Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

10 inorganic borate substances

magnesium metaborate	**237-235-5**	**13703-82-7**
sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form	**231-891-6 [1]; - [2]**	**7775-19-1 [1]; 10555-76-7[2]**
potassium pentaborate	**234-371-7**	**11128-29-3**
potassium metaborate	**237-262-2**	**13709-94-9**
dipotassium tetraborate	**215-575-5**	**1332-77-0**
dipotassium octaborate	**-**	**12008-39-8**
diammonium decaborate	**234-521-1**	**12007-89-5**
calcium tetraborate	**234-511-7**	**12007-56-6**
calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime	**-**	**-**
pentaboron sodium octaoxide	**234-522-7**	**12007-92-0**

CLH-O-0000007417-70-01/F

Adopted

14 March 2024

14 March 2024

CLH-O-0000007417-70-01/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 on **14 March 2024** by **consensus** an opinion on the proposal for harmonised classification and labelling (CLH) of:

No	Chemical name	EC number	CAS number
1	**magnesium metaborate**	**237-235-5**	**13703-82-7**
2	**sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form**	**231-891-6 [1]; - [2]**	**7775-19-1 [1]; 10555-76-7[2]**
3	**potassium pentaborate**	**234-371-7**	**11128-29-3**
4	**potassium metaborate**	**237-262-2**	**13709-94-9**
5	**dipotassium tetraborate**	**215-575-5**	**1332-77-0**
6	**dipotassium octaborate**	**-**	**12008-39-8**
7	**diammonium decaborate**	**234-521-1**	**12007-89-5**
8	**calcium tetraborate**	**234-511-7**	**12007-56-6**
9	**calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime**	**-**	**-**
10	**pentaboron sodium octaoxide**	**234-522-7**	**12007-92-0**

Rapporteur, appointed by RAC: **Lea Stine Tobiassen**

Co-Rapporteur, appointed by RAC: **Peter Hammer Sørensen**

Administrative information on the opinion

Sweden has submitted on **2 February 2023** separate CLH dossiers for each of the ten substances (see above) containing a proposal for a single, same hazard class.

The CLH reports were made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **6 March 2023**.

Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **5 May 2023**.

The following tables provide a summary of the Current Annex VI entries, Dossier submitter proposals, RAC opinions and potential Annex VI entries if agreed by the Commission.

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

1)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	magnesium metaborate	237-235-5	13703-82-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	magnesium metaborate	237-235-5	13703-82-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	magnesium metaborate	237-235-5	13703-82-7	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

2)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form	231-891-6 [1]; - [2]	7775-19-1 [1]; 10555-76-7 [2]	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form	231-891-6 [1]; - [2]	7775-19-1 [1]; 10555-76-7 [2]	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form	231-891-6 [1]; - [2]	7775-19-1 [1]; 10555-76-7 [2]	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

3)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	potassium pentaborate	234-371-7	11128-29-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	potassium pentaborate	234-371-7	11128-29-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	potassium pentaborate	234-371-7	11128-29-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

4)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	potassium metaborate	237-262-2	13709-94-9	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	potassium metaborate	237-262-2	13709-94-9	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	potassium metaborate	237-262-2	13709-94-9	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

5)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	dipotassium tetraborate	215-575-5	1332-77-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	dipotassium tetraborate	215-575-5	1332-77-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	dipotassium tetraborate	215-575-5	1332-77-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

6)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	dipotassium octaborate	-	12008-39-8	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	dipotassium octaborate	-	12008-39-8	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	dipotassium octaborate	-	12008-39-8	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

7)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	diammonium decaborate	234-521-1	12007-89-5	Repr. 1B	360FD	GHS08 Dgr	360FD			Note 11
RAC opinion	TBD	diammonium decaborate	234-521-1	12007-89-5	Repr. 1B	360FD	GHS08 Dgr	360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	diammonium decaborate	234-521-1	12007-89-5	Repr. 1B	360FD	GHS08 Dgr	360FD			Note 11

8)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	calcium tetraborate	234-511-7	12007-56-6	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	calcium tetraborate	234-511-7	12007-56-6	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	calcium tetraborate	234-511-7	12007-56-6	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

