Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

perboric acid, sodium salt [1]; perboric acid, sodium salt, monohydrate [2]; perboric acid (HBO(O2)), sodium salt, monohydrate; sodium peroxoborate [3]; sodium perborate [4]

EC Number: 234-390-0 [1]; 234-390-0 [2]; 239-172-9 [4]
CAS Number: 11138-47-9 [1]; 12040-72-1 [2]; 10332-33-9 [3]; 15120-21-5 [4]

CLH-O-0000007164-77-01/F

Adopted

15 September 2022

15 September 2022

CLH-O-0000007164-77-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name:	**perboric acid, sodium salt [1]; perboric acid, sodium salt, monohydrate [2]; perboric acid (HBO(O2)), sodium salt, monohydrate; sodium peroxoborate [3]; sodium perborate [4]**
EC Number:	**234-390-0 [1]; 234-390-0 [2]; 239-172-9 [4]**
CAS Number:	**11138-47-9 [1]; 12040-72-1 [2]; 10332-33-9 [3]; 15120-21-5 [4]**

The proposal was submitted by **Sweden** and received by RAC on **24 September 2021.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **8 November 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **21 January 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Gerlienke Schuur**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **15 September 2022** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	005-019-00-8	perboric acid, sodium salt [1]; perboric acid, sodium salt, monohydrate [2]; perboric acid ($HBO(O_2)$), sodium salt, monohydrate [3]; sodium peroxoborate; [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	234-390-0 [1] 234-390-0 [2] 231-556-4 [3]	11138-47-9 [1] 12040-72-1 [2] 10332-33-9 [3]	Ox. Sol. 3 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; H60Df: C ≥ 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	
	005-019-01-5	perboric acid, sodium salt [1]; perboric acid, sodium salt, monohydrate [2]; perboric acid ($HBO(O_2)$), sodium salt, monohydrate [3]; sodium peroxoborate; [containing = 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	234-390-0 [1] 234-390-0 [2] 231-556-4 [3]	11138-47-9 [1] 12040-72-1 [2] 10332-33-9 [3]	Ox. Sol. 3 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 %	
	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; H360Df: C ≥ 9 % Repr. 1B; H360D: 6.5 % ≤ 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; H360Df: C ≥ 9 % Repr. 1B; H360D: 6.5 % ≤ C < 9 % Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	
Dossier submitters proposal	**Merge:** 005-019-00-8 005-019-01-5 005-017-00-7 005-017-01-4	**Retain:** perboric acid, sodium salt [1] perboric acid, sodium salt, monohydrate [2] perboric acid ($HBO(O_2)$), sodium salt, monohydrate; sodium peroxoborate [3] sodium perborate [4] **Remove:** sodium peroxometaborate [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm] [containing = 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm] containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm	**Retain:** 234-390-0 [1] 234-390-0 [2] 239-172-9 [4] **Remove:** 231-556-4 [3]	**Retain:** 11138-47-9 [1] 12040-72-1 [2] 10332-33-9 [3] 15120-21-5 [4] **Remove:** 7632-04-4	**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:** Inhalation: ATE = 0.75 mg/L (dusts and mists) Oral: ATE = 890 mg/kg bw/d	
Resulting Annex VI entry if agreed by RAC and COM	TBD	perboric acid, sodium salt [1] perboric acid, sodium salt, monohydrate [2] perboric acid (HBO(O2)), sodium salt, monohydrate; sodium peroxoborate [3] sodium perborate [4]	234-390-0 [1] 234-390-0 [2] 239-172-9 [4]	11138-47-9 [1] 12040-72-1 [2] 10332-33-9 [3] 15120-21-5 [4]	Ox. Sol. 3 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 = 0.75 mg/L (dusts or mists) Oral: ATE = 890 mg/kg bw/d Eye Dam. 1; H318: C ≥ 22 % Eye Irrit. 2; H319: 14 % ≤ C < 22 %	#

#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) is supported by RAC.

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The proposal submitted by Sweden concerns per(oxo)borates with four existing entries in Annex VI to the Regulation (EC) No 1272/2008 (CLP Regulation). Perboric acid, sodium salt, monohydrate (PBS-1) has currently harmonised classification as

- toxic to reproduction for both developmental and fertility effects, i.e. Repr. 1B; H360Df,
- Ox. Sol 2 or 3 (H272),
- STOT SE3 (H335),
- Eye Dam 1 (H319; C $\geqslant$ H318; 22 %) / Eye Irri. 2 (H319; 14 % $\leqslant$ C < 22 %), and
- acutely toxic via inhalation and oral route, i.e. Acute Tox. 3*; H331 (two of the four entries), and Acute Tox. 4*, H302.

