guideline, non-GLP, acute oral toxicity test Limited reporting of methods and results Reliability: 4	Rat, ChR-CD Male n = 5 /dose group	Sodium perborate (hydration degree not specified) Purity: unknown Vehicle: 0.5% aqueous gum guar Oral gavage	3000 and 6000 mg/kg bw 14 days post-exposure observation period	Male: 3600 mg/kg bw	REACH registration (ECHA dissemination, [2020]) Study Report, 1972

Table 8: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
A summary of the reported human data is presented below				

Table 9: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other relevant studies for the acute oral toxicity of perborates were available				

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Animal studies

Sodium per(oxo)borates

- Sodium perborate monohydrate (PBS-1)

The US EPA-guideline acute toxicity studies performed with PBS-1 established an LD_{50} of 1120 mg/kg bw and of 1800 mg/kg bw, in Sprague-Dawley and Wistar rats, respectively (Study report, 1988; Study Report,

1987a). Both studies showed that females are more sensitive than male rats, with the lowest reported ATE of 890 mg/kg bw in the Sprague-Dawley strain.

The reported acute oral toxic effects in both strains consisted of irregular respiration, diarrhoea, bloated abdomen, hypoactivity, ataxia, lethargy, chromorhinorrhea, flaccid muscle tone and negative righting reflex. The necropsy examination revealed very distended stomach, filled with gas, with thickened walls and brown and red-stained glandular mucosa, and enlarged pelvis in the kidneys for both high-dose male and female Sprague-Dawley rats (Study Report, 1988). The necropsy performed in Wistar rats revealed congested and haemorrhagic lungs, liver mottled with dark areas, pale margins of the spleen, distended stomach with gas and white milky fluid, distended red intestines, and some abnormalities of the kidneys (Study Report, 1987a).

An older non-guideline, non-GLP study established an LD_{50} of over the highest tested dose in rats, i.e. > 650 mg/kg bw (Mulinos et al. 1952). Slight hyperaemia of the gastric mucosa and reversible epithelial degeneration of the fundic mucosa were seen. However, the full study was not available for evaluation.

- Sodium perborate tetrahydrate (PBS-4)

The OECD TG 401 acute oral toxicity study performed in rats with PBS-4 established an LD_{50} of 2567 mg/kg bw, while non-guideline, non-GLP acute toxicity studies performed in mice established higher LD_{50} values (> 2730 and 2800 mg/kg bw). Due to the limited reporting of the methods and results sections, no information relating to acute oral toxicity effects and clinical signs in mice was available.

The reported acute oral toxic effects of PBS-4 in the OECD TG 401 study were ruffled fur, blue-coloured extremities, increased salivation, diarrhoea, tremors, hypoactivity, decreased muscle tone, negative righting reflex and clonic cramps. The necropsy examination revealed distended stomach, filled with gas and watery fluid, fluid in the intestines, red glandular mucosa.

- Sodium perborate

An acute oral toxicity study of sodium perborate in rat (Study Report, 1972) with low reliability score (4) was also included in the REACH registration of perboric acid, sodium salt, EC No. 234-390-0. However, since the test substance was not specified and the available information very scarce, this study is not considered further in the assessment of acute oral toxicity but only included for transparency and completeness.

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

According to the disseminated REACH registration dossier[9], based on a non-guideline study performed in rats, an LD_{50} of 3450 mg/kg bw was established for boric acid. Other non-guideline acute oral toxicity studies in rats also reported LD_{50} > 2000 mg/kg bw.

Moreover, acute oral toxicity studies performed in rats for disodium octaborate anhydrate, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and diboron trioxide revealed LD_{50} levels of > 2000 mg/kg bw, for each substance.

Hydrogen peroxide

According to the disseminated REACH registration dossier[10], two acute oral toxicity studies according to OECD TG 401 were performed in rats. Thus, LD_{50} values of 805 mg/kg bw hydrogen peroxide 70% (Study Report, 1996) and of 801 – 872 mg/kg bw hydrogen peroxide 60% (Study Report, 1981) were established.

[9] https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15472/7/3/1

[10] https://echa.europa.eu/registration-dossier/-/registered-dossier/15701/7/3/2

Another acute oral toxicity study (according to US EPA PB 82-232948) performed in rats with hydrogen peroxide 35% established an LD_{50} of 1193 mg/kg bw for males and 1270 mg/kg bw for females (Study Report, 1983).

Other acute oral toxicity studies (non-guideline, non-GLP) in rats reported LD_{50} values of > 225 mg/kg bw for hydrogen peroxide 50% and LD_{50} values of 1520 mg/kg bw for males and 1620 mg/kg bw for females administered hydrogen peroxide 9.6%. Furthermore, an LD_{50} of >5000 mg/kg bw was reported by another non-guideline study for rats administered hydrogen peroxide 10% (Study Report, 1990).

Main acute toxicity effects such as lethargy, immobility, irregular respiration, ataxia and tremors were noted in the above-mentioned studies.

Hydrogen peroxide has a harmonised minimum classification as Acute Tox. 4*, H302.

Human data

Sodium per(oxo)borates

Accidental swallowing cases of powder/liquid detergents or other household products containing sodium per(oxo)borates mostly involving children (0 - 4 years) have been recorded in a UK Poison Centre report (as detailed in the HERA Report, 2002). Effects such as transient irritation of the eyes and mucous membranes were mainly described. No fatalities were reported and approx. 60% of the incidents involving laundry detergents were treated at home. The amounts swallowed in these cases are not noted. However, based upon the available information, it is estimated that a maximum amount of 1.5 g of sodium per(oxo)borate (approx. 5 g of detergent) could be swallowed. This amount results in approx. 150 mg/kg bw for a 10 kg child (HERA Report, 2002).

In the disseminated REACH registration dossier[11], the human health surveillance data on workers employed at detergent production plants do not provide any information on acute oral toxicity of sodium per(oxo)borates.

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

As detailed in the disseminated REACH registration dossier of boric acid[10], intentional or accidental poisoning incidents with boric acid or borate salts have been reported. Based on an old case review study, the human oral lethal dose was reported as 2-3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults. None of the more recent poisoning cases with an estimated dose range of 0.01 – 88.8 g boric acid were reported to be fatal. The reported acute effects are mainly represented by nausea, vomiting, gastric effects, skin flushing, convulsions, depression and vascular collapse.

Hydrogen peroxide

Two case reports involving lethal ingestion of hydrogen peroxide by children were available (EU RAR 2003). The first case report described a 2-year-old child who accidentally ingested 113 to 170 g of hydrogen peroxide 35%, becoming immediately cyanotic and unresponsive, remaining paralysed. The child died on day 4 after arriving at the hospital, where a chest radiograph showed gas accumulation in the right heart ventricle and portal venous system. The autopsy revealed marked diffuse cerebral oedema, due to gas embolism. Assuming a weight of 13 kg and that the child ingested approx. 142 g of a 35% hydrogen peroxide solution, this would correspond to approx. 50 g of hydrogen peroxide, and thus the lethal dose in this case would be approx. 3846 mg/kg bw.

11 https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/11/2

The second case report describes a 16-month-old child who accidentally ingested approx. 230g of hydrogen peroxide 3% and was found dead 10h later. The autopsy revealed foamy blood in the right heart ventricle and the portal venous system, red gastric mucosa, cerebral and lung oedema. Gas embolism was seen in the pulmonary vasculature, intestinal and gastric lymphatics. The ingested dose of hydrogen peroxide would thus correspond to approx. 7g (i.e. 230 g of 35% hydrogen peroxide solution), which further gives a lethal dose of 603 mg/kg bw (taking into account the body weight of 11.6 kg of the child).

Conclusion

The available acute oral toxicity studies for PBS-1 meet the criteria for classification in Acute Tox. 4, where the lowest LD_{50} is 890 mg/kg bw in the female rat. With the exception of one non-guideline study showing LD_{50} values < 2000 mg/kg bw, the data presented on PBS-4 do not warrant classification for oral acute toxicity (>2000 mg/kg bw). It should be noted that the higher toxicity of the monohydrate as compared to the tetrahydrate, is consistent with the lower water content (HERA Report, 2002).

The available studies show that acute oral toxicity of sodium per(oxo)borates is due to the *in vivo* formation of hydrogen peroxide (which leads to local irritation and oxygen accumulation). The reported LD_{50} values for hydrogen peroxide correspond to Category 4 (801 – 872 mg/kg bw). The necropsy results from the PBS-1 and PBS-4 studies are consistent with oxygen formation in visceral cavities (gas embolism) due to the degradation of the formed hydrogen peroxide.

The lowest male/female LD_{50} established in rats for PBS-1 (1120 mg/kg bw) was further used to calculate the LD_{50} for sodium peroxometaborate, according to its H_2O_2 content, based upon the degradation reactions of these two sodium per(oxo)borates and respective molecular masses, taking into account that the molar ratios of sodium peroxometaborate:H_2O_2 and PBS-1:H_2O_2 are 1:1 in each reaction. This yielded an LD_{50} of 918 mg/kg bw for sodium peroxometaborate, which is in line with its hydrogen peroxide content. The higher toxicity of sodium peroxometaborate and PBS-1 as compared to PBS-4 is explained by their higher respective H_2O_2 content (see Table 10 below).

10.1.2 Comparison with the CLP criteria

According to the CLP Regulation (EC) No 1272/2008, classification for acute oral toxicity is required for substances with acute toxicity estimate values (based on LD_{50}) below 2000 mg/kg bw.

The two acute oral toxicity studies performed in rats with PBS-1 established LD_{50} values > 300 and < 2000 mg/kg bw (Category 4), where the lowest LD_{50} was 890 mg/kg bw seen in female rats in Study report, 1988, and in Study report, 1987a the lowest LD50 was 1700 mg/kg in females. According to the Guidance on the application of CLP criteria 3.1.2.3.2 *In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested.* Since there are no apparent reasons for the different results obtained in Study report, 1988 and Study Report, 1987a, apart from using two different rat strains, the lowest available LD50 of 890 mg/kg appears appropriate as a basis to set ATE for PBS-1 In contrast, the LD_{50} established for PBS-4 does not warrant classification. As shown in Table 10, the LD_{50} calculated for sodium peroxometaborate also corresponds to Category 4.

Table 10: Experimental and calculated LD_{50} values for sodium per(oxo)borates

Substance	H_2O_2 content (%)[12]	LD_{50} (mg/kg bw)	Acute Toxicity Hazard Category and Hazard Statement Codes (according to CLP Regulation)
Sodium peroxometaborate	39.1	918 (calculated based on LD_{50} for PBS-1)	Acute Tox.4; H302

[12] Calculated as % of hydrogen peroxide of the molecular masses of each sodium per(oxo)borate, excluding the molecular mass of hydrogen. Based on the method for hydrogen peroxide content calculation provided by the Industry during the TC C&L meetings in 2005-2006 (ECBI/38/03 Add. 10).

Substance	H_2O_2 content (%)[12]	LD_{50} (mg/kg bw)	Acute Toxicity Hazard Category and Hazard Statement Codes (according to CLP Regulation)
PBS-1	32.1	1120 (experimental)	Acute Tox.4; H302
PBS-4	21	2567 (experimental)	-

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Currently, sodium peroxometaborate has a harmonised classification as Acute Tox. 4* (H302) for the oral route of exposure, as listed in two entries (Index No. 005-017-00-7 and 005-017-01-4) in Annex VI of CLP. **A removal of the asterisk (*) indicating minimum classification and the inclusion of an ATE of 918 mg/kg bw is thus proposed. Thus, the new proposed classification for peroxometaborate is: Acute Tox 4, H302, oral: ATE = 918 mg/kg bw/day.**

10.2 Acute toxicity - dermal route

Table 11: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any[13]	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Value LD_{50}	Reference
Sodium perborate monohydrate					
OECD TG 402 (Acute Dermal Toxicity) Reliability: 1	Rabbit, New Zealand White Male/female n = 5/sex/dose group	Sodium perborate monohydrate Purity: unknown Vehicle: water Occlusive dermal application	2000 mg/kg bw Single dermal dose, 24 h exposure 14 days post-exposure observation period	Male/female: > 2000 mg/kg bw	REACH registration (ECHA dissemination, [2020]) Study Report, 1987c See also Annex I to the CLH-report

Table 52: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data on the acute dermal toxicity of sodium per(oxo)borates were available				

Table 63: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other relevant studies for the acute dermal toxicity of perborates were available				

[13] Where applicable and unless stated otherwise, the reliability scores of the studies presented in Table 11 are according to the publicly disseminated REACH Registration dossier for EC no. 234-390-0, available at https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/3/4

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

Animal studies

Sodium per(oxo)borates

The acute dermal toxicity study (OECD TG 402) performed in rabbits with sodium perborate monohydrate established an LD_{50} > 2000 mg/kg bw. Clinical signs such as diarrhoea, few faeces, yellow nasal discharge and anogenital soiling were reported. One male rabbit died on day 13 post-treatment revealing abnormalities of the gastrointestinal tract, spleen, liver and lung. On day 1 post-treatment, 2/9 surviving rabbits showed skin irritation, which decreased in severity during the 14-day observation period, and distended intestines at the necropsy evaluation. No statistically significant effects on body weight were recorded.

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

According to the disseminated REACH registration dossier[12] of boric acid, an LD_{50} > 2000 mg/kg bw was established based on a non-guideline study performed in rabbits. Moreover, acute dermal toxicity studies performed in rats or rabbits for disodium octaboarte anhydrate, disodium tetraborate decahydrate and disodium tetraborate pentahydrate revealed LD_{50} levels of > 2000 mg/kg bw, for each substance.

Hydrogen peroxide

An acute dermal toxicity study performed in rabbits according to EPA PB82-232984 guideline (Study Report, 1982) is available in the disseminated REACH registration dossier[14] of H_2O_2. No deaths occurred and the established LD_{50} value for hydrogen peroxide 35% was > 2000 mg/kg bw. All 10 animals showed erythema, oedema, blanching of the skin after 24 h, and eschar and exfoliation at study cessation. The necropsy examination did not reveal any gross internal lesions.

Other non-guideline acute dermal toxicity studies performed in rabbits established an LD_{50} of 9200 mg/kg bw for 70% hydrogen peroxide, whereas LD_{50} values for rats seem to be > 3500 mg/kg bw for 90% hydrogen peroxide.

Human data

Sodium per(oxo)borates

Several cases describing accidental skin contact with powder/liquid detergents or other household products containing sodium per(oxo)borates mostly involving small children (0 - 4 years) have been recorded in a UK Poison Centre report. No fatalities were reported and none of the exposed children required treatment in a hospital. Most of the injuries were recorded as “chemical injury”, with 2 cases of skin corrosion (HERA Report, 2002).

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

As detailed in the disseminated REACH registration dossier of boric acid[15], several poisoning cases were reported in humans due to the use of skin and mucosa antiseptic pharmaceutical preparations containing boric acid. Moreover, case reports of accidental exposure of the head were also reported, with effects such as general or focal alopecia of the scalp (ATSDR Report, 2010).

[14] https://echa.europa.eu/registration-dossier/-/registered-dossier/15701/7/3/4

[15] https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15472/7/3/4

Hydrogen peroxide

There are no available data on the acute dermal toxicity of hydrogen peroxide in humans. The main effects after dermal exposure consist of local irritation or corrosion and the appearance of white spots on the skin (HERA Report, 2005).