9)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime	-	-	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime	-	-	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime	-	-	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

10)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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 entry	No current Annex VI entry										
Dossier submitters proposal	TBD	pentaboron sodium octaoxide	234-522-7	12007-92-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
RAC opinion	TBD	pentaboron sodium octaoxide	234-522-7	12007-92-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11
Resulting Annex VI entry if agreed by COM	TBD	pentaboron sodium octaoxide	234-522-7	12007-92-0	Repr. 1B	H360FD	GHS08 Dgr	H360FD			Note 11

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The dossier submitter (DS) Sweden has proposed harmonised classification for the hazard class on reproductive toxicity for ten inorganic borates listed below, filing ten separate harmonised classification (CLH) reports. All the ten substances are part of a group of inorganic borates that were included in a Group Regulatory Strategy conducted by the Competent Authority in Sweden in 2020.

The group included borates with alkali metals, alkaline earth metals or ammonium counter ions. The DS assessment for all the ten substances is based on read across of available information from boric acid and borate salts as there are no data available on reproductive toxicity for the salts themselves except for one substance, magnesium metaborate, for which an OECD TG 422 study (28-day reproductive toxicity screening study) was available and was considered by the DS in their evaluation of the data.

The ten inorganic borates are:

1) magnesium metaborate
2) sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form
3) potassium pentaborate
4) potassium metaborate
5) dipotassium tetraborate
6) dipotassium octaborate
7) diammonium decaborate
8) calcium tetraborate
9) calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime
10) pentaboron sodium octaoxide

None of the ten substances are currently included in Annex VI to the Regulation (EC) No. 1272/2008 (CLP Regulation).

The DS proposed to classify the ten inorganic borates as toxic to reproduction in Category 1B for adverse effects on sexual function and fertility and in Category 1B for adverse effects on development, i.e. Repr. 1B (H360FD). The application of the generic classification limit (GCL) and Note 11[1] on additivity of boron content were also proposed. The DS did not propose classification via lactation.

[1] 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 %.", included in 19th ATP to CLH, July 2023.

Read across

According to the DS the ten inorganic borates have similar physicochemical properties and kinetic behaviour (IPCS 1998[2]). The salts will hydrolyse and convert to boric acid (H_3BO_3) at physiological pH in the aqueous layer on the surfaces of the mucosa. Boric acid is the main species at physiological and acidic pHs, the anion ($B(OH)^{4-}$) is the predominant anion at alkaline pH.

In humans and in animals (rats, rabbits, sheep and cattle) excretion following inhalation and oral exposure to boron/boric acid occurs through the kidney, with 92-95 % of the dose found in urine as boric acid. Based on data from animals, it is shown that boric acid is completely absorbed from the gastrointestinal tract and across the pulmonary tissue, whilst dermal absorption was very low (0.5 %). Distribution occurs rapidly in both humans and animals with accumulation in bone.

The DS further pointed to the similarity of the chemical and toxicological effects of boric acid and other borates on a mol boron/L equivalent basis when dissolved in water or biological fluids at the same pH and low concentration (IPCS, 1998).

Data on reproductive toxicity of boric acid and other borates were used for read across for previously agreed harmonised classification of other borates. In the present proposal the DS included reference to the previous RAC opinions on classification of boric acid and borates on reproductive toxicity i.a.:

- In 2014, RAC adopted opinions on the harmonised classification Repr. 1B (H360FD) for boric acid (3), for disodium octaborate anhydrate (4) and for disodium octaborate tetrahydrate (5).
- In 2019, RAC adopted an opinion to apply the GCL of 0.3 % w/w rather than using specific concentration limits (SCLs) for effects on sexual function and fertility and development for seven substances: boric acid, diboron trioxide, tetraboron disodium heptaoxide hydrate, disodium tetraborate anhydrous, orthoboric acid sodium salt, disodium tetraborate decahydrate and disodium tetraborate pentahydrate (6).
- In 2020, RAC adopted a harmonised classification opinion on barium diboron tetraoxide (7)**.**