Currently, the entries also have specific concentration limits (SCLs), which were set at that time based on the developmental effects of the boron moiety (B) using an approach proposed by the German Federal Institute for Occupational Safety and Health (BAuA, 1998).

Table 1: *Overview of entry numbers, substances and notes as presented in the proposal by Sweden*

Current Annex VI entries	International Chemical identification	Specifications	Proposal for one Annex VI entry
005-019-00-8	1. perboric acid, sodium salt[a] 2. perboric acid, sodium salt, monohydrate[a] 3. perboric acid ($HBO(O_2)$), sodium salt, monohydrate[b]	[containing **< 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	1. perboric acid, sodium salt 2. perboric acid, sodium salt, monohydrate 3. perboric acid ($HBO(O_2)$), sodium salt, monohydrate 4. sodium perborate *
005-019-01-5	1. perboric acid, sodium salt[a] 2. perboric acid, sodium salt, monohydrate[a] 3. perboric acid ($HBO(O_2)$), sodium salt, monohydrate[b]	[containing **= 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	
005-017-00-7	4. sodium perborate 5. sodium peroxometaborate[b]	[containing **< 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	
005-017-01-4	4. sodium perborate 5. sodium peroxometaborate[b]	[containing **≥ 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	

[a] Substance number 1 and 2 have similar EC numbers, but a different CAS number
[b] Substance number 3 and 5 have similar EC numbers, but a different CAS number
* For substance number 5 (sodium peroxometaborate), a separate CLH report is submitted.

The changes proposed in the current proposal by the DS are:

- The EC number 231-556-4 is linked to a not well-defined dehydrated sodium perborate (with CAS number 7632-04-4) and is therefore removed.
- Create a separate entry for sodium peroxometaborate, because sodium perborate has a dimeric cyclic structure. On the other hand, sodium peroxometaborate is not a well-defined substance, and it differs from the dimeric cyclic structures of the other sodium per(oxo)borates. In addition, sodium perborate and sodium peroxometaborate have different acute toxicity estimates (ATEs) for acute oral and inhalation toxicity.
- The cut-off values for particle size are not considered justified and hence should be removed, so merging entries 005-019-00-8 and 005-019-01-5.

The harmonised classification on oxidising solids (Ox. Sol.) is not evaluated in the proposal. However, the Dossier Submitter (DS) argues the existing Ox. Sol. 2 classification is due to the inclusion of sodium perborate (CAS 15120-21-5) in the current Annex VI entries 005-017-00-7

and 005-017-01-4. In this proposal Annex VI entries of perboric acid, sodium salt; perboric acid, sodium salt, monohydrate; perboric acid (HBO(O2)), sodium salt, monohydrate and sodium perborate are all covering PBS-1 and merged in one entry with a corresponding harmonised classification of Ox. Sol. 3.
RAC has not assessed this physical hazard and it has not been open for consultation.
Open for discussion are the proposals for harmonised classification on acute toxicity and reproductive toxicity.

Previous RAC evaluations of boric acid and other borates

RAC assessed proposals for harmonised classification of boric acid (CAS 10043-35-3) and several related substances in the past. Harmonised classification for Repr. 1B; H360FD of boric acid and several related compounds was adopted into Annex VI of the CLP regulation during the 1st ATP. In 2014, RAC adopted proposals for harmonised classification for disodium octaborate anhydrate[1] and disodium octaborate tetrahydrate,[2] based on read-across from other borates such as boric acid (Repr. 1B; H360FD). In the same year a proposal for modification of harmonised classification of boric acid from Repr. 1B; H360FD to Repr. 2; H361d was not adopted by RAC.[3] In 2019, RAC adopted a proposal to remove SCLs for effects on sexual function and fertility and development (Repr. 1B; H360FD) for boric acid, diboron trioxide, tetraboron disodium heptaoxide hydrate, disodium tetraborate anhydrous, orthoboric acid sodium salt, disodium tetraborate decahydrate and disodium tetraborate pentahydrate.[4] For all substances, using the new guidance, a GCL of 0.3 % w/w was applied.

PBS-1

In aqueous conditions, sodium per(oxo)borates dissociates into boric acid and hydrogen peroxide. Boric acid is the main product at physiological and acidic pH and hydrogen peroxide decomposes into water and oxygen *in vivo*. Based on available toxicokinetic data for per(oxo)borates and boric acid, absorption is almost 100 % upon oral or inhalation exposure. Minimal absorption is reported upon dermal exposure.
PBS-1 is used as oxidising and bleaching agent in detergents and cleaning products. Only EC 234-390-0 (perboric acid, sodium salt) is registered under REACH (10 000- 100 000 tonnes per annum). This substance is used by consumers, professional workers (widespread uses), in formulation and re-packing in manufacturing.