Conclusion

Read-across of data from PBS-1 was also used in the EU RAR (2007) for the investigation of acute dermal toxicity, in the absence of information on the acute dermal toxicity of sodium peroxometaborate. It can therefore be assumed that the same read-across approach (of experimental data from studies conducted with PBS-1) may be used in order to evaluate the acute dermal toxicity of sodium peroxometaborate.

The available data indicate that sodium per(oxo)borate monohydrate displays low acute dermal toxicity with LD_{50} > 2000 mg/kg bw, and therefore do not require classification. The described animal studies are comparable for per(oxo)borates, boric acid and borate salts and hydrogen peroxide.

10.2.2 Comparison with the CLP criteria

Classification under the CLP regulation (EC No 1272/2008) for acute dermal toxicity is required for substances with acute toxicity estimates (based on LD_{50}) below 2000 mg/kg bw. The reported LD_{50} values for sodium per(oxo)borates do not meet the criteria for acute dermal toxicity.

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Since the experimental data revealed LD_{50} values > 2000 mg/kg bw, classification for acute dermal toxicity of sodium peroxometaborate is not warranted.

10.3 Acute toxicity - inhalation route

Table 74: Summary table of animal studies on acute inhalation toxicity

<table>
<tr><th>Method, guideline, deviations if any[16]</th><th>Species, strain, sex, no/group</th><th>Test substance, form and particle size (MMAD)</th><th>Dose levels, duration of exposure</th><th>Value
LC_{50}</th><th>Reference</th></tr>
<tr><td colspan="6">Sodium perborate tetrahydrate</td></tr>
<tr><td>Non-guideline acute inhalation toxicity study, GLP

Similar to OECD TG 403 (acute inhalation toxicity) with the following deviations: only one sex investigated, macroscopic and histopathological</td><td>Rat, Crl:CD BR

Male

n = 6/dose group</td><td>Sodium perborate tetrahydrate

Purity: 98.6%

MMAD: 3.3, 3.5, 3.5 and 4.2 µm for 0.16, 0.48, 1.10 and 2.90 mg/L, respectively</td><td>0.16, 0.48, 1.10 and 2.90 mg/L

Exposure duration: 4h

14 days post-exposure observation period</td><td>Male: 1.16 mg/L

<table><tr><th>Conc. (mg/L)</th><th>MMAD (µm)</th><th>Lethality</th></tr><tr><td>0.16</td><td>3.3</td><td>0/6</td></tr><tr><td>0.48</td><td>3.5</td><td>1/6</td></tr><tr><td>1.10</td><td>3.5</td><td>3/6</td></tr><tr><td>2.90</td><td>4.2</td><td>5/6</td></tr></table></td><td>Study Report, 1987d

REACH registration (ECHA dissemination, [2020])

See also Annex I to the CLH-report</td></tr>
</table>

[16] Where applicable and unless stated otherwise, the reliability scores of the studies presented in Table 14 are according to the publicly disseminated REACH Registration dossier for EC no. 234-390-0, available at https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/3/3.

Method, guideline, deviations if any[16]	Species, strain, sex, no/group	Test substance, form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
examinations not performed, different humidity range.		Inhalation (nose-only): dust			

Table 85: Summary table of human data on acute inhalation toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No human data on the acute inhalation toxicity of sodium per(oxo)borates were available				

Table 96: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other relevant studies for the acute dermal toxicity of perborates were available				

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Animal studies

Sodium per(oxo)borates

One non-guideline, GLP-compliant study of acceptable quality and reliability assessing the acute inhalation toxicity of PBS-4 in rats was available (Study Report, 1987d). Male rats (6/dose group) were exposed nose-only to 0.16, 0.48, 1.10 and 2.90 mg/L PBS-4, with the MMAD value for the highest concentration slightly over the respirable range (3.3 – 4.2 µm vs. 1 – 4 µm). During or shortly after exposure, males from all dose groups showed red nasal discharge, gasping and compound-covered faces while the rats exposed to ≥ 1.10 mg/L did not exhibit a startle response. A slight to severe decrease in body weight (up to 18%) was recorded within 1 day of exposure. All deaths occurred within 24h after exposure, as follows: 0/6, 1/6, 3/6 and 4/6 at 0.16, 0.48, 1.10 and 2.90 mg/L, respectively. Additionally, 1 rat from the highest dose group died 8 days after exposure. The acute inhalation toxicity effects in the surviving rats consisted of red ocular, nasal or oral discharge, diarrhoea, gasping and lung noise. Necropsy was not performed. An LC_{50} of 1.16 mg/L was calculated by Probit Analysis.

A short description of another non-guideline inhalation toxicity study was available in the EU RAR (2007). Experimental animals (species not specified) were exposed to 3.7, 11.3, 39, 58 and 74 mg/ m^3 of PBS-4 (equivalent to 0.0037, 0.0113, 0.039, 0.058 and 0.074 mg/L). Symptoms of respiratory irritation such as reduced respiration rate and an increase in the total number of cells in the lung lavage fluid were noted at 39-74 mg/m^3. Toxic effects were seen at 74 mg/m^3, however the lethality rate was not reported (Silajev, 1984 as cited in the EU RAR, 2007). The study is poorly described and no information on the exposure conditions and time, number/sex of animals, mortality or the calculation of an LC_{50} was available.

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

According to the disseminated REACH registration dossier[17] of boric acid, based on an OECD TG 403 study performed in rats, an LC_{50} > 2.03 mg/L was established. Half an hour after exposure, effects such as ocular and/or nasal discharge, hunched posture and hypoactivity were noted. In addition, an US EPA FIFRA study performed in rats, reported an LC_{50} of > 2.12 mg/L.

Moreover, acute inhalation toxicity studies performed in rats for disodium octaborate tetrahydrate and disodium tetraborate pentahydrate revealed LC_{50} levels > 2 mg/L, for each substance.

Hydrogen peroxide

As described in the disseminated REACH registration dossier of hydrogen peroxide, based on a GLP-compliant, US EPA guideline (OTS 798.1150) acute inhalation toxicity study in rats, male and female rats were administered 0.17 mg/L H_2O_2 as vapour for 4h, via whole-body exposure. Eye closure, decreased activity, excessive salivation and nasal discharge were reported. A slight decrease in body weight on day 2 post-exposure was noted, but all rats recovered by the termination of the study. No deaths occurred at 0.17 mg/L, i.e. the maximum attainable concentration of hydrogen peroxide 50%, and thus an LC_{50} could not be established. Lung weights were comparable to controls and it was stated that the necropsy examination did not reveal any treatment-related findings (Study Report, 1990b).

A non-guideline, GLP-compliant study investigated the respiratory irritation potential of hydrogen peroxide 50% administered as aerosols (Study Report, 1995a). Four male mice were exposed nose-only to 0.3, 0.616, 1.135 and 1.856 mg/L H2O2 for 30 minutes. The concentration at which a 50% reduction of the respiratory rate was observed was 0.665 mg/L. No animals died during the exposure. The necropsy examination showed local degenerative changes in the liver of 2 males from the lowest and highest dose groups.

Inhalation of highly concentrated solutions of hydrogen peroxide led to severe irritation and inflammation of the mucous membranes, coughing and dyspnoea. Shock, coma, convulsions and pulmonary oedema were reported up to 24-72 h post-exposure in experimental animals administered 90/ hydrogen peroxide as vapour (Watt et al. 2004).

As detailed in the EU RAR (2003) of hydrogen peroxide, mice and rats have been exposed (whole-body) to the vapour of hydrogen peroxide for 4-8 hours in two series of rat studies with a different experimental setup (1) to a calculated concentration of 4,000 mg/m^3 (eq. to 4 mg/L) for 8 hours or, (2) to measured concentrations ranging from 338 to 427 mg/m^3 (eq. to 0.338 to 0.427 mg/L) for 4 or 8 hours. In study (1) no deaths were reported and no signs of intoxication were observed. No abnormal signs were noted in rats other than scratching and licking themselves. Pathological examination revealed congestion in the trachea and lungs. Small, localised areas of pulmonary oedema without haemorrhage and areas of alveolar emphysema were present among the rats killed during the first three days. Most of the lungs exhibited many areas of alveolar emphysema in addition to severe congestion. All other organs examined appeared normal. In study (2) no deaths were reported from either the single four-hour or eight-hour exposure. Pathological examination of the animals showed results similar to those described in study (1). Another poorly reported study which concerned a whole-body (shaved skin) exposure of rats to hydrogen peroxide vapour for 4 hours, gave an LC50 value of 2,000 mg/m3 (eq. to 2 mg/L) and noted that the primary cause of death in the animals was gas embolism (Kondrashov, 1977; as cited in the EU RAR, 2003).
Hydrogen peroxide has a harmonised minimum classification as Acute Tox. 4*, H332

Human data

Sodium per(oxo)borates

[17] https://echa.europa.eu/registration-dossier/-/registered-dossier/15472/7/3/3

No information on the acute inhalation toxicity of sodium per(oxo)borates in humans was available. Health surveillance data on occupational exposure of workers from perborate production factories were available in the disseminated REACH registration dossier[18]. Several unnamed epidemiological studies did not report any effects on the lung function of the workers, measured as forced vital capacity (FVC), forced expiratory volume (FEV), vital capacity (VC) and peak expiratory flow. However, it should be noted that these parameters are not very sensitive for small airway disease. Reversible eye irritation and partially reversible irritative effects on the nasal mucosa were reported.

The below data on boric acid, borate salts and hydrogen peroxide are presented only for comparison.

Boric acid and borate salts

Healthy volunteers were exposed to 0, 5, 10, 20, 30 and 40 mg/m^3 sodium tetraborate pentahydrate as dust for 20 min, while cycling (Cain et al. 2004). Effects such as nasal and throat irritation were seen at levels ≥ 30 mg/m^3, the subjects reporting time-dependent feel due to sodium tetraborate pentahydrate exposure primarily in the nose and hardly in the eyes. Similarly, healthy volunteers were exposed to 0, 10 mg/m^3 sodium borate, and to 0, 2.5, 5 and 10 mg boric acid/m^3 for 47 minutes while exercising (Cain et al. 2008). Increased nasal secretions and decreased nasal airway resistance were observed at 10 mg/m^3 sodium borate.

Hydrogen peroxide

No information on the acute inhalation toxicity of hydrogen peroxide in humans was found. The available reported cases of accidental hydrogen peroxide intoxications mainly involve the oral route (see Section 10.1.1).

Occupational exposure to hydrogen peroxide as aerosols was aetiologically linked with the development of diffuse interstitial lung disease in a 41-year-old dairy worker who also smoked. Withdrawal from exposure to hydrogen peroxide led to an improvement of his condition (Watt et al. 2004).

Conclusion

No acute inhalation toxicity study of sodium peroxometaborate is available. The LC_{50} of 1.16 mg/L for PBS-4 in available acute inhalation toxicity study meets the criteria for classification of PBS-4 as Acute Tox. 4, H332 (1.0 < ATE ≤ 5.0 mg/L). The LC_{50} established for PBS-4 was used to calculate the LC_{50} for sodium peroxometaborate according to their respective H_2O_2 content, based upon their respective hydrolysis reactions and molecular masses, taking into account that molar ratios of PBS-1:H_2O_2 are 1:1 in the hydrolysis reaction. This yielded LC_{50} values of 0.62 mg/L for sodium peroxometaborate. The calculated concentration is in line with the hydrogen peroxide content of each per(oxo)borate (see Table 17 below) that anticipates potentially higher toxicity of sodium peroxometaborate as compared to PBS-4.

In comparison, the reported LC_{50} values for boric acid and borate salts were > 2 mg/L, which therefore do not require classification. The available evidence shows that the higher acute inhalation toxicity of sodium peroxometaborate as compared to borates is due to the *in vivo* formation of hydrogen peroxide, and not due to boron-exposure.

No acute inhalation toxicity studies were available with sodium peroxometaborate or PBS-1. The LC_{50} established for PBS-4 was further used to calculate the LC_{50} values for sodium peroxometaborate and PBS-1 according to their respective H_2O_2 content, based upon their respective degradation reactions and molecular masses, taking into account that molar ratios of sodium peroxometaborate:H_2O_2 and PBS-1:H_2O_2 are 1:1 in each reaction. This yielded LC_{50} values of 0.62 mg/L for sodium peroxometaborate and 0.75 mg/L for PBS-1. These calculated concentrations are in line with the hydrogen peroxide content of each per(oxo)borate (see Table 17 below) that further explains the higher toxicity of PBS-1 and sodium peroxometaborate as compared to PBS-4.

[18] https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/11/2

10.3.2 Comparison with the CLP criteria

According to the CLP Regulation (EC) No 1272/2008, classification for acute inhalation toxicity is required for substances with acute toxicity estimate values (based on LC_{50}) below 5 mg/L, in the case of dusts and mists. Category 3 is assigned for ATE values > 0.5 and ≤ 1 mg/L, while Category 4 is assigned for substances with ATE values > 1 and ≤ 5 mg/L.

The only study available for acute inhalation toxicity was a non-guideline study performed in male rats with PBS-4 that determined an LC50 of 1.16 mg/L which corresponds to Category 4. The study is considered reliable and appropriate as a basis to set ATE for acute inhalation toxicity of sodium peroxometaborate when the LC50 is calculated based on the H2O2 content compared to PBS-4. This basis for ATE is considered more appropriate than using acute toxicity point estimates (Table 3.1.2 in CLP).
As shown in Table 17, the LC_{50} values calculated for sodium peroxometaborate correspond to Category 3.

Table 17: Experimental and calculated LC_{50} values for sodium per(oxo)borates

Substance	H_2O_2 content (%)[19]	LC_{50} (mg/L for dusts and mists)	Acute Toxicity Hazard Category and Hazard Statement Codes (according to CLP Regulation)
Sodium peroxometaborate	39.1	0.62 (calculated based on LC_{50} for PBS-4)	Acute Tox.3, H331
PBS-1	32.1	0.75 (calculated based on LC_{50} for PBS-4)	Acute Tox.3, H331
PBS-4	21	1.16 (experimental)	Acute Tox.4, H332

In addition, the current CLH-report also proposes the removal of the cut-off values for particle size, proposed on the basis of the thoracic fraction concept, discussed and adopted by the Technical Committee for Classification and Labelling (TC C&L) in 2006 (ECBI/90/06 Rev. 8). The main reason for this is that the thoracic fraction is a conservative approach no longer used that leads to differences in classification for acute inhalation toxicity of the same substance.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Currently, sodium peroxometaborate has a harmonised classification as Acute Tox. 3* (H331) as listed in two entries (Index No. 005-017-00-7 and 005-017-01-4) in Annex VI of CLP.

A removal of the asterisk (*) indicating minimum classification and the cut-off values for particle size distribution "[containing ≥ 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]" and "[containing = 0,1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]" is proposed. In addition, an ATE of 0.62 mg/L is also proposed. Thus, the new proposed classification for sodium peroxometaborate is: Acute Tox 3, H331, inhalation: ATE = 0.62 mg/L.

10.4 Skin corrosion/irritation

Hazard class not assessed in this CLH-proposal.

[19] Calculated as % of hydrogen peroxide of the molecular masses of each sodium per(oxo)borate, excluding the molecular mass of hydrogen. Based on the method for hydrogen peroxide content calculation provided by the Industry during the TC C&L meetings in 2005-2006 (ECBI/38/03 Add. 10).