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2 International Programme on Chemical Safety.
http://www.inchem.org/documents/ehc/ehc/ehc204.htm#PartNumber:6

3 ECHA, 2014c: RAC opinion on boric acid
https://echa.europa.eu/documents/10162/4db9bc68-844e-c557-8914-ab491743d471

4 ECHA,2014a: RAC opinion on Disodium octaborate anhydrate
https://echa.europa.eu/documents/10162/7d740d8c-5cd5-872b-5da2-e549983a9ff9

5 ECHA, 2014b: RAC opinion on Disodium octaborate tetrahydrate
https://echa.europa.eu/documents/10162/658b802c-1ca3-663e-4bd4-437369d715de

6 ECHA, 2019: opinion on 7 orthoboron compounds [04.01-ML-014.03] (europa.eu)

7 ECHA, 2020: RAC opinion on barium diboron tetraoxide:
https://echa.europa.eu/documents/10162/584263da-199c-f86f-9b73-422a4f22f1c3

- In 2022, RAC adopted opinions for the harmonised classification of trimethyl borate (8) and on three hydrated perborates (9, 10, 11) amongst other hazard classes as Repr. 1B (H360FD), based on read across from boric acid. In the three recent opinions on perborates, RAC also recommended the inclusion of a Note for the application of additivity when classifying boric acid/borate containing/releasing substances (now implemented in the CLP Regulation as Note 11).

RAC concurs with the DS that read across from boric acid and other borates is relevant and should be applied in the evaluation of the reproductive toxicity of the ten inorganic borates in these dossiers, in line with the previous assessments of borates by RAC.

Comments received during consultation

Comments were received for each of the ten dossiers from one MSCA and one Industry organisation on the proposed classification as Repr. 1B, H360FD.

The MSCA supported the proposed classification based on the read across from animal studies on boric acid and borax that showed impairment of sexual function and fertility (primarily testes and sperm effects) and developmental effects (malformations and reduced mean foetal weight) in different species. The MSCA noted that the human data could not be used to contradict the animal data, as the exposure levels in the epidemiological studies were far below the effect levels seen in the animal studies.

The Industry organisation agreed that read across from boric acid is applicable, and that reproductive toxicity was shown in the animal studies with boron compounds, and also supported the use of Note 11. However, they argued that classification as Repr. 2 H361d (Category 2) would be more appropriate. In their view the negative human evidence was not given sufficient weight. The Industry organisation pointed to the essential function of boron in the body and also claimed that the exposure levels in some of the epidemiological studies are above the LOAELs reported from the animal studies.

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[8] ECHA, 2022a: RAC opinion on trimethyl borate: https://echa.europa.eu/documents/10162/6e75345a-f982-14f7-278b-5b13d79cefff

[9] ECHA, 2022b: RAC opinion on 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]: https://echa.europa.eu/documents/10162/96418a42-3a6b-846c-c914-18411dbb3df6

[10] ECHA, 2022c: RAC opinion on perboric acid, sodium salt [1]; perboric acid, sodium salt, monohydrate [2]; perboric acid (HBO(O2)), sodium salt, monohydrate; sodium peroxoborate [3]; sodium perborate [4]: https://echa.europa.eu/documents/10162/d25c711c-40c4-0ba3-d901-aaf7a78c0154

[11] ECHA, 2022dc: RAC opinion on Sodium peroxometaborate : https://echa.europa.eu/documents/10162/1d8ff99e-6232-bec6-efed-24bb7283bf27

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

Animal data

In the CLH dossier, the DS summarised animal studies on mice, rats and dogs relevant for reproductive toxicity based on previous CLH dossiers on borates and thus previously evaluated by RAC in opinions on boric acid and borates from 2014 and 2022. For nine of the ten borates evaluated in the present opinion, no further animal studies were available. For magnesium metaborate two studies, an OECD TG 422 combined reproductive toxicity study and a short-term repeated dose toxicity study conducted in 2017, were also available.

A summary of findings in the animal studies with boric acid and borax and with one of the ten salts, magnesium metaborate, evaluated in the present opinion, is given in the table below.