Read-across

Read-across to sodium perborate tetrahydrate (PBS-4; CAS 10486-00-7), boric acid and other borates is supported based on hydrolytic and toxicokinetic behavior. Therefore, read-across based on boron content can be applied in line with the previous assessments by RAC for reproductive toxicity.

For acute toxicity, sodium per(oxo)borates show a higher acute toxicity compared to borates, which is caused by the formation of hydrogen peroxide and thus read-across for acute toxicity to

[1] https://echa.europa.eu/documents/10162/7d740d8c-5cd5-872b-5da2-e549983a9ff9

[2] https://echa.europa.eu/documents/10162/658b802c-1ca3-663e-4bd4-437369d715de

[3] https://echa.europa.eu/documents/10162/4db9bc68-844e-c557-8914-ab491743d471

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

borates does not apply. In any case, PBS-1 has been tested in acute oral and dermal studies (see below).

Comments received during consultation

A MSCA noted several inconsistencies in Table 5 in the CLH-dossier. In the responses to the comments (RCOM) the DS made a correction. The corrected version is included in this opinion.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

A harmonised classification Acute Tox. 4* for the oral route is currently in place for all entries for PBS-1 and Acute Tox. 3* for the inhalation route for two entries (Index No. 005-019-00-8 and 005-019-01-5).

Acute oral and dermal toxicity studies are available for PBS-1. No acute inhalation toxicity studies are performed with PBS-1 and therefore read-across is proposed to PBS-4. Data on other boric acid, borate salts and hydrogen peroxide were presented for comparison. These data did not contradict the classification derived from available data on PBS-1 or PBS-4.

The DS proposes removal of the asterisk indicating minimum classification and the inclusion of an ATE of 890 mg/kg bw for the oral route. No classification on acute toxicity was proposed for the dermal route. For the inhalation route, the DS proposes the removal of the asterisk indicating minimum classification and the inclusion of an ATE of 0.75 mg/L, based on hydrogen peroxide release and the respective hydrogen peroxide content. In addition, the removal of the cut-off values for particle size distribution is proposed as the thoracic fraction concept, used by the Technical Committee for Classification and Labelling (TC C&L) in 2006 (ECBI/90/06 Rev. 8), is a conservative approach which is no longer used.

Comments received during consultation

Two Member State Competent Authorities (MSCAs) submitted comments on acute toxicity. One MSCA agreed with the proposals for classification on acute oral and inhalation toxicity and also agreed that the cut-off value of 50 µm for particle size should be removed. Another MSCA supported the DS proposals for classification on acute oral and inhalation toxicity, and no classification on acute dermal toxicity.

Assessment and comparison with the classification criteria

Oral route

Two reliable, GLP-compliant acute oral toxicity studies (EPA OPP 81-1) are available for PBS-1 in Sprague-Dawley or Wistar rats. In these studies, rats (n = 5/sex/group) were administered 500, 1000 and 2000 mg/kg bw or 1200, 1500, 1900, 2500 and 5000 mg/kg bw PBS-1 (purity unknown) via gavage, followed by a 14-day observation period. Lethality was reported on day 0-2 post-exposure, at ≥ 1000 mg/kg bw in Sprague-Dawley rats and at ≥ 1500 mg/kg bw in Wistar rats. Evident acute toxicity was noted (e.g. irregular respiration, diarrhoea, bloated abdomen) and necropsy revealed distended stomach with gas and kidney abnormalities in both strains. Female

rats appeared more sensitive than male rats, with the lowest LD_{50} reported of 890 mg/kg bw. Another acute oral toxicity study in rat is available with some limitations (e.g. strain and sex not specified) and therefore of lower reliability. In this study an LD_{50} of > 650 mg/kg bw is reported.

Use of read-across data is not necessary as studies for PBS-1 are available for this endpoint. However, studies on boric acid, borate salts and hydrogen peroxide are discussed for comparison. For boric acid and borate salts LD_{50} values of > 2000 mg/kg bw are reported based on acute oral toxicity studies in rats. Multiple acute oral toxicity studies in rats are available for hydrogen peroxide; three guideline studies and three non-guideline studies. LD_{50} values reported for hydrogen peroxide depend on concentrations (percentage, see Table 2 below). Oral toxicity of hydrogen peroxide is known and is relevant, depending on its concentration, to assess for comparison with PBS-1.

