Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

perboric acid (H3BO2(O2)), monosodium salt trihydrate [1]; perboric acid, sodium salt, tetrahydrate [2]; perboric acid (HBO(O2)), sodium salt, tetrahydrate; sodium peroxoborate, hexahydrate [3]

EC Number: 239-172-9 [1]; 234-390-0 [2]
CAS Number: 13517-20-9 [1]; 37244-98-7 [2]; 10486-00-7 [3]

CLH-O-0000007161-83-01/F

Adopted

15 September 2022

15 September 2022

CLH-O-0000007161-83-01/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 (H3BO2(O2)), monosodium salt trihydrate [1]; perboric acid, sodium salt, tetrahydrate [2]; perboric acid (HBO(O2)), sodium salt, tetrahydrate; sodium peroxoborate, hexahydrate [3]**
EC Number:	**239-172-9 [1]; 234-390-0 [2]**
CAS Number:	**13517-20-9 [1]; 37244-98-7 [2]; 10486-00-7 [3]**

The proposal was submitted by **Sweden** and received by RAC on **4 October 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	005-018-00-2	perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate; [3] sodium peroxoborate hexahydrate; [containing < 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 234-390-0 [2] 231-556-4 [3]	13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	Repr. 1B STOT SE 3 Eye Dam. 1	H360Df H335 H318	GHS05 GHS08 GHS07 Dgr	H360Df H335 H318		Repr. 1B; H360Df: C ≥ 14 % Repr. 1B; H360D: 10 % ≤ C < 14 % Eye Dam. 1; H318: C ≥ 36 % Eye Irrit. 2; H319: 22 % ≤ C < 36 %	
	005-018-01-X	perboric acid ($H_3BO_2(O_2)$), monosodium salt, trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate; [3] sodium peroxoborate hexahydrate; [containing ≥ 0.1 % (w/w) of particles with an aerodynamic diameter of below 50 µm]	239-172-9 [1] 234-390-0 [2] 231-556-4 [3]	13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	Repr. 1B Acute Tox. 4 * STOT SE 3 Eye Dam. 1	H360Df H332 H335 H318	GHS05 GHS08 GHS07 Dgr	H360Df H332 H335 H318		Repr. 1B; H360Df: C ≥ 14 % Repr. 1B; H360D: 10 % ≤ C < 14 % Eye Dam. 1; H318: C ≥ 36 % Eye Irrit. 2; H319: 22 % ≤ C < 36 %	

Dossier submitters proposal	**Merge:** 005-018-00-2 & 005-018-01-X	**<u>Retain</u>:** perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate; [3] sodium peroxoborate hexahydrate **Remove:** [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]	**<u>Modify:</u>** 239-172-9 [1] 234-390-0 [2]	**<u>Retain:</u>** 13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	**<u>Modify:</u>** Repr.1B Acute Tox. 4	**<u>Modify:</u>** H360FD H332	**<u>Retain:</u>** GHS08 GHS07 Dgr	**<u>Modify:</u>** H360FD H332		**<u>Remove:</u>** Repr. 1B; H360Df: C ≥ 14 % Repr. 1B; H360D: 10 % ≤ C < 14 % **<u>Add:</u>** Inhalation: ATE = 1.16 mg/L	
Resulting Annex VI entry if agreed by RAC and COM	TBD	perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate; [1] perboric acid, sodium salt, tetrahydrate; [2] perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate sodium peroxoborate hexahydrate [3]	239-172-9 [1] 234-390-0 [2]	13517-20-9 [1] 37244-98-7 [2] 10486-00-7 [3]	Repr. 1B Acute Tox. 4 STOT SE 3 Eye Dam. 1	H360FD H332 H335 H318	GHS05 GHS08 GHS07 Dgr	H360FD H332 H335 H318		Inhalation: ATE = 1.2 mg/L (dusts or mists) Eye Dam. 1; H318: C ≥ 36 % Eye Irrit. 2; H319: 22 % ≤ C < 36 %	#

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) supported by RAC.

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The proposal submitted by Sweden concerns per(oxo)borates with two existing entries in Annex VI to the Regulation (EC) No 1272/2008 (CLP Regulation). Perboric acid, sodium salt, tetrahydrate (PBS-4) has currently harmonised classification as

- toxic to reproduction for both developmental and fertility effects, i.e. Repr. 1B (H360Df),
- STOT SE 3 (H335),
- Eye Dam 1 (H318: C $\geqslant$ 36 %) / Eye Irrit. 2 (H319: 22 % $\leqslant$ C < 36 %), and
- acutely toxicity via inhalation, i.e. Acute Tox. 4*, H332 (1 entry).