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this CLH-proposal.

10.6 Respiratory sensitisation

Hazard class not assessed in this CLH-proposal.

10.7 Skin sensitisation

Hazard class not assessed in this CLH-proposal.

10.8 Germ cell mutagenicity

Hazard class not assessed in this CLH-proposal.

10.9 Carcinogenicity

Hazard class not assessed in this CLH-proposal.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 18: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group[20]	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Sodium perborate tetrahydrate (PBS-4)			
OECD TG 407 (Repeated dose 28-day oral toxicity study, OECD TG 1981), carried out according to GLP guidelines Rat (Wistar) male/female n = 5/sex/dose group Reliability: 1 (reliable without restriction)	Test material: sodium perborate tetrahydrate Purity: > 98% <u>Limit test</u>: 0 and 1000 mg/kg bw/day (equivalent to 0 and 70 mg B/kg bw/day, respectively) in 1% aqueous tylose suspension <u>Exposure:</u>	**Effects observed in males**: <u>Clinical signs</u>: - salivation after administration occurred in in 5/5 males from day 7 of treatment - temporary piloerection in 2/5 males - one male showed stilted gait and sunken sides - no deaths were reported <u>Food consumption and body weight</u>: - stat. sign. reduction in food consumption by 15% (17.2 g vs. 20.2 g in controls) - stat. sign. ($p<0.05$) reduction in bw by 16% in the last week of treatment (216.1 g vs 258.4 g in controls) <u>Organ weights</u>: - stat. sign. ($p<0.05$) reduced: absolute brain weights by 9% (1.58 g vs 1.73 g in controls), absolute left kidney weight by 18% (0.80 g vs 0.97 g in controls), absolute heart weight by	Study Report, 1989 REACH registration (ECHA dissemination, [2020]) See also Annex I to the CLH-report

[20] Where applicable and unless stated otherwise, the reliability scores of the studies presented in Table 18 are according to the publicly disseminated REACH Registration dossier for EC no. 234-390-0, available at https://echa.europa.eu/registration-dossier/-/registered-dossier/13523/7/9/2

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group[20]</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td></td><td>28 days, daily via oral gavage</td><td>17% (0.92 g vs 1.11 g in controls)
- stat. sign. reduced absolute testes weight by 18% (left testis: 1.71 g vs. 2.09 g in controls; right testis: 1.74 g vs 2.11 g in controls)
- no stat. sign. differences seen in the relative weights (to body weight) of the testes, brain, kidney or heart
- stat. sign (p<0.05) increased relative adrenal weights by 33 – 37.5% (adrenal left: 0.012 g vs. 0.009 g in controls; adrenal right: 0.011 vs. 0.008 g in controls)

<u>Pathological findings:</u>
- testicular focal tubular atrophy in 3/5 male rats (2/5 in controls, no HCD provided)
- inhibition of spermiation (stage IX and X tubules) in 5/5 male rats (2/5 controls, no HCD provided)
- small spleen in 2/5 (0/5 in controls) and reduction of parenchyma in the spleen in 5/5 (0/5 in controls)
- acanthosis/hyperkeratosis of the stomach in 4/5 males (0/5 in controls) and hyperplasia of fundic mucosa in 5/5 males (0/5 in controls)
- acute brain hemorrhage in 1/5 males (2/5 in controls)
- focal histiocytosis in the lungs in 3/5 males (3/5 in controls) and acute lung hemorrhage 2/5 males (1/5 in controls)

Effects observed in females:
<u>Clinical signs:</u>
- salivation after administration in 4/5 females from day 8 of treatment and temporary piloerection in 1/5 females
- no deaths were reported

<u>Food consumption and body weight</u>:
- no stat. sign differences in food consumption (14.3 g vs. 14.6 g in controls)
- no stat. sign. differences in body weights (167 g vs. 166.1 g in controls)

<u>Organ weights</u>:
- stat. sign (p<0.05) increased relative liver weight by 10% (4.87 g vs 4.44 g in controls)

<u>Pathological findings:</u>
- inflammation of the liver in 5/5 females
- acanthosis/hyperkeratosis of the stomach in 4/5 females (1/5 in controls), hyperplasia of fundic mucosa in 4/5 females (0/5 in controls) and subacute gastritis in 1/5 females (0/5 in controls)
- acute brain hemorrhage in 1/5 females (1/5 in controls)
- focal histiocytosis in the lungs in 5/5 females (4/5 in controls)</td><td></td></tr>
<tr><td colspan="4">Boric acid and borates</td></tr>
<tr><td>Two-year feeding study</td><td>Test material: boric acid</td><td>Testes atrophy was observed at 24 months, as shown below:
<table><tr><th>Dose level (mg B/kg bw/day)</th><th>0</th><th>5.9</th><th>17.5</th><th>58.5</th></tr></table></td><td>REACH registration (ECHA</td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group[20]</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>No guideline specified

Rat (Sprague-Dawley) male/female

n = 35/sex/dose group with 70/sex/dose group as controls</td><td>Purity: unknown

<u>Doses/conc.</u>:
0, 117, 350 and 1170 ppm boron, (eq. 0, 5.9, 17.5 and 58.5 mg B/kg bw/day, respectively)

<u>Exposure</u>:
24 months, daily in feed.</td><td><table><tr><td>No. of animals</td><td>3/10</td><td>1/10</td><td>4/10</td><td>10/10</td></tr></table>
At 58.5 mg B/kg bw/day, seminiferous tubular degeneration and testicular atrophy were observed at 6, 12 and 24 months of treatment.

LOAEL for fertility in rats = 58.5 mg B/kg bw/ day

NOAEL for fertility in rats = 17.5 mg B/kg bw/day</td><td>dissemination, [2020])

Study Report, 1966d

Weir and Fisher, 1972

Weir, 1996a[21]</td></tr>
<tr><td>Two-year feeding study

No guideline specified

Rat (Sprague-Dawley) male/female

n = 35/sex/dose group with 70/sex/dose group as controls</td><td>Test material: disodium tetraborate tetrahydrate

Purity: unknown

<u>Doses/conc.</u>:
0, 1030, 3080 and 10300 ppm boron (eq. to 0, 5.9, 17.5 and 58.5 mg B/kg bw/day, respectively)

<u>Exposure</u>:
24 months, daily in feed.</td><td>Testes atrophy was observed at 24 months, as shown below:

<table><tr><th>Dose level (mg B/kg bw/day)</th><th>0</th><th>5.9</th><th>17.5</th><th>58.5</th></tr><tr><td>No. of animals</td><td>3/10</td><td>1/10</td><td>4/10</td><td>10/10</td></tr></table>
LOAEL for fertility in rats = 58.5 mg B/kg bw/ day

NOAEL for fertility in rats = 17.5 mg B/kg bw/day</td><td>REACH registration (ECHA dissemination, [2020])

Study Report, 1967

Weir and Fisher, 1972

Weir, 1996b[22]</td></tr>
</table>

Table 19: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data on the effects of per(oxo)borates on human sexual function and fertility were available				

Table 100: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference

[21] As cited in the RAC Opinions on disodium octaborate anhydrate and disodium octaborate tetrahydrate (2014).

[22] As cited in the RAC Opinions on disodium octaborate anhydrate and disodium octaborate tetrahydrate (2014).

No other studies with per(oxo)borates relevant for investigating sexual function and fertility were available

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

10.10.2.1 Read-across data on PBS-4 from animal studies

In a 28-day limit test (OECD TG 407, 1989), male and female rats (5/sex/dose) were administered sodium perborate tetrahydrate (PBS-4) via oral gavage at 0 and 1000 mg/kg bw/day (equivalent to 0 and 70 mg B/kg bw/day, respectively). According to OECD TG 407, a limit test should be performed if, from assessment of other data, no effects would be expected at a dose of 1000 mg/kg bw/day. A dose-range finding study was performed with 1000 mg/kg bw/day for 23 days. Salivation and reddening of the glandular stomach were seen. According to these findings, the dose level of 1000 mg/kg bw/day was selected for the 28-day repeated dose limit toxicity study.

In the limit test, a 18% stat. sign. decrease in absolute testes weight was reported, while the relative testes weights were not stat. sign. reduced (7.98 g vs 8.09 g in controls). Testicular focal tubular atrophy and inhibition of spermiation was seen in 3/5 and 5/5 rats, respectively, with a high incidence recorded in control rats (2/5 for both effects). The study author considered these effects as spontaneous findings in Wistar rats and therefore not related to treatment, although HCD were not provided. Histological examinations of the testes did not reveal any signs of toxicity. However, testes were fixed with formalin, a method that leads to cellular shrinkage and only allows the detection of major effects. Using more sensitive methods of histopathology, i.e. perfusion with glutaraldehyde/paraformaldehyde and embedding with methacrylate revealed more subtle effects with boric acid and borate salts (Ku et al. 1993; Treinen and Chapin, 1991).

A statistically significant ($p<0.05$) reduction in food consumption (by 15%) and body weight (by 16%) were seen in male rats while the food consumption and body weight of female rats were not affected. Statistically significant reduced absolute weights of brain, kidney and heart were reduced by 9%, 18% and 17%, respectively.

Effects such as acanthosis/hyperkeratosis of the stomach and hyperplasia of the fundic mucosa were reported for both male and female rats. Small spleen and reduction of parenchyma in the spleen were seen only in males. Lung effects (acute hemorrhage and focal histiocytosis) and acute brain hemorrhage were reported in both males and females.

As detailed in the EU RAR (2007), the results of the limit test were discussed at the Specialised Experts (SE) meeting[23] in October 2004, where it was debated if the reduction in absolute testes weight was a consequence of reduction in body weight gain or a treatment-related effect. The general influence of food uptake and restriction on the weight development of rats based on studies with the same exposure time was taken into account (see Table 21). For comparison, in a study with boric acid, a reduction in body weight gain and absolute testes weight was reported, while no information on relative testes weight was available (Ku et al. 1993). In a study that investigated the effects of food restriction on common toxicity parameters in male rats, the relative testes weights increased, with a 3% reduction in the absolute weight of the testes (Oishi et al. 1979). However, the study performed by Feron et al. (1973) showed reduced relative and absolute testes weight as a consequence of cellulose-rich diet used to prevent the rats from starving.

[23] The Specialised Experts meeting was previous to the TC C&L meetings (March and November 2005; March 2006) where the classification proposals for perboric acid, sodium salt monohydrate and perboric acid, sodium salt tetrahydrate were discussed and adopted.

Table 21: Influence of body weight gain on absolute and relative testes weights (as detailed in the EU RAR, 2007)

	Study Report, 1989	Ku et al. 1993	Oishi et al. 1979	Feron et al. 1973
Species (Strain)	Rat (Wistar)	Rat (F344)	Rat (Wistar)	Rat (Wistar)
Treatment	PBS-4	Boric acid	Food restriction	Increased cellulose in diet (45-70%)
Dose	1000 mg/kg bw (eq. to 70 mg B/kg bw)	9000 ppm (in diet) (eq. to 68 mg B/kg bw)	-	-
Duration of treatment	28 days	30 days (60 and 90 days)	28 days	28 days (and 91 days)
Food intake	↓ 15%	↓ 11%	↓ 25 - 30%	-
Reduction in bw gain	15%	16%	approx. 30%	22%
Relative testes weight compared to controls	unchanged	not given	↑ 31%	↓ 13%
Absolute testes weights compared to controls	↓ 18%	↓ approx. 20%	↓ 3%	↓ 25%

The Specialised Experts concluded that the decrease in absolute testes weights seen in the 28-day study with PBS-4 is likely treatment-related, as there is a common view that that brain and testes weights are generally not affected by a reduction in body weight. However, it should be noted that the study also showed stat. sign. reduced brain, heart and kidney weights. Finally, it was stated at the Specialised Experts meeting that reduced testes weights as early signs of testicular toxicity cannot be dismissed in view of the known testicular toxicity of the boric acid and borate salts.

As stated in the Background (section 0 of this CLH-report), the Specialised Experts concluded that the findings of the 28-day repeated dose toxicity study alone are limited and insufficient for the purpose of classification, and that the data on boric acid and borates have to be taken into consideration for read-across. Thus, the classification of sodium per(oxo)borates was based on read-across from boric acid/borates. However, it is not clear to the dossier submitter why the resulting classification of per(oxo)borates was Repr, 2; H361f and not category 1B similar to boric acid. In the current CLH-proposal of PBS-1 the assessment of adverse effects on sexual function and fertility is based on read-across of data from studies of oral exposure to boric acid and borate salts and data from the 28-day repeated dose toxicity study of PBS-4 is considered as supporting evidence in a weight of evidence assessment.

10.10.2.2 Read-across data on boric acid and borate salts from animal studies

The studies with boric acid and borate salts presented above (Table 17) have already been assessed and appointed key studies by the Committee for Risk Assessment (RAC) in 2014 (RAC opinion on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate). It was concluded by RAC that repeated dose toxicity studies and studies investigating reproductive toxicity performed with boric acid and borate salts in several species (mice, rats and dogs) clearly indicated that boron affects the testes, thus impairing fertility. There was no evidence that impaired fertility was secondary to other toxic effects.

Based on the results of a 2-year feeding study performed with boric acid in rats (Study Report, 1966d) and supported by a similar study with disodium tetraborate decahydrate (Study Report, 1967), the NOAEL for effects on fertility is 17.5 mg B/kg bw/day, while the LOAEL is 58.5 mg B/kg bw/day.

10.10.2.3 Comparison with data on hydrogen peroxide from animal studies

Available studies on reproductive toxicity of hydrogen peroxide are only described for comparison and to support the read-across hypothesis that it is boric acid that is responsible for the reproductive toxicity and that hydrogen peroxide, also being a degradation product of sodium per(oxo)borates, is not expected to contribute to reproductive toxicity. No guideline studies were available for a complete evaluation of reproductive toxicity of hydrogen peroxide and the available studies do not show any clear effects on sexual function and fertility. However, it is noted (and as also highlighted in the EU RAR of hydrogen peroxide (2003)), that the results of the presented studies cannot be considered as conclusive due to their various study design limitations (lack of control groups, low sample size) and very limited reporting. Nevertheless, hydrogen peroxide administration is expected to firstly cause local effects, nutritional disturbances and general toxicity in the tested animals (EU RAR, 2003).

Wales et al. (1959) administered 0.33, 1 or 3% H_2O_2 in drinking water to three groups of 12 male albino mice; the solutions were changed twice weekly. The mice from the high dose group refused to drink and after 5 days were removed from the experiment having lost about 20% of their body weight. The remaining two groups were each divided randomly into four subgroups of 3 animals: (1) two female mice were placed with each male of the subgroup on day 7 and again (with two other females) on day 28 of treatment; (2) and (3) two subgroups of males were placed with females on day 21: the animals in one of the groups continued on hydrogen peroxide, for the other group hydrogen peroxide was replaced with tap water (ensuring no consumption of hydrogen peroxide by the females); (4) the three male mice were killed on day 21 and the epididymal spermatozoa were examined. All female mice mated to treated males became pregnant within a few days and in each case healthy offspring were born in litters of normal size (data not shown). Pregnant mice that continued to consume 1% H_2O_2 in water up until near term showed a delay in parturition compared to dams using tap water (not clear if stat. sign.). No effects were seen on the concentration, morphology and motility of the mouse spermatozoa from the three mice in subgroup 4.