Table 2: *Reported LD_{50} values for hydrogen peroxide*

H_2O_2 (%)	LD_{50} (mg/kg bw)
9.6	1520-1620 (m: 1520; f: 1620)
10	>5000
35	1193-1270 (m: 1193; f: 1270)
50	>225
60	801-872
70	805

In humans, upon exposure to sodium per(oxo)borates, irritation is reported but no related deaths. For boric acids, borate salts and hydrogen peroxide exposure-related deaths are known. Toxic effects such as vomiting, gastric effects and convulsions are reported for boric acid. Autopsy upon accidental exposure to hydrogen peroxide in children revealed gas oedema-related findings, such as gas accumulation in the right heart ventricle.

The data from the two reliable acute oral toxicity studies in rats with PBS-1 are preferred over the less reliable study. RAC agrees with the DS that the lowest LD_{50} value of 890 mg/kg bw is most appropriate as ATE. This ATE falls within the limits of Category 4 (oral LD_{50} is >300 but $\leqslant$ 2000 mg/kg bw). Therefore, RAC agrees with the DS to remove the asterisk indicating minimum classification and the inclusion of an ATE of 890 mg/kg bw. This results in classification Acute Tox. 4; H302, oral: ATE = 890 mg/kg bw.

Dermal route

In an acute dermal toxicity study (OECD TG 402), New Zealand White rabbits (n = 5/sex/group) received a single dermal application (24 h) of 2000 mg PBS-1 (purity unknown)/kg bw. Clinical signs (e.g. diarrhoea, few faeces, yellow nasal discharge and anogenital soiling) were reported, which decreased in severity over time. Skin irritation (decreased in severity in recovery period) on day 1 post-treatment and distended intestines at necropsy were noted in 2/9 animals. One death (male) on day 13 post-treatment was noted, including abnormalities: gastrointestinal tract, spleen, liver and lung) were reported. An LD_{50} of > 2000 mg/kg bw is derived based on this study.

LD_{50} values of > 2000 mg/kg bw are reported for boric acid and borate salts (e.g. boric acid) and hydrogen peroxide.

Cases of poisoning in humans upon dermal contact to sodium per(oxo)borates are known, but none of these cases resulted in fatalities or required treatment.

Available data together demonstrate low acute dermal toxicity for PBS-1 and LD_{50} values are > 2000 mg/kg bw. RAC agrees with the DS that classification of PBS-1 for acute dermal toxicity is not warranted.

Inhalation route

There are no acute inhalation toxicity studies available for PBS-1. Read-across to PBS-4 can be applied based on one reliable acute inhalation toxicity study (similar to OECD TG 403) in rats. Sprague-Dawley rats (male, n=6/group) were exposed (nose-only) to 0.16, 0.48, 1.10 and 2.90 mg/L PBS-4 (aerosols; purity 98.6%; mass median aerodynamic diameter (MMAD) 3.3-4.2 µm) for 4 h, followed by a 14-day observation period. Clinical signs (red ocular, nasal or oral discharge, diarrhoea, gasping and lung noise), reduced body weight (≤ 18 %) and lethality were noted (24 h post-exposure: 0/6, 1/6, 3/6, 4/6; 8 days post-exposure: 1 death at highest dose). An LC_{50} of 1.16 mg/L was derived from this study. The MMAD of PBS-4 in the high-dose group in the acute inhalation toxicity study is slightly above the range generally used for classification (CLP Guidance 3.1.2.3.2.). Nevertheless, these data are relevant for classification as signs of toxicity were noted in a lower dose group (at 1.10 mg/L) as well.

Another non-test guideline inhalation toxicity study is available for PBS-4 with major limitations (e.g. limited documentation on methods and results, no calculations available for the LC_{50} value). This study is therefore not further considered.

LC_{50} values of > 2 mg/L are derived for boric acid and borate salts based on animal studies on boric acid, disodium octaborate tetrahydrate and disodium tetraborate pentahydrate. In addition, multiple animal studies are described for hydrogen peroxide. However, in most studies no LC_{50} values could be derived as no deaths or evident toxicity were observed. Inhalation of hydrogen peroxide leads to severe irritation and inflammation of the mucous membranes, coughing and dyspnoea. Hydrogen peroxide has a harmonised minimum classification as Acute Tox. 4*, H332.

No human data for sodium per(oxo)borates, boric acid, borate salts or hydrogen peroxide relevant for classification are available. Nasal secretions and irritation, and decreased nasal airway resistance in healthy volunteers were noted upon exposure to sodium tetraborate pentahydrate (dust; 0-40 mg/m^3) or boric acid (0-10 mg/m^3). No information on the acute inhalation toxicity of hydrogen peroxide in humans was found.