Study type (duration), Substance(s)	**Species, strain No. of animals**	**Dosing (mg B/kg bw/d)**	**Results**	**Reference (Year)**
90-day-study Boric acid (BA) or borax	Rats, Sprague-Dawley 10/sex/dose	0, 2.6, 8.8, 26.3, 87.5, and 262.5*	From 26.3 mg B/kg bw/d* ↑ Testes atrophy ↓ Absolute uterus weight (27% BA; 42% Borax)	Weir 1966 Weir and Fisher 1972
90-day study Boric acid or borax	Dogs (Beagle) 5/sex/dose	0, 0.4, 4.3, and 43.7*	43.7 mg B/kg bw/d*: ↑ Severe testicular atrophy ↑ Complete degeneration of the spermatogenic epithelium (4/4, i.e one death)	Weir 1966 Weir and Fisher 1972
3-generation study, 2 litters/ generation Boric acid or borax	Rats, Sprague-Dawley 8 males and 16 females /dose	0, 5.9, 17.5 and 58.5	All P0 pairs sterile at 58.5 mg B/kg bw/d ↑ Testes atrophy (8/8) ↓ Viable sperm (total lack of sperm 8/8) ↓ Ovulation (no incidence reported)	Weir 1966 Weir and Fisher 1972
2 years Boric acid	Rats, Sprague-Dawley 35/sex/dose	0, 5.9, 17.5 and 58.5	58.5 mg B/kg bw/d: ↑ Seminiferous tubule degeneration ↑ Testicular atrophy	Weir 1966 Weir and Fisher 1972
30 and 60 days Borax	Rats	0, 25, 50 and 100*	From 50 mg B/kg bw/d – 30 days: ↓ Absolute epididymis weight ↓ No of different stages of germ cells in testes ↓ Pregnancy rates	Lee *et al.*, 1978
Continuous breeding for 27 weeks Boric acid	Mouse (Swiss) n = 19/sex/dose	0, 26.6, 111.3 and 221	From 26.6 mg B/kg bw/d ↓ Number and motility of sperm ↑ Abnormal sperm Decreasing fertility index with generations	Fail *et al.*, 1991
Study on effects of boron on testes 4, 7, 14, 21 and 28 days Boric acid	Rat (Fischer 344), 5 males/ duration	0 and 189	189 mg B/kg bw/d - all exposure durations from 4 days ↓ Testosterone levels, ↓ spermiation Loss of spermatozytes and spermatids	Treinen and Chapin 1991

9-week study on testicular toxicity Boric acid	Rat (Fischer 344) 6 males/group	0, 26, 38, 52 and 68	26/38 mg B/kg bw/d Inhibited spermiation progressing to sperm depletion and testes atrophy.	Ku *et al.,* 1993
Study on fertility 60 days Boric acid	Rats (White outbread) 6 males, untreated females	0, 1, 10	10 mg B/kg bw/d ↓ fertility index (62.5 % vs 89 % in controls, stat. not stated) ↑ pre-implantation loss (23.81 % vs 2.69 %, p ⩽ 0.05) 1 mg B/kg bw/d ↓ fertility index (86 %)	Marat *et al.,* 2018
Subacute study 4-6 weeks Boric acid	Mice (Swiss Albino) 10 males/dose	0, 20.1, 43.8, 78.8	43.8 mg B/ kg bw/d ↓ Sperm motility (78;72.5; 68.5; 54.0*) ↑ Malondialdehyde (MBA) 20.1 mg B/ kg bw/d ↓ Live sperm cells (74, 68.0*, 68.2*; 57.0*) ↓ Glutathione (GSH) ↑ DNA damage (0.00; 3.30*; 6.20*; 14:4*)	Aktas *et al.,* 2020
28 days combined RDT and repro screening test (OECD 422) ***Mg metaborate***	Rats, Sprague Dawley 10 (m/f) + 5 top dose and controls (m/f)	0, 3.0; 10; 25; 60 [0, 15, 50, 125, 300 mg Mg metaborate/kg bw/d]	59.1 mg B/kg bw/d ↓ BWG 15.5/21.7 % (m/f). ↓ Absolute testes and epididymis weights ↑ Germ cell degeneration (minimal to marked) ↑ Gestation length 22.5 days vs 21.3 in controls (HCD:20.9-22.1) 24.6 mg B/kg bw/d ↑ gestation length of 22 days	Anon., 2017, NB only summary available.