Similarly, three male albino rabbits were administered 0.33, 1 or 3% H_2O_2 in drinking water for 6 weeks, their semen being assessed at weekly intervals. No anomalies were detected in the collected sperm samples. Within the same study, Wales et al. (1959) also demonstrated in an *in vitro* experiment that rabbit semen was more resistant to exogenous hydrogen peroxide (the spermatozoa were not completely immobilised at 3000 ppm H_2O_2) than semen from bull, fowl, dog, ram, mouse and human. Rabbit seminal plasma had a particularly high capacity to decompose hydrogen peroxide, presumably due to a higher catalase content.

In a study conducted by Hankin (1958), three weanling Osborne-Mendel female rats were administered 0.45% H_2O_2 in drinking water for 5 months. After cessation of treatment, they were given tap-water and mated with untreated males. The author reported that normal litters were produced and that long-term treatment with hydrogen peroxide did not have an effect on reproduction in female rats. Six untreated male litter mates were divided in two groups, one receiving 0.45% H_2O_2 and the others tap water, for 9 months. A decrease in average body weight for the male rats administered H_2O_2 (411 g) as compared to the ones on tap water (521 g), was observed. Within 2 weeks after the cessation of treatment, the treated male rats began to gain weight.

A short description of an experimental study investigating the reproductive effects of hydrogen peroxide is enclosed in the EU RAR of hydrogen peroxide (2003). Male and female rats were administered hydrogen peroxide daily by gavage at doses of 1/10-1/5 LD_{50} (not specified) for 45 days (Antonova et al., 1974; as cited in the EU RAR, 2003). Females from the high dose group showed modifications of the oestrus cycle, while high dose group males showed reduced mobility of spermatozoa (not clear if stat. sign. different than controls), without an effect on the testis weight. In another experiment (not clear if performed by the same authors) male and female rats received daily doses of 0.005, 0.05, 0.5, 5, or 50 mg H_2O_2/kg bw by gavage for 6 months and were mated afterwards. Variations of the oestrus cycle in females were observed during

treatment at 0.50 and 50 mg/kg bw. Reduced mobility of spermatozoa in males was observed at 50 mg/kg. No changes were found in the morphology and weight of the testes. Among the high dose females, 3/9 produced litters, compared to 7/9 in the control group. In addition, litter size and bodyweight gain of the offspring of the high dose females were reduced as compared to controls (not clear if stat. sign.). Due to inadequate reporting, the study findings cannot be assessed.

10.10.2.4 Read-across from human data on boron compounds

No human data for the assessment of adverse effects of per(oxo)borates on sexual function and fertility were available.

Epidemiological studies investigating the effects of environmental and occupational boron exposure are available in the open literature. The studies published until March 2014 on the potential effects of boron on fertility were discussed in the RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. The data consist of epidemiological studies of males exposed to B environmentally and/or occupationally. The RAC concluded that the human studies show no clear evidence of adverse effects on male fertility by B. The exposure to B in these studies were well below the LOAELs for fertility reported from studies in animals. RAC pointed out that these epidemiologically studies had several study design limitations and should therefore be regarded as additional information.

Several studies have been published since March 2014, mainly investigating the occupational exposure to boron. In 2018, Duydu et al. (2018a) published a cross-sectional study evaluating the hormone levels and sperm parameters in male workers occupationally exposed to boron in Turkey. The authors found no association between blood B levels and semen parameters or hormone levels (FSH, LH, FSH). The mean blood B level in the extreme exposure group was 0.57 μg/g. An earlier study by the same research group was also negative at a lower maximum exposure level (Duydu et al. 2011). For comparison, Ku et al. (1993) reported mildly inhibited spermiation in a group of rats administered boric acid with mean serum boron level of 6.7 μg/g. The study performed by Duydu et al. (2018a) has been assessed by RAC in the Opinion on barium diboron tetraoxide (2020), where it was concluded that even if the epidemiological data show no clear effects on fertility and sexual function, they are not considered to contradict the effects seen in animal studies. Moreover, there is no evidence that the effects observed in animals are not relevant to humans.

Investigation of Y:X sperm ratio in occupationally exposed workers (Yalcin et al. 2019; Duydu et al. 2019; Robbins et al. 2008)

A recent study assessing the association between boron exposure and Y:X chromosome ratio in men occupationally exposed in a boric acid production zone in Turkey was published (Yalcin et al. 2019). The aim of this study was to either refute or confirm the inverse association between the high level of boron exposure and the decrease in Y:X sperm ratio in men from China, in a similar study conducted by Robbins et al. (2008). The semen samples assessed for the purpose of this recent study were obtained within the scope of an earlier project ("Boron Project – I"; 2008 – 2010) and cryopreserved in liquid nitrogen. The total number of remaining samples was 163, out of which 86 were from workers assigned to the exposed group (i.e. working in the boric acid production facilities) and 77 from workers assigned to the control group (i.e. working in the steam power plant, energy supply unit, demineralised water plant, mechanical workshop etc.). The biological samples were analysed for B content through inductively coupled plasma mass spectrometry, while the Y:X sperm ratio was determined using fluorescence *in situ* hybridisation (FISH).

The mean blood boron concentrations of the exposed workers were stat. sign. higher than the controls (141.55 ± 80.43 vs. 63.56 ± 43.89 ng B/g blood, respectively; $p<0.05$). Similarly, the semen B levels of the exposed workers were stat. sign. higher than of the control group (1703.42 ± 1895.09 vs. 1127.78 ± 1713.96 ng B/g semen, respectively; $p<0.05$). These stat. sign. increases in both semen and blood B levels were brought forward by Yalcin and colleagues as an argument to support the high level of daily B exposure (DBE) for the workers assigned in the exposure group. However, no DBE levels for the 86 exposed workers were provided in the study. In the previous work, the exposed group was divided into low, medium and high exposure groups with DBE levels of 7.39 ± 3.97, 11.02 ± 4.61 and 14.45 ± 6.57 mg B/day, respectively

(Duydu et al. 2011). Regarding the blood B levels of controls, it should be noted that the previous studies report levels below the limit of quantification (LOQ), i.e. 48.5 ng B/g blood (Duydu et al. 2011), whereas the blood B levels for the control group reported by Yalcin et al. (2019) are above the LOQ, i.e. 63.56 ± 43.89 ng B/g blood (see Table 22 below). The DBE levels seem to correlate with the blood B levels for both controls and exposed Turkish and Chinese workers. However, the blood B levels for controls and exposed groups seem to lead to significantly higher semen B concentrations in the Turkish workers, as compared to blood B levels of the Chinese workers that present approx. 3-fold increased levels (141.55 ± 80.43 vs. 515.4 ± 805.7 ng B/g blood for the exposed Turkish and Chinese workers, respectively; Table 22).

Yalcin and colleagues did not find a stat. sign. correlation (Pearson, $p>0.05$) between blood/semen B levels and Y:X sperm ratio in workers assigned to the exposed group, and no shift towards female babies at birth was observed (see Table 22). It was thus concluded by the authors that the presented results refute the positive association between high B exposure levels and decreased Y:X sperm ratios, as reported by Robbins et al. (2008).

However, the study conducted by Yalcin et al. (2019) presents several limitations which might have influenced the results. Firstly, even if the workers constituting the control group were not selected from boric acid and borate salts production areas, they were still exposed to B through drinking water from the central cafeteria and/or infirmary of the plant. The high B contamination (9.47 ± 0.18 mg B/L) of these water sources was not anticipated in the planning phase of the study and thus, this "background" exposure led to relatively high exposure of the control group. This is also reflected by the fact that the DBE levels for the Turkish control group were twice as high as for the Chinese control group that was not environmentally exposed (4.68 ± 1.63 vs. 2.3 ± 3.0 mg B/day; Table 25). Secondly, the exposure levels for the workers in the high exposure group were lower than the NOAEL set for male rat fertility. Assuming an average body weight of 70 kg, the high exposure group DBE levels can be converted to 0.2 ± 0.09 mg B/kg bw/day which is considerably lower than the NOAEL of 17.5 mg B/kg bw/day set for male rats.

Table 22: Characteristics of male workers assigned to the control and exposed groups

Number of participants	**Mean age ± SD (years)**	**Mean duration of employment ± SD (years)**	**Mean total daily B exposure ± SD (mg B/day)**	**Mean blood B level ± SD (ng B/g blood)**	**Mean semen B level ± SD (ng B/g semen)**	**Mean Y:X sperm ratio ± SD (FISH)**	**Boys at birth (%)**
Robbins et al. 2008 (China)							
n = 44 (controls)	31.3 ± 5.4	-	2.3 ± 3.0	45.5 ± 22.5	203.9 ± 105.7	0.99 ± 0.03	76.7
n = 39 (environmentally exposed)	30.0 ± 6.1	-	4.3 ± 3.1	109.11 ± 111.2	297.3 ± 273.0	0.96* ± 0.04	42.3
n = 63 (occupationally exposed)	31.2 ± 4.4	-	41.2 ± 37.4	515.4 ± 805.7	806.0 ± 612.6	0.93* ± 0.03	57.7
Yalcin et al. 2019 (Turkey)							
n = 77 (controls, however, environmentally exposed)	42.86 ± 5.06	18.02 ± 6.58	4.68 ± 1.63[#]	63.56 ± 43.89	1127.78 ± 1713.96	0.99 ± 0.03	48.5
n = 86 (occupationally and environmentally exposed)	42.45 ± 4.61	15.76 ± 7.16	7.39 ± 3.97 - 14.45 ± 6.57[#]	141.55 ± 80.43	1703.42 ± 1895.09	0.99 ± 0.02	54

FISH = Fluorescence in situ Hybridisation

* statistically significantly different from controls ($p<0.05$)

[#] the mean DBE levels were calculated and reported by the same authors in a previous publication (Duydu et al. 2011), where the group of exposed workers was further divided into low (DBE = 7.39 ± 3.97 mg B/day; n = 72), medium (DBE = 11.02 ± 4.61; n = 44) and high (DBE = 14.45 ± 6.57; n = 39) exposure groups.

Duydu et al. (2019) further investigated the Y:X chromosome sperm ratio in B-exposed workers from tw boron mining facilities located in Bandirma and Bigadic, Turkey. Similarly, the semen samples assessed for the purpose of this study were obtained within the scope of earlier projects, i.e. "Boron Project – I" (2008 – 2010), "Boron project – II" (2014 – 2017), and cryopreserved in liquid nitrogen. A total of 304 biological samples (i.e. blood, semen and urine) were collected and analysed for B content and Y:X sperm ratio using mass spectrometry and FISH, respectively. Based on the blood B content, the workers were assigned into 5 different groups: controls (< 50 ng B/g blood), low exposure (> 50 – 100 ng B/g blood), medium exposure (> 100 – 150 ng B/g blood), high exposure (> 150 – 400 ng B/g blood) and extreme exposure groups (> 400 ng B/g blood) (see Table 23). The measured B semen levels were 36, 21, 12.4, 5.1 and 3 times higher than the blood B levels of the controls, low, medium, high and extreme exposure groups, respectively, which indicates that the male reproductive organs represent an accumulation site for B. Overall, the authors did not find a stat. sign. ($p>0.05$) association between B exposure and Y:X sperm ratios, the mean Y:X sperm ratios of the different exposure groups were not stat. sign. different in pairwise comparisons ($p>0.05$), and no B-associated shift in sex ratios at birth towards female offspring was seen. A negative association ($p < 0.05$) between reported pesticide application (information gathered through questionnaires) and Y:X sperm ratio for the total study group was seen.

However, the study presents several limitations that might have impacted the reported results. The different exposure groups were assigned based on blood B concentrations instead of DBE. This is reflected by the very high semen B levels measured in the workers assigned to the control group. The highest individual semen B value attributed to the control group exceeds the highest measured individual value from the extreme exposure group, i.e. 8597 vs. 8086 ng B/g semen, respectively. In addition, the control group was environmentally exposed to B through drinking water. It is important to note the mean semen B levels show a very large variation (e.g. 1598.46 ± 2027.85 ng B/g semen), including in the control group (i.e. 1077.11 ± 1845.34 ng B/g semen), therefore adding an extra layer of difficulty for identifying potential effects. Moreover, based on an average body weight of 70 kg, the extreme DBE values calculated by this study will be 0.64 ± 0.26 mg B/kg bw/day, and the maximum individual DBE (i.e. 106.8 mg B/day) will be converted to 1.52 mg B/kg bw/day. As also indicated above, these values are considerably lower than the LOAEL for fertility in male rats (58.5 mg B/kg bw/day) and the NOAEL for rat fertility (i.e. 17.5 mg B/kg bw/day), set by the RAC (Opinion on boric acid, 2014).

Table 23: Boron concentrations in biological fluids, DBE and other characteristics of male workers assigned to the control and exposed groups of workers

Number of participants	**Mean age ± SD (years)**	**Mean duration of employment ± SD (years)**	**Mean total daily B exposure (DBE) ± SD (mg B/day)**	**Mean blood B level ± SD (ng B/g blood)**	**Mean semen B level ± SD (ng B/g semen)**	**Mean Y:X sperm ratio ± SD (FISH)**	**Boys at birth (%)**
Duydu et al. 2019 (Turkey)							
n = 38 (controls, environmentally exposed)	42. 89 ± 5.32 (26 – 48)	18.20 ± 6.49 (2 – 26)	4.57 ± 1.69 (0.20 – 7.54)	30.00 ± 10.12 (16.23 – 49.23)	1077.11 ± 1845.34 (52 – 8597)	0.98 ± 0.03 (0.85 – 1.02)	53.73
n = 60 (low exposure)	41.50 ± 6.05 (23 – 49)	15.79 ± 7.47 (0.17 – 23)	8.32 ± 5.71 (2.56 – 35.61)	76.00 ± 15.22 (50.17 – 99.91)	1598.46 ± 2027.85 (111 - 8615)	0.99 ± 0.02 (0.89 – 1.04)	45.95
n = 50 (medium exposure)	40.22 ± 6.09	15. 74 ± 7.51	14.81 ± 9.99 (2.56 – 47.18)	122.88 ± 15.34 (101.28 – 149.84)	1526.93 ± 1265.36 (189 – 4897)	0.99 ± 0.02 (0.94 – 1.09)	52.94

Number of participants	Mean age ± SD (years)	Mean duration of employment ± SD (years)	Mean total daily B exposure (DBE) ± SD (mg B/day)	Mean blood B level ± SD (ng B/g blood)	Mean semen B level ± SD (ng B/g semen)	Mean Y:X sperm ratio ± SD (FISH)	Boys at birth (%)
	(27 – 48)	(1 – 25)					
n = 87 (high exposure)	37.26 ± 7.46 (22 – 53)	9.15 ± 6.42 (0.5 – 23)	23.50 ± 13.94 (3.32 – 55.10)	247.37 ± 71.32 (150.99 – 391.92)	1259.65 ± 1446.11 (100 – 10542)	0.99 ± 0.02 (0.86 – 1.03)	55.63
n = 69 (extreme exposure)	36.61 ± 6.68 (23 – 50)	6.65 ± 4.84 (1 – 26)	44.91 ± 18.32 (7.95 – 106.79)	553.83 ± 149.52 (401.62 – 1099.93)	1643.23 ± 965.44 (188 – 8086)	0.99 ± 0.02 (0.95 – 1.06)	53.57

FISH = Fluorescence in situ Hybridisation

Other studies (Basaran et al. 2019; Bolt et al. 2020)

The DNA damage in lymphocytes, sperm and buccal cells of occupationally (n = 102), occupationally and environmentally (n = 110) exposed male workers from Bandirma and Bigadic, respectively, was analysed through comet and micronucleus assays (Basaran et al. 2019). The biological samples were obtained within the scope of "Boron project – II" (2014 – 2017). As also reported above, based on their blood B levels, the 212 participants were assigned into 5 different exposure groups: very low exposure (< 100 ng B/g blood), low exposure (101 – 150 ng B/g blood), medium exposure (151 – 450 ng B/g blood), high exposure (451 – 650 ng B/g blood) and overexposure groups (> 651 ng B/g blood) (see Table 24 below). The DBE and blood B levels corresponding to the 5 different exposure groups were not given in this article. Demographic information as well as information on potential confounders (alcohol, smoking, pesticide exposure) was gathered through a questionnaire. However, it was not further detailed if these potential confounders may have affected the study results. No stat. sign. increases in DNA damage in blood, sperm and buccal cells were observed between the B-exposed groups. No stat. sign. differences were found for neither alkaline nor neutral comet assay in the sperm cells. No correlations were seen between the measured blood B levels of the 5 different groups and tail intensity values of the sperm samples, lymphocyte samples, frequencies of micronucleus (MN), binucleated (BN), condensed chromatin (CC), karyorrhectic (KHC), karyolitic (KYL), pyknotic (PYC) and nuclear bud (NBUD) cells. Based upon these results, the authors concluded that extreme occupational exposure to B (i.e. > 651 ng b/g blood) does not induce DNA damage in lymphocytes, sperm or buccal cells. These results are in line with those reported previously by the same authors (Duydu et al. 2012; Basaran et al. 2012) and indicate that no statistically significantly increases in DNA-damage or changes on semen parameters were found in the B-exposed Turkish workers.