The DS anticipates a higher toxicity of PBS-1 compared to PBS-4 based on the hydrogen peroxide content. This is supported also by the difference in classification for acute oral toxicy i.e Category 4 for PBS-1 and no classification for PBS-4. Although there is some uncertainty in the extrapolation from PBS-4 to PBS-1, RAC agrees with the DS to use the PBS-4 data. RAC derives an ATE of 0.75 mg/L, based on a calculation on molecular weight of the monomers[5].

RAC agrees with the DS that the removal of the cut-off values for particle size is justified, as the MMAD of PBS-4 in the available acute inhalation toxicity study are relevant for classification.

To conclude, RAC supports the proposal for the removal of the asterisk indicating minimum classification and removal of the cut-off values for particle size distribution for PBS-1. The derived ATE of 0.75 mg/L falls within Category 3 (inhalation LC_{50} (dusts or mists) > 0.5 but ≤ 1 mg/L).

[5] Calculation based on molecular weight (monomer): MW PBS-1 vs. PBS-4 leads to [100/154]*1.16 mg/L = 0.75 mg/L.
The option of the DS: H_2O_2 content as stated in CLH report, PBS-1 32.1% and PBS-4 21.0 %. leads to [21/32.1]*1.16 mg/L=0.75 mg/L

This results in harmonised classification on Acute Tox. 3; H331, inhalation ATE=0.75 mg/L (dusts or mists).

Overall conclusion

For PBS-1 the following classification is warranted:

- Acute Tox. 4; H302 with ATE= 890 mg/kg bw for the oral route,
- No classification for dermal route and
- Acute Tox. 3; H331 with ATE=0.75 mg/L (dusts or mists) for inhalation route.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

A change to classification from Repr. 2; H361f to Repr. 1B; H360F is proposed by the DS.

There are no studies available on adverse effects on sexual function and fertility for PBS-1. Read-across to data from PBS-4, boric acid and borates is proposed. Adverse effects on male fertility were the main findings in those studies.

The majority of the available epidemiological studies for boron have been previously assessed in the RAC opinions for boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate (2014). The DS concluded based on these studies and recent available studies that although no clear boron-induced adverse effects on fertility and sexual function were shown, these data do not contradict the animal data. The DS provided data on hydrogen peroxide for comparison and to support the read-across hypothesis that boric acid, not hydrogen peroxide, is responsible for the reproductive toxicity.

The DS derived an ED_{10} of 159 mg PBS-1/kg bw/d, based on an ED_{10} of 17.5 mg B/kg bw/d for testes atrophy. This results in an ED_{10} in the medium potency group ($4 < ED_{10} < 400$ mg/kg bw/d) with a generic concentration limit (GCL) of 0.3 % w/w.

Developmental effects

The DS proposes no change in the current harmonised classification of Repr. 1B; H360D for PBS-1. However, a change of the current SCLs into the GCL is proposed.

No developmental studies are available for PBS-1 and therefore read-across to PBS-4 is proposed. A reliable and GLP-compliant oral prenatal developmental toxicity study (PNDT; OECD TG 414) is available for PBS-4. For developmental toxicity, a NOAEL and LOAEL of 100 and 300 mg/kg bw/d are derived (respectively), based on increased post-implantation loss and resorptions, and decreased foetal body weight and number of live foetuses.

RAC has previously assessed epidemiological data on developmental effects upon occupational and environmental exposure to boron. In two recent prospective studies an inverse association on birth size and a possible negative effect on postnatal growth were found. In contrast, no boron-mediated effects on pregnancy outcomes were noted in another retrospective study. According to the DS, these human data are additional information for the assessment of human relevance of the developmental toxicity observed in animal studies and do not contradict these data.

The DS proposes replacing the SCLs for the GCL of 0.3 % w/w. PBS-1 falls in the medium potency group, established on an ED_{10} (LOAEL) of 191 mg PBS-1/kg bw/d.

Effects on or via lactation

The DS does not propose classification for adverse effects on or via lactation. No relevant data are available for per(oxo)borates on adverse effects on or via lactation.

Comments received during consultation

Two comments on toxicity to reproduction were submitted, both by MSCAs. Both supported the DS proposal for classification for Repr. 1B; H360FD and classification in the medium potency group. The other MSCA derived other ED_{10} values for development than the DS. The DS acknowledged there was a mistake and added a corrected table of ED_{10} values in the response to comments.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

No reproduction toxicity studies are available for PBS-1. Read-across to PBS-4, boric acid and borate salts is therefore proposed.