* The dose levels in the table are based on a background document on boron from the US EPA[12] using generic conversion factors from ppm B to mg B/kg bw/d (0.05 and 0.025 for rats and dogs, respectively). Thus, the doses differ from those given in the current CLH dossiers for the ten borates, which is based on information from previous CLH dossiers on boric acid and borax.

The present ten dossiers summarised studies on boric acid and borax already referenced in the 2014 opinions on boric acid and borates. These included elder dietary studies on boric acid: a 28-day study in rats (Treinen and Chapin, 1991) and a 90-day study in rats and in dogs, 2-year feeding study in rats and a 3-generation study in rats (Weir, 1966 and Weir and Fisher, 1972) and a continuous breeding study in mice (Fail *et al.,* 1991), a gavage 9-week study in rats (Ku *et al.,* 1993) and a feeding study in rats for 30 and 60 days with borax (Lee *et al.,* 1978).

In addition, a study on the effects of boric acid on rat fertility (Marat *et al.,* 2018) over 60 days (similar to dominant lethal test) was already included in the CLH-proposal for barium diboron tetraoxide (ECHA, 2020) and the subsequent RAC opinion (ECHA, 2022a). A sub-acute study (4 or 6 weeks) in mouse on the effects of boric acid on testes (Aktas *et al.,* 2020) was included in the CLH-proposal on trimethyl borate (ECHA, 2021d) and the subsequent RAC opinion (ECHA, 2022a).

The testes and the epididymides were identified as the main target organs for toxicity of boric acid in rats, mice and dogs. Reduced testis weights occurred from 52 mg B/kg bw/d in rats (90-day study, Weir *et al.,* 1966/1972) and in mice from 111.3 mg B/kg bw/d (continuous breeding

[12] US EPA (2008): Heath effect support document for boron: https://www.epa.gov/sites/default/files/2014-09/documents/health_effects_support_document_for_boron.pdf

study, Fail *et al.,* 1991). Histopathology revealed testes atrophy in rats from 47.2 mg B/kg bw/d in a 90-day study and at 58.5 mg/B/kg bw/d in the 3-generation study (Weir *et al.,* 1966/1972). This effect was also reported in dogs from 43.7 mg B/kg bw/d, in a 90-day study albeit in the presence of general toxicity (Weir *et al.,* 1966/1972). Decreased epididymus weight was reported at 38 mg B/kg bw/d (rats, 90-day study), 111.3 mg B/kg bw/d in mice (Fail *et al.,* 1991). Tubular degeneration and reduced number of spermatozoa, spermatocytes and spermatids were reported in rats in a 9-week study from 1993, in a 28-day study from 2020 and in a 30-day and 60-day study from 1978 and in mice from 111.3 mg B/kg bw/d in the continuous breeding study from 1991. Sperm motility was also affected in this mouse study, from 26.6 mg B/kg bw/d.

In female rats treated 90-days with boric acid and borax (Weir *et al.,* 1966) uterus weights were decreased at 157.5 mg B/kg bw/d. However, information on general toxicity was missing.

Fertility indices was reduced in mice in the continuous breeding study from 95% in the first litter to 5% in the fourth litter. Fertility of male rats was also affected in the 3-generation study (Weir *et al.,* 1972) at 58.5 mg B kg bw/d as no females were impregnated, and only 1 of 16 females were impregnated when mated with control males. In a study with 30-day and 60-day exposures of rats from 1978, pregnancy rates were reduced up to 80-100% at 100 and 200 mg B/kg bw/d at 2-4 weeks post treatment.