As also stated in the RAC Opinion on boric acid (2014), the Turkish studies were initially set up based on the assumption that different occupational categories would give groups with quantitatively different exposure to B. However, high B concentrations in drinking water resulted in high exposure also in the controls (without occupational exposure). Therefore, participants were grouped according to blood concentrations of B rather than based on occupational exposure, and it is not clear how well these groups were matched. Moreover, the group sizes for the very low, low and overexposure groups were limited (i.e. n = 12, 17 and 25, respectively), thus leading to low statistical power.

Table 24: Comet assay results in sperm samples, lymphocytes and buccal cells according to the different exposure groups

Number of participants	Mean tail intensity ± SD in sperm (alkaline comet assay) (%)	Mean tail intensity ± SD in sperm (neutral comet assay) (%)	Mean tail intensity ± SD in lymphocytes (comet assay) (%)	Mean micronucleus frequencies in buccal cells ± SD (micronucleus assay)
Basaran et al. 2019 (Turkey)				
n = 12 (very low exposure)	5.37 ± 1.63 (3.1 – 8.42)	6.31 ± 1.16 (5.13 – 8.49)	6.0 ± 2.69 (2.82 – 11.95)	3.54 ± 2.73* (1 – 9)
n = 17 (low exposure)	5.61 ± 1.2 (3.97 – 8.96)	6.09 ± 1.1 (4.22 – 7.81)	7.79 ± 5.18 (1.85 – 24.5)	5.13 ± 4.69 (0 – 19)
n = 108 (medium exposure)	6.03 ± 4.83 (2.6 – 49.71)	6.23 ± 1.36 (3.95 – 13.68)	7.5 ± 5.34 (1.64 – 27.47)	4.32 ± 3.82 (0 – 19)
n = 50 (high exposure)	5.55 ± 1.88 (2.81 – 13.73)	6.16 ± 1.26 (4.12 – 9.66)	8.7 ± 7.94 (1.38 – 36.0)	4.56 ± 3.61 (0 – 16)
n = 25 (extreme exposure)	5.36 ± 1.88 (3.04 – 12.32)	5.71 ± 0.97 (4.24 – 8.4)	5.04 ± 2.26 (0.65 – 10.08)	4.06 ± 2.93* (0 – 10)

Correlations of blood B levels and genotoxicity parameters									
Correlations between blood B level and:	Sperm DNA damage	Lymphocyte DNA damage	MN	BN	CC	KHC	KYL	PYC	NBUD
Pearson correlations	0.028	-0.024	0.023	-0.052	-0.156*	0.047	-0.045	0.058	0.023

*Statistically significant difference between groups ($p<0.05$); MN – micronucleus; BN – binucleated; CC – condensed chromatin; KHC – karyorrhectic; KYL – karyolitic; PYC – pyknotic; NBUD – nuclear bud.

A review paper on the effects of boron compounds on human reproduction was recently published (Bolt et al. 2020). The results of several reproductive toxicity studies in humans from Argentina, China and Turkey are detailed, discussed and the measured DBE levels are compared to the NOAELs for fertility and developmental toxicity established in rats (see Table 25 below). Based on these previously published epidemiological studies, Bolt and colleagues state that, compared to the B blood levels at the boron-related NOAELs for male fertility and for developmental toxicity in rats, the blood level means of the highest occupational exposure groups in China and in Turkey are lower by factors of > 4 and > 2, respectively. Part of the persons in the highest B exposure groups in China and in Turkey reach or exceed the experimental B blood levels at the NOAEL for developmental toxicity in rats. Part of the persons in the highest B exposure group in China reach or exceed the experimental B blood levels at the NOAEL for impaired male rat fertility. In this sense, the highest individual blood B level recorded from occupationally exposed workers from China is 3568.9 ng B/g blood, corresponding to a maximum individual DBE of 470 mg B/ day. The latter would thus correspond to a value of 6.7 mg B/kg bw/day if a 70 kg average body weight is assumed, that is considerably lower than the NOAEL for rat fertility of 17.5 mg B/kg bw/day. Moreover, the study conducted by Robbins et al. (2010) presents a series of limitations, such as the influence of different lifestyle factors, co-exposure to other minerals in relatively high concentrations (e.g. Mg) and fertility being assessed through questionnaires/interviews.

Table 25: Human and experimental exposure to boric acid/borate salts and associated blood boron levels [24]

[24] The experimental studies and some of the epidemiological studies presented in this table were included in the CLH-report for boric acid (2013) and have already been assessed by RAC (RAC Opinion on boric acid, 2014).

Human studies	Estimated DBE (mg/day)	Blood B levels (ng B/ g blood)
Bolt et al. 2020 (review)		
Turkey, ENV - High dose group I (Sayli et al. 1998; Korkmaz et al. 2007)	6.8 (1.8 – 2.3)	-
Argentina, ENV - Total cohort of mothers (Igra et al. 2016)	-	130* (0.73 – 610)*
Turkey, ENV + OCCUP - High exposure group (Tuccar et al. 1998)	14.5 (3.3 – 36)	220 (150 – 450)
Turkey, ENV - High exposure group (women) (Duydu et al. 2018b)	25 (10 – 58)	280 (152 – 980)
USA, OCCUP - High dust exposure group (Culver et al. 1994)	58	260 (up to max. 330)
China, OCCUP - High exposure group (Robbins et al. 2010; Scialli et al. 2010 - review)	37 (2.3 – 470)	500 (20 – 3600)
Turkey, OCCUP - Extreme exposure group (Duydu et al. 2019)	45 (8.0 – 200)	550 (400 – 2000)
NOAEL for male rat fertility (mg/kg bw/day) (Weir et al. 1972)	17.5	2300#
NOAEL for developmental toxicity in rats (mg/kg bw/day) (Price et al. 1996)	9.6	1270

ENV = environmental exposure, OCCUP = occupational exposure;
*Assuming equal distribution of B between serum and blood cells;
#Calculated by Bolt et al. (2020)

Furthermore, Bolt and colleagues state that human B exposures, even in the highest exposed cohorts, are still too low to reach the blood concentrations in order to exert toxic effects on reproduction. Thus, under the most extreme occupational exposure reported, concentrations of B within the human body that are reprotoxic cannot be reached. The authors conclude that based on these epidemiological data, the current categorisation of inorganic boron compounds should be reconsidered.

However, it should be kept in mind that no studies on effects on fertility and sexual function in humans are available at exposure and/or blood B levels corresponding to the animal LOAELs. Assuming a blood density of 1060 kg/m^3 and taking into account the uncertainty factors for inter-species and intra-human variability (EFSA 2012), the LOAEL of 58.5 mg B/kg bw/day set for rat fertility would correspond to approx. 7360 ng B/g blood in humans; the highest individual blood B level recorded in human samples was 3568.9 ng B/g blood (Robbins et al. 2010). Furthermore, there are no available data indicating that boron toxicokinetics from animals would not be relevant for humans. Finally, the available epidemiological studies showing no effects on fertility and semen parameters, FSH, LH and testosterone levels at DBE levels that were substantially below the LOAELs and even NOAELs from corresponding animal studies, do not contradict the experimental data showing clear effects of impaired fertility in male rats.

Conclusion on human data

The available epidemiological studies did not show clear boron-induced adverse effects on sexual function and fertility. As described above, the studies had several methodological limitations and were designed to mostly investigate male fertility. Other limitations are generally small sample sizes and/or decreased participation rates. It should also be noted that the estimated human exposure levels (DBE) of the high,

extreme and overexposure groups in these studies were considerably lower than the NOAELs and LOAELs reported for rat fertility. No studies on effects on fertility and sexual function in humans are available at DBE levels corresponding to the animal LOAELs.

Hence, as was also highlighted by the RAC (Opinions on boric acid (2014), disodium octaborate anhydrate (2014) and disodium octaborate tetraborate (2014)) it is concluded that the available human data on fertility and sexual function do not contradict the animal data. The human data are therefore considered as additional information.

Overall, the available human data do not contradict the experimental data seen across several species (mice, rats and dogs) and give no evidence to support that the effects seen in animals are not relevant for humans.

10.10.3 Comparison with the CLP criteria

Sodium peroxometaborate has a harmonised classification as Repr. 2; H361f. **A change to the classification is proposed**.

No guideline reproductive toxicity study with per(oxo)borates was available for the assessment of adverse effects on sexual function and fertility. The 28-day limit test (OECD TG 407; Study report, 1989) performed with PBS-4 in rats showed effects such as decreased absolute testes weight, testicular focal tubular atrophy and inhibition of spermiation at the only administered dose of 1000 mg/kg bw/day (eq. to 70 mg B/kg bw/day), in the absence of any histological signs of toxicity. However, it has to be noted that these effects were seen in the presence of general toxicity (stat. sign. reduced body weight and food consumption) in the exposed group and that the method used for histological examination (fixation of tissues with formalin) led to cellular shrinkage, thus only allowing for the detection of major effects. Due to study design limitations (e.g. only one dose level, few animals) and poor reporting, this study alone is considered insufficient for the purpose of classification. As the common view that per(oxo)borates are expected to have the same effects as boric acid was already expressed in 2005 at the TC C&L meeting (ECBI/60/05 Rev. 3), data from studies of oral exposure to boric acid and borate salts are therefore read-across in order to support the assessment of sexual function and fertility of per(oxo)borates. Their toxicokinetic and toxicological properties after oral exposure are expected to be similar to those of boric acid and borates, on a B-equivalents basis.

The studies performed with boric acid and borate salts have been previously assessed by the RAC (RAC Opinions on boric acid; disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014 and on barium diboron tetraoxide, 2020). It was concluded by RAC that the repeated dose and reproductive toxicity studies in rats, mice and dogs clearly show that boron impairs fertility through effects on the testes. The observed effects were consistent throughout the different species and there were no indications that impaired fertility was secondary to other toxic effects.

In conclusion, the overall weight of evidence of available information, a large body of evidence from read-across data on animal studies on boric acid and borate salts and supporting evidence from read-across of experimental data on PBS-4 coming from the 28-day limit test, provide clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects. Thus, classification of sodium peroxometaborate as **Repr. 1B, H360F** is warranted.

Classification as Repr. 1A is not appropriate as it should be based on human data. No human data assessing the reproductive toxicity on sodium per(oxo)borates were available. The available epidemiological data on boric acid and borate salts do not provide clear evidence of adverse effects on sexual function and fertility at boron exposure levels that were well below the LOAELs from corresponding animal studies. The overall negative human data do not contradict the animal data, and there is no evidence to indicate that the observed effects in animal studies are not relevant for humans.

Classification in Repr. 2 is not justified since the evidence for adverse effects on sexual function and fertility based on read-across from boric acid, with supporting evidence from read-across data on PBS-4, is considered to be clear and not some evidence. Moreover, the read-across from boric acid is considered robust and appropriate for the endpoint and applicable for sodium peroxometaborate.

Specific concentration limits for adverse effects on sexual function and fertility

As detailed in the proposal for SCLs for sodium per(oxo)borates drafted by Austria and The Netherlands, the SCLs for fertility of the per(oxo)borates (i.e. 9% for PBS-1 and 14% for PBS-4) were calculated based on the old SCLs for boric acid (i.e. 5.5%) that were set by using the approach proposed by BauA (1998), and corrected for the difference in boron content (ECBI/38/03 Add.17).

Since the per(oxo)borates covered by the present proposal was subject to harmonised classification, new recommendations on how to derive concentration limits for reproductive toxicity have been agreed upon (CLP Guidance, 2017). Section VI.5.1.1.4 of the CLP Guidance (2017) states that "*Several other options for a method for determining SCLs were discussed including a method that was used by the TC C&L in a limited number of cases in the past. This method is based on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and 416. This method would result in an individual SCL for each substance. This would indicate a precision that cannot be expected from standard reproduction studies. Also, this would result in an SCL for most substances and in a GCL for only some substances. Therefore, this method was not considered*".
Moreover, in 2019, the RAC has concluded on the harmonisation of GCL of 0.3% w/w for boric acid and six borates that have a harmonised classification as Repr. 1B (RAC Opinion, 2019).

According to the CLP Guidance (2017), concentration limits for effects on sexual function and fertility are derived by calculating the reproductive toxicity dose descriptor, i.e. ED10 (the dose level at which a change of 10% compared to the concurrent control group is observed). It should be noted that, the available data on per(oxo)borates were not robust enough in order to derive the ED10, and thus read-across data on boric acid and borate salts were used. According to the RAC (RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014), testes atrophy was identified as the most sensitive effect on fertility in rats, based upon a 2-year feeding study with boric acid (Weir 1966, as cited in the CLH-report for boric acid, 2013). There is no reason to reconsider this conclusion based on the human information published since 2014. At the end of the treatment (24 months), the incidence of testicular atrophy was 30%, 10%, 40% and 100% at 0, 5.9, 17.5 and 58.5 mg B/kg bw/day, respectively. Based upon these results, the ED10 would therefore be 17.5 mg B/kg bw/day.

Correcting for the percentage of boron, the ED10 of 17.5 mg B/kg bw/day would correspond to 135 mg sodium peroxometaborate (see Table 33). According to section 3.7.2.6.3 of the CLP Guidance (2017), a substance with a 4 < ED10 < 400 mg/kg bw/day belongs to the medium potency group. None of the modifying factors related to type or severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bio-accumulation applies for sodium peroxometaborate.

The **medium potency group with a GCL of 0.3% w/w** should therefore be assigned to sodium peroxometaborate.