In a repeated dose 28-day oral toxicity limit test (OECD TG 407, GLP) Wistar rats (n = 5/sex/group) were exposed to 0 or 1000 mg/kg bw/d PBS-4 (> 98 % purity) via oral gavage. The following was reported:

- clinical signs (salivation, temporary piloerection),
- reduced body weight (-16 %) and food consumption in males
- changes in organ weights in males (absolute: e.g. kidney, heart, testes; relative: adrenal glands) and females (only relative liver weight) and
- testicular focal tubular atrophy and inhibition of spermiation.

Clear evidence of adverse effects on male fertility, in addition to general toxicity, was thus demonstrated. RAC agrees that reduced testes weight here was substance related and is likely an early sign of testicular toxicity as also induced by boric acid and borate salts.

The DS noted that in a Specialised Experts meeting in 2004, experts concluded that changes in testicular weight were likely attributed to substance exposure and not to reduced body weight. However, it was also concluded these findings on male fertility alone were limited and not sufficient for classification. In general, repeated dose toxicity studies are less sensitive to detect adverse effects on fertility than reproductive toxicity studies due to the limited number of animals per group. This leads to a low statistical power to detect such adverse effects. This is especially true for this study and the fact only one dose group was included (limit test). Further, no information on the severity of the effects is provided. RAC notes that the weak evidence in the 28-day limit test study with PBS-4 might be due to the short duration, as in the study with boric

acid, effects started after 2 weeks but worsened until weeks 6-9.[6] All in all, the repeated dose toxicity study is regarded as supportive evidence for adverse effects on male fertility.

RAC agrees read-across to boric acid is justified, based on hydrolysis, and similar toxicokinetics and toxicological profile. DS described two relevant studies with boric acid and disodium tetraborate decahydrate. Histopathological changes in the testes (testes atrophy and seminiferous tubular degeneration) have been demonstrated upon exposure to boric acid or disodium tetraborate decahydrate (purity unknown; 0, 5.9, 17.5 and 58.5 mg B/kg bw/d) in two-year feeding studies (no guideline specified) in Sprague-Dawley rats (n = 35/sex/dose group with 70/sex/dose group as controls), as previously assessed by RAC. In addition, shorter oestrous cycles, reduced sperm motility and spermatozoa concentration have been noted due to exposure in boric acid in mice, rats and dogs. Adverse effects on sexual function and fertility in males and females, due to exposure boric acid and borate salts, resulting in impaired fertility have thus been noted in multiple studies and species. Further studies with boric acid were described in other RAC opinions[6] leading to classification as Category 1B for fertility based on alterations to the male reproductive system and impaired fertility in several species.

RAC notes that the DS refers to disodium tetraborate tetrahydrate in Table 17 of the CLH report but to disodium tetraborate decahydrate in section 10.10.2.2. RAC referred to disodium tetraborate decahydrate in the opinions on disodium octaborate anhydrate and tetrahydrate cited by the DS. Hence, RAC refers to disodium tetraborate decahydrate in this opinion as well.

For hydrogen peroxide, no guideline studies are available, and the available non-guideline studies have several limitations. Adverse effects on fertility and sexual function (e.g. variations of the oestrus cycle and reduced mobility of spermatozoa) were seen upon exposure to hydrogen peroxide. However, effects of hydrogen peroxide are mainly local and resulting in general toxicity. Altogether, data on adverse effects on fertility and sexual function are not considered conclusive due to various study limitations.

Effects of environmental and occupational exposure to boron have been studied in multiple epidemiological studies. RAC previously concluded that no clear evidence of boron-induced adverse effects on male fertility was present. Newer studies focussing on occupational exposure to boron do not demonstrate adverse effects on male fertility and sexual function. Researchers have found a statistically significant higher boron level in semen of high-exposed workers compared to the control group. However, several limitations (e.g. assignment of group based on blood boron concentrations, high exposure to boron also in control group drinking water, low statistical power) might have impacted study results. Epidemiological studies thus do not show clear evidence for adverse effects on fertility and sexual function related to boron exposure. Besides study limitations, estimated (daily) exposure levels to boron in humans are considerably lower compared to NOAELs and LOAELs for adverse effects on fertility and sexual function in animal studies. Thus, epidemiological data on fertility and sexual function do not contradict animal data.

Conclusion

For PBS-1, read-across to boric acid and borate salts is justified. Clear evidence of adverse effects on male fertility (testes atrophy and seminiferous tubular degeneration in rats) is available for boric acid and disodium tetraborate tetrahydrate, which RAC previously has assessed. The effects

[6] https://echa.europa.eu/documents/10162/19507471-2f49-9564-d788-0452b1e124ab

on testes in the available repeated dose toxicity study with read-across substance PBS-4 is regarded as supportive evidence for adverse effects on male fertility. These effects on testes induced by per(oxo)borates are likely caused via formation of boric acid and not by hydrogen peroxide.