Currently, the entries also have various 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).

Table1: *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**
005-018-00-2	1. perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate 2. perboric acid, sodium salt, tetrahydrate 3. perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate sodium peroxoborate hexahydrate	[containing **< 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	1. perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate 2. perboric acid, sodium salt, tetrahydrate 3. perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate
005-018-01-X	1. perboric acid ($H_3BO_2(O_2)$), monosodium salt trihydrate 2. perboric acid, sodium salt, tetrahydrate 3. perboric acid ($HBO(O_2)$), sodium salt, tetrahydrate sodium peroxoborate hexahydrate	[containing **= 0.1 % (w/w)** of particles with an aerodynamic diameter of below 50 µm]	

The changes proposed in the current proposal by the Dossier Submitter (DS) are:

- Remove EC 231-556-4 from the entries, since this EC number is linked to a not well-defined dehydrated sodium perborate (with CAS number 7632-04-4).
- The cut-off values for particle size are not considered justified and hence should be removed, so merging entries 005-018-00-2 and 005-018-01-X.

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 previously assessed proposals for harmonised classification of boric acid and several related substances in the past. 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. In the same year a proposal for the modification of the 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 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-4

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 expected upon oral or inhalation exposure. Minimal absorption is expected upon dermal exposure.

PBS-4 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 monohydrate (PBS-1; CAS 10332-33-9), 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 borates does not apply. In any case, PBS-4 has been tested in acute oral and inhalation studies (see below).

Comments received during consultation

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

[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

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

A harmonised classification Acute Tox. 4* for the inhalation route is currently in place for both entries for PBS-4 and no classification for oral and dermal routes.

Several acute oral toxicity studies are available with PBS-4 and all had LD_{50} values above 2000 mg/kg bw. No acute dermal study is available with PBS-4, read-across is proposed to PBS-1. An acute inhalation toxicity study with PBS-4 is available. 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 no classification for oral acute toxicity, based on LD_{50} values above 2000 mg/kg bw in studies with PBS-4. No classification on acute toxicity was prosed for the dermal route, based on read-across with PBS-1. For the inhalation route, the DS proposes the removal of the asterisk indicating minimum classification and the inclusion of an ATE of 1.16 mg/L, based on the study with PBS-4. 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 inhalation toxicity with an ATE of 1.16 mg/L and the removal of the cut-off value of 50 µm for particle size. Another MSCA supported the DS proposals for classification on acute inhalation toxicity with an ATE of 1.16 mg/L, and no classification for acute oral and dermal toxicity.

Assessment and comparison with the classification criteria

Oral route

One reliable acute oral toxicity study is available for PBS-4. Wistar rats (n = 3/sex/group) were administered 2150, 2610 and 3160 mg PBS-4 (purity unknown)/kg bw via gavage, followed by a 14-day observation period. Lethality was reported at ≥ 2610 mg/kg bw on day 0 or 1 post-exposure. Evident acute toxicity was noted (e.g. ruffled fur, blue-coloured extremities, diarrhoea) and necropsy revealed distended stomach with gas, fluid in intestines and red glandular mucosa. Female rats appeared more sensitive than male rats, with the lowest LD_{50} reported of 2360 mg/kg bw. A non-guideline study in mice (strain not specified) is available where animals (n = 3/sex/group) were exposed to 1330, 2000, 3000 and 4500 mg PBS-4 (purity unknown)/kg bw via gavage, followed by a 21-day observation period. A LD_{50} of 2800 mg/kg bw is reported. Also other acute oral toxicity studies in rats and mice are available with several limitations (e.g. strain, sex, no. of animals not specified) and therefore of low reliability. These studies will not be further assessed as more reliable studies are available.

Use of read-across data is not necessary as studies for PBS-4 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-4.

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.

Considering a weight-of-evidence approach, the data from the reliable acute oral toxicity studies in rats with PBS-4 is preferred over the less reliable studies in rats or mice or read-across. RAC agrees with the DS that classification on acute oral toxicity is not warranted as reported LD_{50} values for PBS-4 are > 2000 mg/kg bw.