10.10.4 Adverse effects on development

Table 26: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group[25]	Test substance, dose levels duration of exposure	Results	Reference
Sodium perborate tetrahydrate (PBS-4)			
OECD TG 414 (Prenatal developmental toxicity study), carried out according to GLP guidelines Rat (Sprague-Dawley), females n = 25/dose group Reliability: 1 (reliable without restriction)	Test material: sodium perborate tetrahydrate (PBS-4) Purity: unknown Vehicle: 1% aqueous methyl cellulose <u>Doses</u>: 0, 100, 300 and 1000 mg/kg bw/day (eq. to 0, 7, 21 and 70 mg B/kg bw/day, respectively) <u>Exposure:</u> GD 6-15, via oral gavage	**NOAEL for maternal toxicity** = 100 mg PBS-4/kg bw/day (eq. to 7 mg B/kg bw/day) **LOAEL for maternal toxicity** (decreased bw, bw gain and food intake) = 300 mg PBS-4/kg bw/day (eq. to 21 B/kg bw/day) **NOAEL for developmental toxicity** = 100 mg PBS-4/kg bw/day (eq. to 7 mg B/kg bw/day) **LOAEL for developmental toxicity** (increased post-implantation loss, increased number of resorptions, decreased number of live foetuses, decreased foetal weight) = 300 mg PBS-4/kg bw/day (eq. to 21 B/kg bw/day) **Maternal effects:** - at 300 and 1000 mg /kg bw/day: stat. sign. ($p<0.05$) reduced bw during GD 15-20, (on GD 20: 369.4 g and 366 g, respectively, vs. 410.9 g in controls) - at 300 and 1000 mg /kg bw/day: stat. sign. ($p<0.05$) reduced bw gain during GD 1-20 (119.2 g and 110.89 g, respectively, vs. 153.81 g in controls) - the body weight gain excluding gravid uterine weight was stat. sign ($p<0.05$) decreased only at the mid dose level (67.2g, 59.7 g, 50.9* g and 55.1 g at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - no clinical signs, behavioural changes, deaths or pathological findings were reported at any of the dose levels - 21/25, 20/25, 20/25 and 19/25 dams gravid at 0, 100, 300 and 100 mg /kg bw/day, respectively (2 and 1 dams with complete resorptions at 300 and 1000 mg/kg bw, respectively) **Foetal effects**: - at 1000 mg/kg bw/day stat. sign. ($p<0.05$) increased number of resorptions/litter, within the HCD range (1.53 vs. 0.43 in controls; HCD: 0.7 ± 1.1) - at 300 and 1000 mg /kg bw/day stat. sign. ($p<0.05$) decreased live foetus weight (3.28 g and 2.4 g, respectively, vs. 3.69 g in controls; outside of the HCD: 3.7 g ± 0.4) - increased post-implantation loss, stat. sign. ($p<0.05$) at the high dose level (2.91%, 2.39%, 13.54%, 15.2%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - decreased number of live foetuses, stat. sign. ($p<0.05$) at mid and high dose levels (311, 295, 256*, 242* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - dose-dependently but not stat. sign decreased number of live	Study Report, 1995b EU RAR (2007) See also Annex I to the CLH-report

[25] Where applicable and unless stated otherwise, the reliability scores of the studies presented in Table 26 are according to the publicly disseminated REACH Registration dossier for EC no. 234-390-0, available at https://www.echa.europa.eu/en/web/guest/registration-dossier/-/registered-dossier/13523/7/9/3

Method, guideline, deviations if any, species, strain, sex, no/group[25]	Test substance, dose levels duration of exposure	Results	Reference
		foetuses/litter (14.8, 14.75, 14.2, 13.4 at 0, 100, 300 and 1000 mg/kg bw/day, respectively; HCD:14.4 ± 3.3) - dose-dependently reduced litter weight, stat. sign. ($p<0.05$) at the high dose level (54.97, 52.62, 46.49, 32.52* g at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - at 100 mg/kg bw/day external malformations were seen in 6 plurimalformed foetuses: ablepharia (5), acrania (6), exencephaly (6), exophthalmia (3), macroglossia (6), cleft palate (5), cleft lip (2), facial cleft (1) **Skeletal and cranial effects:** - reduced rib XIII (uni- and bilateral) in 0.64%, 0%, 3% and 9%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively - rib XII/XIII in 0.64%, 2%, 0.77% and 11.38%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively - stat. sign. ($p<0.05$) increased incidences of wavy rib at the mid and high dose levels (1.30%, .70%, 13.20%* and 7.30%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - in controls, 1 foetus with scoliosis and bifurcated 8th rib - at 1000 mg/kg bw/day, 2 foetuses from 2 different litters with fused ribs - dose-dependently and stat. sign ($p<0.05$) increased incidences of supraoccipital incomplete ossification at all dose levels (26.92%, 38.89%*, 45.73%* and 76.42* at 0, 100, 300 and 1000 mg/kg bw/day, respectively), outside of the HCD range (0 – 35.90%) - dose-dependently and stat. sign ($p<0.05$) increased incidences of unossified 5th sternbrae at all dose levels (35%, 60.42%*, 70.50%* and 100%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively), outside of the HCD range (19.91 – 51.16%) - dose-dependently and stat. sign ($p<0.05$) increased incidences of unossified 6th sternbrae at all dose levels (25%, 34%*, 54.20%* and 89.43%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - dose-dependently increased incidences of incomplete ossification of 4th sternbrae (7%, 11.11%, 15.50%* and 48.78%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) **Visceral effects:** - at 1000 mg /kg bw/day only, cardiovascular effects in 5.88% (vascular ring, displaced or double aortic arch, displaced botallus duct), malformations of the eyes in 3.36% (anophthalmia or microphthalmia) and CNS effects (enlarged lateral ventricles of the brain) in 1.68% of the foetuses - stat. sign. ($p<0.05$) increased incidences of dilated or convoluted ureter at all dose levels (28.40%, 44.82%*, 42%* and 79%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - stat. sign. ($p<0.05$) increased incidences of dilated renal pelvis at all dose levels (4.51%, 17.24%*, 11%* and 38.60%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively) - absence of renal papillae was stat. sign. ($p<0.05$) increased only at the high dose level (0.64%, 0.70%, 0.78% and 6.72%* at 0, 100, 300 and 1000 mg/kg bw/day, respectively)	

Table 27: Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Mother-child cohort study (prospective)	Boron environmental exposure via drinking water of pregnant women residing in Northern Argentina	n = 194 mothers 1-3 samples of serum, whole blood and urine was taken during pregnancy. Infant weight, length and head circumference was measured at birth.	Serum B > 80 µg/L were found to be inversely associated with birth length. An increase in the serum B of 100 µg/L in the last trimester was associated with a decrease of 0.9 cm ($p<0.05$) in new-born length and a decrease of 120g ($p<0.05$) in new-born weight.	Igra et al. 2016
Epidemiological study (retrospective)	Boron, environmental exposure	Females residing in Marmara, Turkey. n: 190 Pregnancy outcomes (sex ratio, preterm birth, birth weights, congenital anomalies, abortions, miscarriage, stillbirth, early neonatal death, neonatal death and infant death) determined based on questionnaire. Boron blood levels at time of pregnancy were estimated from levels at time of study.	No boron-mediated differences on pregnancy outcomes was detected between exposure groups (low exposure n=143; medium exposure n=29 and high exposure n=27) Estimated blood boron levels ranged from 151.81 to 957.66 (mean 274.58) ng/g in the high exposure group.	Duydu et al., 2018b
Mother-child cohort study (prospective, follow-up until 6 months of age)	Boron, environmental exposure via drinking water of pregnant women residing in Northern Argentina	n = 194 mothers, 120 infants Infant urine and whole blood were collected at the two follow-ups after birth (at 3 and 6 months). Infant weight, length and head circumference were measured at the two follow-ups after birth. This study is a follow-up of the same mother-child cohort as was investigated by Igra et al. 2016.	At 0 – 3 months: each doubling of B levels in infant urine was associated with a decrease in bodyweight of 141 g ($p<0.05$) and a decrease in infant head circumference of 0.39 cm ($p<0.05$). At 3 – 6 months: each doubling of B in infant urine was associated with a 200 g ($p<0.05$) in infant weight and decrease of 0.57 cm ($p<0.05$) in infant length.	Hjelm et al. 2019

Table 28: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No other relevant studies for the assessment of developmental toxicity were available				

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

10.10.5.1 Read-across data on PBS-4 from animal studies

A prenatal developmental toxicity study (OECD TG 414, GLP; Study Report, 1995b) performed in rats with PBS-4 was available in the registration dossier of EC No. 234-390-0 (perboric acid, sodium salt). Female rats (n = 25/dose group) were administered 0, 100, 300 and 1000 mg PBS-4/kg bw/day (eq. to 0, 7, 21 and 70 mg B/kg bw/day, respectively) in 1% aqueous methyl cellulose during GD 6-15, via oral gavage. The dams were scheduled for necropsy and caesarean section on GD 20. No clinical signs, behavioural changes, pathological findings or maternal deaths were reported. Maternal effects consisted of dose-dependently and stat. sign. ($p<0.05$) reduced bodyweight and bodyweight gain at 300 and 1000 mg/kg bw/day. These effects cannot however be considered as clear signs of maternal toxicity since the reduced weight gain may be related to reduced foetal weights and the resorptions detected. Moreover, no effects can be seen on body weight gain of the females from the lowest and highest dose levels by excluding the gravid uterine weight (see Table 29 below). The NOAEL for maternal toxicity was set by the authors of the study at 100 mg/kg bw/day.

A dose-dependent increase in post-implantation loss that was stat. sign. ($p<0.05$) at 300 and 1000 mg/kg bw/day was seen. The total number of resorptions per litter was stat. sign. ($p<0.05$) increased at 1000 mg/kg bw/day and within the HCD range (1.53 vs. 0.43; HCD: 0.7 ± 1.1). A dose-dependent decrease in the number of live foetuses that was stat. sign. ($p<0.05$) at 300 and 1000 mg/kg bw/day was reported. The number of live foetuses/litter was also dose-dependently but not stat. sign. ($p>0.05$) decreased, however within the HCD range. Dose-dependent decreases in the live foetal weight ($p<0.05$ at 300 and 1000 mg/kg bw/day) and litter weight ($p<0.05$ at 1000 mg/kg bw/day; lower than the HCD foetal weight) were also seen.
According to OECD GD 43, if historical control data are used, the most appropriate of these are from studies conducted in the same laboratory, within a reasonable amount of time prior to the study being interpreted (e.g., ± 2 years) in order to avoid genetic drift in the laboratory animal population, and under the same study conditions (e.g., identical species, strain, source, age, vehicle, route and duration of administration, technical personnel, etc.). In the study report for OECD TG 414 study, it is stated that the historical control data is based on 2146 foetuses during years 1992-1993. Thus, the time prior to the study is appropriate. However, with regards to study conditions (e.g., laboratory, identical species, strain, source, age, vehicle, route and duration of administration, technical personnel, etc) the dossier submitter have no information to enable assessment of the relevance.

At 100 mg/kg bw/day, six foetuses (2% vs. 0% in controls; $p<0.05$) with external malformations (ablepharia, acrania, exopthalmia, macroglossia, cleft palate, cleft lip and facial cleft) were found. The authors of the study considered this finding as incidental due to the lack of dose-response and since these effects were present only in 2 litters and not at the other dose levels, where different types of malformations were seen. This can also be supported by the fact that with other boron compounds such as boric acid and borates which have very similar developmental effects to sodium per(oxo)borates, these types of external malformations were not seen. Since the malformations seen at the mid and high dose levels are of a different nature, the assumption of a syndrome of genetic origin was proposed and discussed in the EU RAR (2007). However, no information on the mating male was available to support this assumption. These external malformations were not taken into account by the study authors when deriving the NOAEL for developmental effects, i.e. 100 mg/kg bw/day.

Malformations of the cardio-vascular system (displaced or double aortic arch, displaced botallus duct and vascular ring) and of the eyes (anophthalmia or microphthalmia) were seen in 5.88% and 3.36% vs. 0% in controls, respectively, of the foetuses at 1000 mg/kg bw/day (stat. sign; $p<0.05$; no HCD provided for these specific developmental effects). Effects on the kidneys such as dilated renal pelvis and absence of renal papillae were reported at all dose levels. The CNS effects (enlarged lateral ventricles of the brain) seen at 1000 mg/kg bw/day (1.68% vs. 0% in controls) were considered as visceral anomalies by the authors of the study. According to the RAC opinion on boric acid (2014), the enlargement of the lateral ventricles in the brain is considered a common malformation of boric acid administration.

A dose-related effect on the ossification and skeletal system was seen. The reported effects consisted of dose-dependently increased incidences of supraoccipital incomplete ossification, stat. sign. ($p<0.05$) and outside of the HCD range in all treated groups (26.92%, 38.89%, 45.73% and 76.42% at 0, 100, 300 and 1000 mg/kg bw, respectively; 0 - 35.90% HCD; stat. sign. $p<0.05$) and incomplete ossification of head and hyoid bone (at all dose levels), pelvic girdle and pubis (at the mid- and high-dose levels) and unossified vertebrae (at the high dose level). The incidences of unossified 5th sternbrae were stat. sign. ($p<0.05$) and dose-dependently increased and outside of the HCD range in all treated dose groups (60.42%, 70.50% and 100 % at 100, 300 and 1000 mg/kg bw, respectively, vs. 35% in controls; 19.910 – 51.160 HCD; stat. sign. $p<0.05$). Similarly, the incidences of unossified 6th sternbrae were dose-dependently and stat. sign ($p<0.05$) increased (34%, 54.20%, 89.43% at 100, 300 and 1000 mg/kg bw, respectively, vs. 25% in controls; no HCD provided). A dose-dependent increase in the incidences of incomplete ossification of the 4th sternbrae was also reported (11.11%, 15.50% and 48.78% at 100, 300 and 1000 mg/kg bw, respectively, vs. 7% in controls; no HCD provided). Wavy ribs were reported in 1.30%, 0.70%, 13.20% and 7.30% of the examined foetuses at 0, 100, 300 and 1000 mg/kg bw, respectively. Rib XII/XIII, reported as a skeletal variation, was seen in 0.64%, 2%, 0.80% and 11.38% of the foetuses at 0, 100, 300 and 1000 mg/kg bw, respectively. Since this effect was not described nor highlighted in the study summary, the significance of this skeletal variation remains unclear. Short rib XIII (uni- or bilateral) was seen in 0.6%, 0%, 3% and 9% of the foetuses at 0, 100, 300 and 1000 mg/kg bw, respectively.

For comparison and in support of the findings in the PNDT study of PBS-4, the RAC has previously concluded that the most sensitive effect on development by boric acid and borates is the increased incidence of agenesis or shortening of rib XIII (RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate, 2014). This effect alongside other dose-dependently increased incidences of skeletal effects were reported in the PNDT study performed with PBS-4. Also, very similar effects for borates and per(oxo)borates can be seen in the craniofacial (effects on the eyes: micro- or anophthalmia), kidney (hypoplasia, hydronephrosis, dilated renal pelvis, absence of renal papillae) and cardiovascular (displaced or double aortic arch) malformations, but also cerebral effects (enlarged lateral ventricles of the brain). Therefore, it can be stated that the embryotoxic effects of PBS-4 are due to the boron moiety, as the malformations observed at the mid and high dose levels are similar to those induced by boric acid and borates. Divergence of effects (i.e. increased foetal lethality) may be explained by differences in administration (oral gavage, feed) and absorption.