Adverse effects on the testes in rats seen in absence of other toxicity are relevant to humans. RAC agrees with the DS that the adjustment of the classification for Repr. from Category 2 to Category 1B on adverse effects on sexual function and fertility is warranted for PBS-1.

Developmental effects

No developmental toxicity studies are available for PBS-1, but a PNDT study (OECD TG 414) is available for PBS-4. In this study, female rats (n = 25/group) were exposed to 0, 100, 300 and 1000 mg PBS-4 (purity unknown)/kg bw/d on Gestational Day 6 to 15 via oral gavage. No clinical signs, behavioural changes, pathological findings or maternal deaths were noted. Body weight and body weight gain were statistically significantly reduced in dams exposed to 300 (including and excluding gravid uterine weight) and 1000 (only including gravid uterine weight) mg/kg bw/d. Number of resorptions and post-implantation loss increased, while number of live foetuses and foetal body weight (-11 to -35 %) decreased at ≥ 300 mg/kg bw/d. In addition, increased incidence of skeletal abnormalities and variations (at ≥ 300 mg/kg bw/d; e.g. wavy rib, unossified or incomplete ossification sternebrae), renal and ureter abnormalities and variations (at 300 or 1000 mg/kg bw/d; e.g. absence renal papillae, dilated renal pelvis), and cardiovascular malformations (at 1000 mg/kg bw/d) were observed.

Adverse effects on development were noted in absence of maternal toxicity. Maternal body weight gain excluding gravid uterine weight was statistically significantly reduced in the mid-dose group and not in other dose groups. Decreased maternal body weight (gain) was likely intrauterine, as a result of resorptions, post-implantation loss and reduced foetal body weight. The main adverse effects on development considered in this study are increased number of resorptions and post-implantation loss, and decreased number of live foetuses and foetal body weight.

For boric acid, adverse effects on development at the lowest LOAEL (13.3 mg B/ kg bw/d) available included reduced mean foetal body weight per litter, shortening of the 13th rib and wavy rib (Price et al., 1996, a follow-up study of Heindel et al., 1992). In addition, cardiovascular malformations, enlargement of lateral ventricles in the brain and agenesis were noted.[7] A clear overlap of adverse effects of development can be seen in the PNDT study for PBS-4 and other studies available for boric acid.

Human data available for possible boron-induced adverse effects on development have been evaluated by RAC in opinions regarding boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. Since then, new prospective mother-child cohort studies were published. Two prospective studies have been published investigating environmental exposure to boron in a mother-child cohort in Argentina (Igra et al., 2016; Hjelm et al., 2019). A dose-dependent effect on birth size and a possible negative effect on postnatal growth up to 6 months of age were shown due to exposure to boron but an adverse effect due to combined exposure to lithium cannot be excluded. On the other hand, no boron-mediated effects on pregnancy outcomes were noted in a retrospective study in a female cohort in Turkey (Duydu et al., 2018b). RAC agrees

[7] Opinion of boric acid, diboron trioxide etc. https://echa.europa.eu/documents/10162/584263da-199c-f86f-9b73-422a4f22f1c3

with the DS that these studies are additional evidence for adverse effects on development for per(oxo)borates.

Conclusion

Adverse effects on development (resorptions, post-implantation loss, reduced number of live foetuses and foetal body weight) in absence of maternal toxicity were demonstrated for PBS-4 in a PNDT study. This study is regarded as key study for PBS-1, based on read-across to PBS-4. In addition, supportive evidence is found in developmental toxicity studies for boric acid, such as by Price et al. (1996) and Heindel et al. (1992). Markedly increased incidence of agenesis of rib XIII was observed from 58 mg B/kg bw/d. The equivalent dose of PBS-1 (527 mg/kg bw/d) would probably not cause excessive maternal toxicity. Epidemiological studies on boron are also supportive.

Classification of Repr. 1B; H360D is justified for PBS-1. RAC agrees with the DS that no change to the current classification is necessary.

Effects on or via lactation

No studies are available for per(oxo)borates on adverse effects on or via lactation. Studies are available for boric acid and borate salts, where diffusion of boron from maternal serum to breast milk was shown in humans. Development was affected in humans due to boron exposure. However, prenatal and postnatal exposure cannot be separated.