For magnesium metaborate, the findings from a GLP compliant screening reproductive test (OECD TG 422) in rats from 2017 was additionally included in the CLH dossier for that substance. The study included four dose groups up to 300 mg/kg bw/d (corresponding to approximately 60 mg B/kg bw/d) and two recovery groups (14 days) of 5 animals/sex at the high and the control dose levels.

Reduction in body weight gain (BWG) of 13.7 % and 15.5 % were reported in males of the highest dose groups (~60 mg B/kg bw/d) in the primary and recovery groups, respectively. In females, significant BWG reduction up to 21.7 % were seen at gestational days (GD) 14, 17 and 20. BWG was not affected in other dose groups.

The testis and epididymides were identified as target organs. Lower testicular weights and marked to severe testicular tubular degeneration/atrophy were observed at the highest dose after the regular dosing for 28 days. Lower epididymal weights, reduced epididymal luminal sperm count and finding of degenerate germ cells in the tubules were also observed at this dose level. The effects were more severe in the recovery group.

The mean gestation length was increased compared to the control group (22.5 d vs. 21.3 d) in the high dose group females (with and without recovery) and in the second highest dose group (125 mg/kg bw/d, ~25 mg B/kg bw/d) (22 d vs. 21.3 in controls).

The DS stressed that read across from boric acid and borax in relation to classification is relevant for all ten substances, including magnesium metaborate, for which the findings from the recent OECD TG 422 study concurred with the findings in the studies with boric acid and borax as to the effects of the boron ion on fertility and sexual function.

Human data:

Epidemiological studies investigating the effects of environmental and occupational boron exposure are available in the open literature and was submitted by the DS. The available published studies were discussed in the previously adopted RAC opinions and lately in the opinions of trimethyl borate and on three hydrated perborates (2022).

The RAC concluded in the previous opinions that the human studies showed no clear evidence of adverse effects on male fertility by boron. The exposure to boron in these studies were well below the LOAELs for fertility effects reported from studies in animals. RAC pointed out that these

epidemiological studies had several study design limitations and should therefore be regarded as additional information.

Few studies have been published recently, investigating the occupational exposure to boron. The most recently published studies are briefly described here with the aim of understanding to which daily dose intervals workers have been exposed to. The studies primarily deal with fertility.

A recent study was published assessing the association between boron exposure and Y:X chromosome ratio in men occupationally exposed in a boric acid production zone in Turkey (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 study by Robbins *et al*. (2008) was criticized by many authors due to weaknesses in the study design and is now retracted.

The semen samples assessed for the purpose of this recent study by Yalcin *et al.* were obtained within the scope of an earlier project ("Boron Project – I"; 2008 – 2010).

Yalcin and colleagues did not find a statistically significant correlation between blood/semen boron levels and Y:X sperm ratio in workers assigned to the exposed group, and no shift towards female babies at birth was observed.

However, the study conducted by Yalcin *et al.* 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 boron through drinking water from the central cafeteria and/or infirmary of the plant. The high boron contamination (9.47 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 Daily Boron Exposure (DBE) levels for the Turkish control group were twice as high as for the Chinese control group that was not environmentally exposed (4.68 vs. 2.3 mg B/day).

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 mg B/kg bw/d which is considerably lower than the NOAEL of 17.5 mg B/kg bw/d set for male rats.

Further, the group by Duydu *et al.* (2019) investigated the Y:X chromosome sperm ratio in boron exposed workers from two boron mining facilities located in Bandirma and Bigadic in 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).

Overall, the authors did not find a statistically significant association between B exposure and Y:X sperm ratios, the mean Y:X sperm ratios of the different exposure groups were not statistically significantly different in pairwise comparisons, and no boron associated shift in sex ratios at birth towards female offspring was seen. A negative association between reported pesticide application 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 boron concentrations instead of DBE. This is reflected by the very high semen boron levels measured in the workers assigned to the control group. The highest individual semen boron 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 boron through drinking water. It is important to note the mean semen boron 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 are 0.64 ± 0.26 mg B/kg bw/d, and the maximum individual DBE (i.e. 106.8 mg B/d) converted is 1.52 mg B/kg bw/d. As also indicated above, these values were considerably lower than the LOAEL for fertility in male rats (58.5 mg B/kg bw/d) and the NOAEL for rat fertility (i.e. 17.5 mg B/kg bw/d), set by the RAC (ECHA, 2014a).