Table 29: Results of the prenatal developmental toxicity study (OECD TG 414; GLP) with PBS-4 in rats (Study Report, 1995b; EU RAR, 2007)

	HCD on 2146 foetuses (1992-1993)	**Dose levels (mg/kg bw/day)**			
		0	**100**	**300**	**1000**
No. of pregnant females	-	21	20	20[&]	19[#]
No. of litters	-	21	20	18	18
Maternal body weight (g; group mean and gain)					
GD 6	-	288.7	283.6	277.6	282.2
GD 15	-	333.3	329.5	315.8*	314.3*
GD 20	-	410.9	400.3	369.4*	366.0*
GD 0-20, gain	-	153.8	144.5	119.2*	110.9*
GD 0-20 (gain excluding gravid uterine weight)	-	67.2	59.7	50.9*	55.1
Reproductive parameters					
Gravid uterine weight (g)	-	86.6	84.8	68.3*	55.8*
No. dams with early resorptions	-	7/21	7/20	7/20	13*/19

		HCD on 2146 foetuses (1992-1993)	Dose levels (mg/kg bw/day)			
			0	100	300	1000
No. dams with late resorptions		-	1/21	0/20	0/20	2/19
No. of implantations/no. of corpora lutea		-	320/369	301/345	272/332	272*/352
No. of early resorptions		-	8	7	12	24*
Total no. of resorptions		-	9	7	16*	29*
Post-implantation loss (%)		-	2.91	2.39	13.54*	15.20*
Foetal parameters						
No. of live foetuses		-	311	295	256*	242*
No. of dead foetuses		-	0	0	0	1
No. of live foetuses/litter		14.4 ± 3.3	14.80	14.75	14.22	13.44
No. of resorptions/litter		0.7 ± 1.1	0.43	0.35	0.80	1.53*
Live foetus weight (g)		3.7 ± 0.4	3.69	3.57	3.28*	2.4*
Live litter weight (g)		53.9	54.97	52.62	46.49	32.52*
Placenta weight (g)		0.5 ± 0.08	0.5	0.51	0.48	0.37*
Malformations, abnormalities and variations as reported by the study authors (Study Report, 1995b)						
No. of foetuses examined for skeletal/visceral		-	156/155	144/145	129/127	123/119
Malformations (%)	External	0 – 0.120	0	2*[a]	0	0
	Skeletal	0	0.64[b]	0	0	1.62[b]
	Overall visceral, including:	0.020	0	0	0	9.20*[c]
	Cardio-vascular effects	-	0	0	0	5.88*[c]
	Eye effects	-	0	0	0	3.36[c]
Abnormalities (%)	External	0.115	0	0	0	0
	Overall skeletal, including:					
	Wavy rib ([d])	-	1.30	0.70	13.20*	7.30*
	Supraoccipital incomplete ossification ([e])	0 – 35.90	26.92	38.89*	45.73*	76.42*
	Overall visceral, including:	0.415	0.64	1.37	1.57	7.56*[f]
	Enlarged lateral ventricles of the brain	-	0	0	0	1.68[f]
	Absence of renal papillae	-	0.64	0.70	0.78	6.72*[f]
Variations (%)	**Overall skeletal, including:**					
	Reduced rib XIII unilateral ([g])	-	0	0	1.55	4.07
	Reduced rib XIII bilateral ([g])	-	0.64	0	1.55	4.88
	Ribs XIII punctate unilateral ([h])	-	0.64	2.08	0	14.63*
	Ribs XIII punctate bilateral ([h])	-	1.28	1.39	2.33	6.50

		HCD on 2146 foetuses (1992-1993)	Dose levels (mg/kg bw/day)			
			0	100	300	1000
	Ribs XII/XIII (i)	-	0.64	2.1	0.78	11.38*
	Ribs XIII/XIV ([j])	-	1.92	0.69	0	0
	Ribs XIV punctate unilateral ([k])	-	1.92	0.69	0	0
	Unossified 5th sternbrae	19.910 – 51.160	35	60.42*	70.50*	100*
	Unossified 6th sternbrae	-	25	34	54.20*	89.43*
	Incomplete ossification of 4th sternbrae	-	7	11.11	15.50*	48.78*
	Overall visceral, including:					
	Dilated or convoluted ureter	-	28.40	44.82*	42*	79*
	Dilated renal pelvis	-	4.51	17.24*	11*	38.60*

[&] Two dams with complete resorptions

[#] One dam with complete resorptions

* Statistically significant effect $p < 0.05$; statistical analysis by Chi-squared and Fischer's exact test or ANOVA parametric or nonparametric, where applicable, compared to controls

[a] 6 plurimalformed foetuses (of 295 total foetuses): ablepharia (5), acrania (6), exencephaly (6), exophthalmia (3), macroglossia (6), cleft palate (5), cleft lip (2), facial cleft(1)

[b] 1 foetus with scoliosis and bifurcated 8th rib (controls); 2 foetuses of 2 different litters with fused ribs (1000 mg/kg bw/day)

[c] 11 foetuses: microphthalmia or anophthalmia (4), vascular ring (2), bilateral hydronephrosis (1), displaced or double aortic arch (3), displaced botallus duct (2), hypoplasia of kidney (1); the 7 foetuses with cardio-vascular effects were from 5 different litters; the 4 foetuses with eye effects were from 3 different litters

[d] wavy rib: 2 (from 2 different litters), 1, 17 (from 5 different litters) and 9 (from 3 different litters) foetuses at **0, 100, 300 and 1000 mg/kg bw/day, respectively**

[e] Supraoccipital incomplete ossification in 251 foetuses: 42 (from 14 litters), 56 (from 20 litters), 59 (from 15 litters) and 94 (from 16 litters) at 0, 100, 300 and 1000 mg/kg bw/day, respectively

[f] 9 foetuses: dilated lateral cerebral ventricles (2 foetuses of the same litter), absence of renal papillae (8 foetuses of 4 different litters), hemorrhagic kidney (1)

[g] Reduced rib XIII unilateral in 0, 0, 2 and 5 foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively
Reduced rib XIII bilateral in 1, 0, 2 and 6 foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively

[h] Ribs XIII punctate unilateral in in 1, 3, 0 and 18 foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively
Ribs XIII punctate bilateral in 2, 2, 3 and 8 at 0, 100, 300 and 1000 mg/kg bw/day, respectively

[i] Ribs XII/XIII in 1, 3 (from the same litter), 1 and 14 (from 10 different litters) foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively

[j] Ribs XIII/XIV in 3, 1, 0 and 0 foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively

[k] Ribs XIV punctate unilateral in 3, 1, 0 and 0 foetuses at 0, 100, 300 and 1000 mg/kg bw/day, respectively

10.10.5.2 Human data on boron compounds

No human data for the assessment of adverse effects of per(oxo)borates on development were available. Epidemiological studies available on the potential effects of boron exposure have therefore been included in the weight of evidence assessment for the conclusion on classification and consideration of human relevance. This is justified on the basis of hydrolytic and toxicokinetic behaviour of per(oxo)borates.

Epidemiological studies on possible adverse pregnancy outcomes in female workers, or females environmentally exposed to boron via food or drinking water were not available in 2014, and such data was therefore not discussed in the 2014 RAC opinions on boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate.

In 2016, Igra et al. has published a prospective mother-child cohort study investigating environmental exposure of boron through drinking water on pregnant women from Argentina. A statistically significant inverse association was found between serum blood boron levels >80 µg/L and birth length (newborns were

0.7 cm shorter per each 100 µg/L increase in serum boron levels). Moreover, this association was more pronounced (increased by 28%) during the third trimester of pregnancy, when the highest serum boron concentrations were the highest (0.73 – 447 µg/L). However, it cannot be excluded that the observed effects can be the result of a combined exposure to lithium.

In 2018, Duydu et al. (2018b) published a retrospective cohort study investigating birth weights of newborns and pregnancy outcomes of females environmentally exposed to boron via drinking water in Turkey. The study had several limitations (self-reporting, low sample size, boron levels measured only after birth). For comparison, the mean blood boron level at the rat developmental NOAEL (9.6 mg B/kg bw/day) was 1.3 µg B/g blood (Price et al. 1996a, 1997), whereas the mean blood boron concentration in the high exposure group from the epidemiological study was 0.27 µg B/g blood.

These two epidemiological studies have been assessed by RAC in the Opinion on barium diboron tetraoxide (2020). The RAC concluded that even if these studies show no clear effects on development of the offspring, there is no evidence that the effects observed in animals are not relevant to humans.

In 2019, Hjelm et al. have published a follow-up study of the mother-child cohort (n = 194) investigated previously by Igra et al. (2016). In order to evaluate the potential impact of pre- and post-natal boron exposure on infant growth, samples of maternal drinking water, placenta, urine, whole blood and breast milk were collected. Both maternal and infant samples were analysed for arsenic and lithium that were also present in the drinking water. This study has not been assessed by RAC previously in the Opinion on barium diboron tetraoxide (2020).

Boron concentrations in drinking water ranged between 377 – 16076 µg B/L (median: 5863 µg B/L; n = 114). As shown in Table 30, concentrations of B in maternal serum were similar to those in whole blood (third trimester, GW 28-39), both showing a moderate correlation with concentrations in drinking water (rs = 0.28; p = 0.0001). Maternal blood B levels markedly increased from late pregnancy, GW 33 on average (median value: 140 µg B/L, n = 78), to the first follow-up post-partum (median values: 263 µg B/L, n = 108). A strong correlation between B in cord blood and cord serum was also seen (rs = 0.82). The authors suggested that the high B concentrations in cord serum (median: 196 µg B/L, i.e. just in between the concentration in maternal serum in GW 33 and that at the first follow-up about 50 days post-partum) is indicative of a rapid transfer to the foetus. The correlation of B concentrations in cord blood with those in placenta (rs = 0.73; p < 0.001) was stronger than the correlation with concentrations in maternal blood at GW 33 (rs = 0.41; p < 0.001). Boron concentrations in breast milk (median: 274 µg/L at 0–3 months after delivery) were similar to and strongly correlated with those in maternal serum (median: 266 µg B/L; rs = 0.94). The correlation with arsenic and lithium in breast milk was rs = 0.49 and 0.64, respectively, but there was no association between the breast milk concentrations of boron and those of calcium, magnesium, phosphorous, zinc, iron and selenium (rs > 0.1).

Median birth weight was 3050 g and 8% of the infants had low birth weight (i.e. < 2500 g). In total, 76% of the infants were exclusively breastfed at the follow-up at 0-3 months and 57% at 3 – 6 months, as reported by the mothers. The correlation between B concentrations in infant urine collected at 0 – 3 months after birth and breast milk became markedly stronger if restricted to infants who were reported to be exclusively breastfed (rs = 0.68; p < 0.001). The boron concentrations in urine of infants who were reported to be exclusively breastfed at 0 – 3 months (median: 541 µg B/L, n = 81) were approx. twice as high as those in the breast milk they received (median: 266 µg/L, collected within an hour of the infant urine sampling). An even bigger difference was found for the exclusively breastfed infants at 3 – 6 months (median urine: 1327 µg B/L, median breast milk: 293 µg B/L, n = 55). The authors suggested that the higher B concentrations in urine of the infants that were not exclusively breastfed demonstrate the strong impact of water intake on infant boron exposure; this was particularly evident at 3–6 months, when fewer infants were exclusively breastfed.

The authors used two cross-sectional analysis models, adjusting for infant age only (Model A) and for infant age and several other parameters, including lithium and arsenic concentrations in maternal blood and urine during pregnancy (Model B), for both follow-up periods (Table 30). A significant inverse association of B in infant urine with infant weight, at 0 – 3 months was observed (Model A). A non-stat. sign. tendency of

shorter infants at higher B concentrations in cord blood was noticed after the 0 – 3 months follow-up (Model B; p = 0.08). At 0 – 3 months, adjusting for additional covariates (Model B) gave rise to a stronger inverse association of urinary B and infant body weight, and also the inverse association with head circumference became stat. significant (p < 0.05). Each 2-fold increase of B levels in infant urine was associated with a decrease in bodyweight of 141 g and a decrease in infant head circumference of 0.39 cm. Neither arsenic, nor lithium in infant urine was significant in the models. At the 3 – 6 months follow-up, each 2-fold increase of B concentrations in infant urine was associated with a decrease of 200 g in infant weight and a decrease of 0.57 cm in infant length (Model B).

The study had a high participation rate (88%) and a prospective design with measurements of the infants at birth and two follow-ups during the first 6 months, but a small sample size. A limitation is the exposure to other metals, such as lithium, of the infants that also received drinking water. The concentrations of lithium were correlated with those of boron in the exposure biomarkers, and all exposures were lower in exclusively breastfed infants than in those also given drinking water. However, the measures of exposure to lithium (and arsenic) were generally not significant in the used statistical models (with and without metal adjustments). Previous studies correlated high altitude with low birth weight. Hjelm and colleagues underlined that even if the current study was performed in the Andes at 3100 – 4070 m above sea level, most of the mothers were of indigenous origin. The ancestors of these women lived in villages situated at high altitude in the Andes and this has resulted in adaptation to high altitude, including reproductive fitness.

In conclusion, the results of the study conducted by Hjelm et al. (2019) show a strong correlation between B in maternal serum and breast milk which indicates that exposure to B in early infancy was inversely associated with infant weight, length and head circumference during the first 6 months of life. These results are in line with the previously published findings of the same research group, showing that maternal serum B concentrations during pregnancy were associated with impaired foetal growth in the same mother-child cohort (Igra et al. 2016).

Table 30: Boron exposure markers prenatally and in early infancy

Perinatal exposure markers		**Median (range) boron concentrations (µg/L)**
Hjelm et al. 2019 (Argentina)		
Prenatal exposure markers (n = 78)	Maternal serum (last trimester)	134 (30 – 447)
	Maternal whole blood (last trimester)	140 (27 – 332)
	Placenta (µg/kg)	133 (1.1 – 605)
	Cord blood serum	196 (69 – 658)
	Cord whole blood	177 (29 – 600)
First follow-up (0 – 3 months after birth; n = 108)	Maternal serum	266 (47 – 624)
	Maternal whole blood	263 (66 – 750)
	Breast milk	274 (46 – 786)
	Infant urine*	689 (105 – 9200)
Second follow-up (3 – months after birth; n = 93)	Breast milk	293 (65 – 1386)
	Infant whole blood	127 (37 – 1351)
	Infant urine*	1784 (389 – 15068)

*Adjusted to mean osmolality (122 and 223 mOsm/kg at 0 – 3 and 3 – 6 months, respectively).