Potential mode-of-action

There are no data presented in the CLH dossier on the mode-of-action of borates for the induction of adverse effects on male fertility and development. Available epidemiological studies for boron are considered as supportive evidence that adverse effects on development in rats are relevant to humans.

Specific concentration limits

Adverse effects on sexual function and fertility

The DS derived a ED_{10} value of 159 mg/kg bw/d based on a ED_{10} of 17.5 mg B/kg bw/d for testes atrophy from the 2-year feeding study with boric acid, as cited in the CLH report for boric acid (see Table 3 below). This ED_{10} value is within the limits of the medium potency group (4 to 400 mg/kg bw/d) for the GCL, and thus a SCL is not justified.

Table 3: *ED_{10} value for adverse effects on sexual function and fertility (Weir, 1966)*

	Dose levels (mg B/kg bw/d)				**ED_{10} (mg B/kg bw/d)**	**ED_{10} fertility (mg kg PBS-1/kg bw/d) corrected for B content**	**Allocation of potency group**
	0	**5.9**	**17.5**	**58.5**			
Testes atrophy (incidence)	3/10	1/10	4/10	10/10	17.5	17.5/0.11 = 159	Medium, GCL of 0.3 %

Developmental effects

An ED_{10} of 191 mg/kg bw/d is derived for PBS-1, based on a LOAEL for developmental toxicity of 300 mg/kg bw/d for PBS-4 and within the limits of the medium potency group (4 to 400 mg/kg bw/d) for the GCL. As noted by the DS, ED_{10} values based on developmental effects individually for PBS-4 (e.g. post-implantation loss, reduced foetal body weight and litter weight) and converted values based on boron content for PBS-1 are also within the limits of the medium potency group (see Table 4 below). Alternatively, the lowest LOAEL (13.3 mg B/kg bw/d) available for boric acid as presented by Price et al. (1996), equivalent to 121 mg PBS-1/kg bw/d, can be used. This converted value is also within the limits of the medium potency group (see Table 4 below).

Table 4: *ED_{10} values for developmental effects as provided by the DS in the RCOM and by RAC (2019)*

	Dose levels (mg PBS-4/kg bw/d)				**ED_{10} ***			**Allocation of potency group**
	0	**100**	**300**	**1000**	**mg PBS-4/kg bw/d**	**mg B/kg bw/d**	**mg PBS-1/kg bw/d**	
Live foetus weight (g)	3.69	3.57	3.28	2.4	~~127.5~~ 271.7	~~9~~ 19	173	Medium, GCL of 0.3 %
Litter weight (g)	54.97	52.62	46.49	32.52	~~197.2~~ 202.7	~~13.8~~ 14.2	129	Medium, GCL of 0.3 %
Post-implantation loss (%)	2.91	2.39	13.54	15.2	288.8	20.2	184	Medium, GCL of 0.3 %
LOAEL (PBS-4) for developmental effects					300	21	191	Medium, GCL of 0.3 %
LOAEL (boric acid) for developmental effects (Price et al., 1996)					-	13.3	121	Medium, GCL of 0.3 %

*adapted by DS after comments in the consultation (numbers in red colour are the agreed changes compared to the original CLH-report).

<u>Overall conclusion</u>

There is some evidence for reproductive toxicity of boron in humans, and this data can be used for PBS-1 based on read-across. However, these data are not sufficient for classification. Therefore, Category 1A is not warranted.

Adverse effects on male fertility (testes atrophy and seminiferous tubular degeneration) were observed in animal studies based on read-across to PBS-4, boric acid and borate salts. Death of the organism and retarded growth observed for PBS-4 in animals are clear evidence of adverse effects on development and used for read-across. These adverse effects are not considered secondary to general toxicity and are considered relevant for humans. RAC concludes that Category 1B is warranted for sexual function and fertility and on development, in agreement with the classifications proposed by the DS. RAC supports the DS proposal for no classification on effects on or via lactation.

Together this results in classification Repr.1B; H360FD without any specific concentration limit.

Inclusion of a Note

The DS proposed 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): "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 $\geqslant$ 0.3 %."

The Commission is currently discussing a text for a note (note 11[8]), to be assigned to boron compounds for classification of mixtures as reproductive toxicant based on the additivity approach which applies to substances whose hazard is due to the presence or formation of a common molecular entity (i.e., boric acid in this case).

Since the reproductive toxicity of PBS-1 is due to its hydrolytic product boric acid, RAC considers that additivity is also applicable to PBS-1.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).

8 Note 11: The classification of mixtures as reproductive toxicant is necessary if the sum of the concentrations of individual boron compounds that are classified as reproductive toxicant in the mixture as placed on the market is ≥ 0.3 %.