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

The DNA damage in lymphocytes, sperm and buccal cells of occupationally (n = 102), and 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 boron 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 over exposure groups (> 651 ng B/g blood). The authors concluded that extreme occupational exposure to boron (i.e. > 651 ng b/g blood) did not induce DNA damage in lymphocytes, sperm or buccal cells. These results were in line with those reported previously by the same authors (Duydu *et al.,* 2012; Basaran *et al.,* 2012) and indicated that no statistically significant increases in DNA-damage or changes on semen parameters were found in the boron exposed Turkish workers.

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 below). Based on these previously published epidemiological studies, Bolt and colleagues stated that, compared to the boron 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 boron exposure groups in China and in Turkey reached or exceeded the experimental boron blood levels at the NOAEL for developmental toxicity in rats. Part of the persons in the highest boron exposure group in China reached or exceeded the experimental boron blood levels at the NOAEL for impaired male rat fertility. In this sense, the highest individual blood boron 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/d. The latter would thus correspond to a value of 6.7 mg B/kg bw/d if a 70 kg average body weight is assumed, and that is considerably lower than the NOAEL for rat fertility of 17.5 mg B/kg bw/d. 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 at relatively high concentrations (e.g. Mg) and fertility being assessed through questionnaires/interviews.

***Table**: Human and experimental exposure to boric acid/borate salts and associated blood boron levels*

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)*

Human studies	Estimated DBE (mg/day)	Blood B levels (ng B/ g blood)
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/d) (Weir et al., 1972)	17.5	2300#
NOAEL for developmental toxicity in rats (mg/kg bw/d) (Price et al., 1996a)	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 stated that human boron exposures, even in the highest exposed cohorts, were 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 boron within the human body that are reprotoxic cannot be reached. The authors concluded 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 sexual function and fertility in humans are available at exposure and/or blood boron levels corresponding to the animal LOAELs. Assuming a blood density of 1060 kg/m^3 and considering the uncertainty factors for inter-species and intra-human variability (EFSA, 2012), the LOAEL of 58.5 mg B/kg bw/d set for rat fertility would correspond approximately to 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).

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.

RAC conclusion on classification for sexual function and fertility

RAC agrees with the DS that adverse effects on sexual function and fertility has been demonstrated in several animal studies following exposure to boric acid and borate salts, as described in previous CLH dossiers and RAC opinions issued on borates.

In males, decreased weight and histopathological changes in the testes (testes atrophy and seminiferous tubular degeneration) and epididymides as well as reduced sperm motility and sperm concentration have been demonstrated upon exposure to boric acid or borax in mice, rats and dogs in several studies. In females, effects on the length of the oestrus cycle have also been reported.

The recent combined repeated dose and reproduction screening test available on one of the ten substances, magnesium metaborate, indicated similar effects on reproductive organs.

The few epidemiological studies available since the last CLH boron assessment in 2020 concerned effects on sexual function and fertility. None of these studies showed clear boron-induced adverse effects on sexual function and fertility in humans. As described above, the studies had several methodological limitations and were designed to mostly investigate male fertility. Other limitations in general were 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 over exposure groups in these studies were considerably lower than the NOAELs and LOAELs reported for rat fertility. No studies on effects on sexual function and fertility in humans are available at DBE levels corresponding to the animal LOAELs.

In the comments from an Industry organisation it is stated that based on the human data it is improbable that borates will cause effects on fertility or development in humans. RAC notes that the exposure levels used in the human studies are much lower than that used in the animal studies. RAC also notes that the classification criteria under CLP Regulation do not include the assessment of exposure in different uses of a substance, the probability of the occurrence of an effect, and do not include any risk assessment in relation to different uses. Rather, classification under CLP Regulation is based on the evaluation of the inherent toxicological properties of the substance. The aim of the CLP Regulation is to identify all the intrinsic adverse properties of a substance irrespective of its use.