Table 31: Early life boron exposure and infant anthropometry (multivariable-adjusted linear regression analysis) as published by Hjelm et al. (2019)

Exposure as boron concentration (µg/L)	Infant outcomes					
	Weight (g)/log_2 B (µg/L) (95% CI)	p-value	Length (cm) /log_2 B (µg/L) (95% CI)	p-value	Head circumference (cm) /log_2 B (µg/L) (95% CI)	p-value
First follow-up (0 – 3 months)						
Maternal serum blood (last trimester)	**n = 140/138**		**n = 140/131**		**n = 136/121**	
Model A[a]	-29 (-108:51)	0.477	-0,19 (-0.50; 0.12)	0.221	-0.05 (-0.23; 0.12)	0.545
Model B[b]	-30 (-100; 41)	0.405	-0.23 (-0.50;0.05)	0.103	-0.06 (-0.25; 0.12)	0.509
Cord blood	**n = 92/83**		**n = 92/80**		**n = 90/71**	
Model A[a]	-63 (-234; 108)	0.464	-0.46 (-1.0; 0.13)	0.126	0.06 (-0.35; 0.47)	0.765
Model B[b]	-77 (-223; 69)	0.297	-0.52 (-1.1; 0.07)	0.082	-0.16 (-0.56; 0.25)	0.447
Infant urine (0 – 3 months)	**n = 113/112**		**n = 113/109**		**n = 113/100**	
Model A[a]	-83 (-158; -8.1)	0.030	0.04 (-0.26; 0.34)	0.798	-0.01 (-0.20; 0.19)	0.943
Model B[b]	-141 (-240; -42)	0.006	-0.07 (-0.53; 0.40)	0.773	-0.39 (-0.74; -0.04)	0.028
Second follow-up (3 – 6 months)						
Infant urine (0 – 3 months)	**n = 111/109/109**		**n = 111/106/106**		**n = 106/93/93**	
Model A[a]	-94 (-197; 8.5)	0.072	- 0.00 (-0.31; 0.31)	0.988	-0.04 (-0.22; 0.14)	0.665
Model B[c]	-200 (-377; -23)	0.027	-0.57 (-1.1; -0.03)	0.040	-0.30 (-0.64; 0.04)	0.083
Model C[d]	-176 (-343; -8.9)	0.039	-0.66 (-1.2; -0.11)	0.019	-0.23 (-0.52; 0.06)	0.125
Infant urine (3 – 6 months)	**n = 112/107**		**n = 112/101**		**n = 112/94**	
Model A[a]	-111 (-229; 6.0)	0.063	-0.34 (-0.70; 0.01)	0.059	-0.12 (-0.31; 0.08)	0.231
Model B[c]	60 (-154; 273)	0.580	-0.48 (-1.2; 0.26)	0.202	-0.21 (-0.62; 0.19)	0.304
Infant whole blood (3 – 6 months)	**n = 106/92**		**n = 106/87**		**n = 106/82**	
Model A[a]	-51 (-180; 78)	0.436	-0.12 (-0.50; 0.26)	0.528	-0.12 (-0.32; 0.07)	0.217
Model B[c]	-34 (-190; 123)	0.667	-0.10 (-0.60; 0.40)	0.694	-0.14 (-0.43; 0.15)	0.330

a Adjusted for infant age (days).
b Adjusted for infant age, birth weight, length, head circumference, sex, mothers height (cm), exclusively breastfed (yes/no) and lithium concentrations (log_2 µg/L) in maternal whole blood during pregnancy or infant urine, and arsenic concentrations (log_2 µg/L) in maternal urine during pregnancy or infant urine.
c Adjusted for infant age, birth weight, length, head circumference, sex, mothers height (cm), exclusively breastfed (yes/no) at time of exposure measurement, lithium concentrations (log_2 µg/L) in infant urine and arsenic concentrations (log_2 µg/L) in infant urine.
d As Model B[c], but adjusted for weight, length or head circumference at 0 – 3 months instead of at birth.

Conclusion on human data

The human data on developmental effects of boron should be seen as additional information for the assessment of human relevance of the observed developmental toxicity of PBS-4 in animal studies in a weight of evidence assessment. The retrospective study (Duydu et al. 2018b) reports no adverse effects on development at exposure levels that were well below the NOAEL for developmental effects in rats. The

blood B levels for the women in the highest exposure group (mean value of 274.6 ng B/g blood, highest individual value was 957.7 ng B/g blood) were below those corresponding to the NOAEL for developmental effects in rats (i.e. 9.6 mg B/kg bw/day corresponding to 1270 ng B/g blood; Price et al. 1997). This study presents several limitations, mainly associated with the retrospective study design and small sample size.

The prospective study conducted by Igra et al. (2016) detected a dose-dependent influence on birth size at B exposure levels (that were below the NOAEL for developmental effects in animal studies) but it could not be excluded that the results were influenced by co-exposure to lithium. The follow-up results of the same mother-child cohort published by the same research group provides the first evidence that exposure to B during early infancy (via breast milk and drinking water) may have a negative effect on post-natal growth up to 6 months of age (Hjelm et al. 2019). The lithium concentrations correlated with those of B in the assessed exposure biomarkers. However, it should be noted that adjusting for Li and As concentrations in maternal whole blood and infant urine resulted in a stronger inverse association of urinary B and infant body weight, the inverse association with infant head circumference becoming stat. significant at the first follow-up.

Assuming a blood density of 1060 g/L, the highest individual maternal serum B concentration of 624 µg/L measured at the first follow-up, would result in 589 ng B/g blood. This value is below the level of 1270 ng B/g blood that corresponds to the NOAEL for developmental effects in rats. However, the two prospective studies are the first to show developmental effects of perinatal environmental B exposure.

Overall, the available human data on boron do not contradict the experimental data coming from studies performed with per(oxo)borates in rats and give no evidence to support that the effects seen in animals are not relevant for humans. Moreover, the same conclusion was stated in RAC opinions (2014 and 2020) on, boric acid and or borate salts where experimental data across several species (mice, rats and rabbits) are available.

10.10.6 Comparison with the CLP criteria

Sodium peroxometaborate has a harmonised classification as Repr. 1B; H360D based on one PNDT study of PBS-4 in rat. **No change to the classification is proposed**.

There is clear evidence of structural abnormalities, death of the organism and retarded growth based on read-across from PBS-4. Classification in Repr. 1B, H360D is therefore warranted. Moreover, the recorded effects are relevant for humans, and are not considered to be secondary to maternal toxicity. Although not included in the previous decision on classification by the TC C&L, available data on boric acid could also be considered in the weight of evidence since read-across from boric acid to per(oxo) borates for developmental toxicity is appropriate. In the current proposal human data on boron were included to assess human relevance and the available data give no evidence to support that the effects seen in animals are not relevant for humans.

Classification in Repr. 1A, H360D is not justified since there is no human data demonstrating that per(oxo)borates have adverse effect on human fetal development. There is also no human data on boron that demonstrates clear evidence of adverse effect on human fetal development.

Classification in Repr. 2 is not justified since the evidence for developmental toxicity from existing experimental data on PBS-4 is considered to be clear and not some evidence of developmental toxicity.

<u>Specific concentration limits for adverse effects on the development of the offspring</u>

As detailed in the proposal for SCLs for sodium per(oxo)borates drafted by Austria and The Netherlands, the classification was based on the developmental effects seen at 300 and 1000 mg/kg bw/day in the OECD TG PNDT study with PBS-4 (ECBI/38/03 Add.17). While it was acknowledged that PBS-4 induced similar types of malformations on rat foetuses as boric acid and borates, it was not clearly stated if the classification was solely based on the observed malformations or on the total weight of evidence of developmental effects.

The current SCLs for adverse effects on development of the per(oxo)borates (i.e. $6.5\% \leq C < 9\%$) included in that proposal were calculated using the approach proposed by BauA (1998), based on the limit dose of

1000 mg/kg bw/day as described in the OECD TG 414, and using the NOAEL for developmental effects (i.e. 100 mg/kg bw/day) set by the authors of the PNDT study with PBS-4. This yielded an SCL of 10% for PBS-4 that was further used to calculate the SCL for PBS-1, taking into account the molecular weights of both per(oxo)borates and thus, yielding a value of 6.5% for PBS-1 (ECBI/38/03 Add.17).

Since the per(oxo)borates covered by the present proposal was subject to harmonised classification, new recommendations on how to derive concentration limits for reproductive toxicity have been agreed upon (CLP Guidance, 2017). Section VI.5.1.1.4 of the CLP Guidance (2017) states that "*Several other options for a method for determining SCLs were discussed including a method that was used by the TC C&L in a limited number of cases in the past. This method is based on the limit dose of 1000 mg/kg bw/day, as described in the test guideline OECD 414 and 416. This method would result in an individual SCL for each substance. This would indicate a precision that cannot be expected from standard reproduction studies. Also, this would result in an SCL for most substances and in a GCL for only some substances. Therefore, this method was not considered*".

In 2019, the RAC has removed the SCLs calculated based on the old method and concluded on the harmonisation of GCL of 0.3% w/w for boric acid and six sodium borates that have a harmonised classification as Repr. 1B.

In the available PNDT study with PBS-4, developmental effects such as skeletal, eye, CNS and cardio-vascular malformations typical for boron-exposure were seen. Other developmental effects such as increased resorptions and post-implantation loss, decreased number of live foetuses, decreased foetal and litter weights were also reported. As the incidences of typical boron-exposure malformations are low, it is not possible to derive an ED10: skeletal (short rib XIII in 0.6%, 0%, 3% and 9% of the foetuses at 0, 100, 300 and 1000 mg/kg bw, respectively), eye (anophthalmia and microphthalmia seen only at 1000 mg/kg bw/day in 3.36% of the foetuses), CNS (enlarged lateral ventricles of the brain seen only at 1000 mg/kg bw/day in 1.68 of the foetuses) and cardio-vascular (seen only at 1000 mg/kg bw/day in 5.88% of the foetuses) malformations.

Thus, the LOAEL for developmental effects should be used for setting the SCLs, as according to the CLP Guidance (2017). The LOAEL for developmental effects in the PNDT study with PBS-4 is 300 mg/kg bw/day (eq. to 21 mg B/kg bw/day). Since the ED10 (LOAEL) is ≥ 4 mg/kg bw/day and ≤ 400 mg/kg bw/day (Table 3.14 of the CLP guidance) the medium potency group with a GCL of 0.3% w/w would therefore be assigned to PBS-4 (and consequently to sodium peroxometaborate, correcting for B-content).

It is worth noting that a difference between effects seen in developmental studies performed with boric acid and borates and the PNDT study performed with PBS-4 is increased foetal lethality. This effect can also be used for ED10 derivation, as death of the developing organism is one of the major manifestations of developmental toxicity. On a boron-equivalent basis, there is little difference between using the LOAEL or post-implantation loss for ED10 derivation (21 mg B/kg bw/day vs. 20.2 mg B/kg bw/day, respectively). For the purpose of transparency, it can be noted that linear interpolation between the doses for the other developmental effects that allow for ED10 derivation, including post-implantation loss, gives rise to ED10-values for PBS-4 which also are ≥ 4 mg/kg bw/day and ≤ 400 mg/kg bw/day. Not only the lowest ED10 but all ED10-values are within the range for the medium potency group (Table 32).

Table 32: Determination of ED10-values based on developmental effects of PBS-4

Developmental effects	**Dose levels (mg PBS-4/kg bw/day)**	**ED10 (linear interpolation of available doses)**	**Allocation of potency**

	0	100	300	1000	(mg PBS-4/kg bw/day)	mg B/kg bw/day	group*
Live foetus weight (g)	3.69	3.57	3.28	2.4	127.5	9	Medium, GCL of 0.3%
Litter weight (g)	54.97	52.62	46.49	32.52	197.2	13.8	Medium, GCL of 0.3%
Post-implantation loss (%)	2.91	2.39	13.54	15.2	288.8	20.2	Medium, GCL of 0.3%
LOAEL for developmental effects					300	21	Medium, GCL of 0.3%

*According to Table 3.14 of the CLP Guidance (2017)

In accordance with the CLP Guidance (Section 3.7.2.6.5.), modifying factors should be considered when assigning the final potency group. None of the modifying factors related to type or severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bio-accumulation applies for the sodium per(oxo)borates.

Therefore, PBS-4 should be assigned to the medium potency group with a GCL of 0.3% w/w. Correcting for the percentage of boron (calculations are available in Table 33), the LOAEL of 21 mg B/kg bw/day would correspond to 161.5 mg sodium peroxometaborate/kg bw/day. Thus, sodium peroxometaborate falls within the range of the **medium potency group for adverse effects on development, for which the GCL of 0.3% w/w** should apply.

10.10.7 Adverse effects on or via lactation

No data for the assessment of adverse effects on or via lactation for per(oxo)borates were available.

Since boric acid is an *in vivo* degradation product of per(oxo)borates, read-across of data from boric acid and borates is used. A recent epidemiological study found a strong correlation between B in maternal serum (266 µg/L) and breast milk (274 µg/L), indicating that there is no regulation of B in the mammary gland, but possible transfer by passive diffusion (Hjelm et al. 2019). Due to rapid excretion of B in the urine, the B levels of maternal serum and breast milk were reported to be only a fraction (approx. 5%) of those measured in the drinking water (5800 µg/L). The authors found that B exposure (via breast milk and drinking water) had a continuous effect on infant growth (up to 6 months of age), being associated with stat. sign. decreases in infant weight and length. In addition, boron compounds have been found in human breast milk (BfR, 2005), with reported (background) concentrations of approximately 4 µg B/L (Hunt et al. 2005, as reported in WHO, 2009) and in an experiment where 1 – 13 g of boric acid was given to lactating women, levels between 10 – 285 mg B/L were found in milk (Moseman, 1994).

However, it is not possible to distinguish between prenatal and postnatal exposure and the available data are not sufficient to conclude that boron is present in potentially toxic levels in breast milk.

Therefore, classification of sodium peroxometaborate for adverse effects on or via lactation is not warranted.

10.10.8 Conclusion on classification and labelling for reproductive toxicity

Based on a total weight of evidence (read-across data from PBS-4 and read-across data from boric acid and sodium borates), classification in category 1B for adverse effects on sexual function and fertility (**Repr. 1B; H360F**) for sodium peroxometaborate (Index No. 005-017-00-7 and 005-017-01-4) is considered appropriate.

Moreover, sodium peroxometaborate (Index No. 005-017-00-7 and 005-017-01-4) has a harmonised classification in category 1B for adverse effects on the development of the offspring (**Repr. 1B; H360D**). No change to the classification is proposed. Withdrawal of the specific concentration limits is warranted and therefore the **GCLs of 0.3%** apply for both adverse effects on sexual function and fertility, and for adverse effects on the development of the offspring (see Table 33 below).

Table 33: Derivation of ED10 values and concentration limits for sodium peroxometaborate based on boron content

Substance name	Molecular formula	EC No.	CAS No.	Molecular weight (g/mol)	Conversion factor for equivalent dose of boron (B)*	ED10 fertility**, corrected for B content (mg/kg bw/day)	LOAEL for development***, corrected for B content (mg/kg bw/day)	Proposed GCL fertility (% w/w)	Proposed GCL development (% w/w)
Sodium peroxometaborate;	BO_3Na	231-556-4	7632-04-4	81.8	0.13	17.5/0.13 = 135	21/0.13 = 161.5	**0.3**	**0.3**

* Molecular weight of boron is 10.81 g/mol.
** Based on read-across from boric acid and borate salts, for which the LOAEL for effects on sexual function and fertility was set at 17.5 mg B/kg bw/day.
*** Based on the LOAEL for developmental effects of 300 mg/kg bw/day PBS-4 (eq. to 21 mg B/kg bw/day), from an OECD TG 414 study performed in rats.

10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this CLH-proposal.

10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this CLH-proposal.

10.13 Aspiration hazard

Hazard class not assessed in this CLH-proposal.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this CLH-proposal.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this CLH-proposal.

13 ADDITIONAL LABELLING

14 REFERENCES

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15 ANNEXES

Annex I to CLH-proposal.