Dermal route

No acute dermal toxicity studies are available for PBS-4 and therefore read-across to PBS-1 is proposed. In an acute dermal toxicity study, 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 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. A 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 read-across 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-4 for acute dermal toxicity is not warranted.

Inhalation route

In a reliable acute inhalation toxicity study rats (male, n = 6/group, similar to OECD TG 403) 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, 5/6; 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 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. 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.

To conclude, RAC supports the proposal for the removal of the asterisk indicating minimum classification and the cut-off values for particle size distribution for PBS-4. For ATE 1.2 mg/L can be used and it falls within Category 4 (inhalation LC_{50} (dusts or mists) >1.0 but ≤ 5.0 mg/L). This results in harmonised classification Acute Tox. 4, H332, inhalation: ATE=1.2 mg/L (dusts or mists).

Overall conclusion

For PBS-4 the following classification is warranted:

- Acute Tox. 4, H332, with an ATE of 1.2 mg/L (dusts or mists) for the inhalation route, and
- No classification for the dermal and oral 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.

In a reliable 28-day oral toxicity limit test available (OECD TG 407, GLP) in rats for PBS-4, statistically significantly decreased absolute testes weight (-18 %) and histopathological changes (focal tubular atrophy and inhibition of spermiation) in the testes were noted. It was concluded that these findings on male fertility alone were in a limited study and not sufficient for classification.

According to the DS read-across to boric acid and borates is supported for per(oxo)borates based on hydrolytic and toxicokinetic behaviour. 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.

DS derived an ED_{10} of 250 mg PBS-4/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-4. However, a change of the current SCLs into the GCL 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 upon exposure to PBS-4.

The DS proposes replacing the specific concentration limit (SCL) for the GCL of 0.3 % w/w. PBS-4 falls in the medium potency group, established on an ED_{10} (LOAEL) of 300 mg/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

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 study might be due to the short duration, as in one study with boric acid, effects started after 2 weeks but worsened until weeks 6-9.[5] 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[5] 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 16 of the CLH report but 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 guidelines 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/or occupational exposure to boron have been studied in multiple epidemiological studies. RAC evaluated these epidemiological data in opinions for boric acid, disodium octaborate anhydrate and disodium octaborate tetrahydrate. RAC concluded that no

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

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

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 on testes in the available repeated dose toxicity study with PBS-4 is regarded as supportive evidence for adverse effects on male fertility. These effects on testis 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 adjustment of the classification for Repr. from Category 2 to Category 1B on adverse effects on sexual function and fertility is warranted for PBS-4.

Developmental effects

In a PNDT study (OECD TG 414), 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 of Heindel study, 1992). In addition, cardiovascular malformations, enlargement of lateral ventricles in the brain and agenesis were noted. 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. 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). Since then, new prospective mother-child cohort studies were published. 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 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 a key study. In addition, supportive evidence is found in developmental toxicity studies on 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. Epidemiological studies on boron are also supportive.

Classification of Repr. 1B, H360D is justified for PBS-4. 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 an ED_{10} value of 250 mg/kg bw/d based on an 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} (mg PBS-4/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	17.5/0.07 = 250	Medium, GCL of 0.3 %

Developmental effects

An ED_{10} of 300 mg/kg bw/d is derived for PBS-4, 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) 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 190 mg PBS-4/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)* ***Error! Bookmark not defined.***

	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-4/kg bw/d (converted for boron content)**	
Live foetus weight (g)	3.69	3.57	3.28	2.4	~~127.5~~ 271.7	~~9~~ 19		Medium, GCL of 0.3 %
Litter weight (g)	54.97	52.62	46.49	32.52	~~197.2~~ 202.7	~~13.8~~ 14.2		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 (PBS-4) for developmental effects					300	21		Medium, GCL of 0.3 %
LOAEL (boric acid) for developmental effects (Price et al., 1996)					-	13.3	13.3/0.07= 190	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).

Overall conclusion

There is some evidence for reproductive toxicity of boron in humans, and this data can be used for PBS-4 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 for PBS-4 and read-across to 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's proposal for no classification on effects on or via lactation.

Together this results in **classification as 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[6]), 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-4 is due to its hydrolytic product boric acid, RAC considers that additivity is also applicable to PBS-4.

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 DS; the evaluation performed by RAC is contained in 'RAC boxes'.

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

6 COM draft for 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 %.