Based on the total weight of evidence, toxicity data from three species (mice, rats, and dogs) provide clear evidence of an adverse effect of the boron ion on sexual function and fertility in the absence of other toxic effects. No evidence of reproductive toxicity was observed in the epidemiological studies, but they were designed to cover only male fertility effects and had methodological limitations. No mechanism of action or differences in metabolism are established that would raise doubt on the relevance of the animal findings in humans. In line with CLP, Annex 1, Section 1.1.1.4, it is overall concluded that the negative human data do not contradict the animal data. Therefore, there is no evidence that the effects observed in animals are not relevant to humans.

Hence, as highlighted by the RAC (Opinions on boric acid (2014a), disodium octaborate anhydrate (2014b), disodium octaborate tetraborate (2014c), on the revision of concentration limits for reproductive toxicity for seven borates (2019), and on barium diboron tetraoxide (2020)), the available human data cannot be used to overrule 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. Therefore, RAC considers the human epidemiological data as additional information for the assessment.

In conclusion, RAC agrees with the DS that the ten inorganic borates in this opinion warrant classification in Category 1B for fertility, Repr. 1B; H360F, based on the alterations to the male reproductive system and impaired fertility in several animal species. The classification is based on read across from the consistent findings from the animal data on boric acid and borate salts, as in RAC's previous opinions on borates, and supplemented by the OECD TG 422 study on magnesium metaborate.

Concentration limits

Based on an ED_{10} of 17.5 mg B/kg bw/d for testes atrophy in a 2-year rat chronic toxicity study (Weir *et al.,* 1966) on boron salts, and as no modifying factors (severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bioaccumulation) apply, the DS proposed that the ten inorganic boron salts in the present opinion should be assigned the medium potency group ($4 < ED_{10} < 400$ mg/kg bw/d) with a generic concentration limit (GCL) of 0.3 % w/w. RAC agrees with this calculation and resulting use of the GCLs of 0.3 % for Repr. 1B; H360F.

Developmental toxicity

Animal data

The DS proposal referred to read across from the available animal data on boric acid and borax that have been included in previous CLH dossiers on boron salts and have thus been assessed in previous RAC opinions.

The read across is supplemented in the dossier with data on magnesium metaborate i.e. screening reproductive test.

The previously assessed data consistently demonstrated developmental toxicity of the boron ion in studies in rats, mice and rabbits, with the rat as the most sensitive species.

The developmental effects reported included:

- increased incidence of foetal deaths and decreased birth index in mice (continuous breeding study by Fail *et al.,* 1991) and increased number of resorptions in rats (PNDT study by Heindel *et al.,* 1992, 60-day treatment of males premating, Marat *et al.,* 2018) and in rabbits (Price *et al.,* 1996b/ Heindel *et al.,* 1994)
- reduced foetal weights in rats (Price *et al.,* 1996a) and in mice (Fail *et al.,* 1991)
- skeleton malformations in rats (agenesis or shortening of rib XIII) (Heindel *et al.,* 1992, Price *et al.,* 1996a) and in rabbits (non-statistically significant effects on sternum and ribs). (Price *et al.,* 1996b/Heindel *et al.,* 1994)
- visceral malformations of eyes and central nervous system (enlargement of lateral ventricles in the brain) and cardiovascular system (septal defect, enlarged aorta) in rats and mice (Heindel *et al.,* 1992) and in rabbits (Price et al, 1996b/Heindel *et al.,* 1994).

The developmental effects in rats and mice were seen at doses that were not toxic to the dams. In the rabbits, the developmental effects were reported at doses with some maternal toxicity and the maternal LOAEL was set at the same level as the foetus LOAEL.

The DS summarised the findings of the screening reproductive toxicity study in rats on magnesium metaborate (REACH registration data). The study used doses of 0, 15, 125 and 300 mg/kg bw/d (corresponding to around approximately 0, 0.75, 6.25 and 15 mg B/kg bw/d). Mean live litter size was reduced at the high dose group. Also, one litter was lost by PND 2 and pup survival was further affected up to day 7. Lower mean live litter size at 300 mg/kg bw/d (2.8 pups as compared to 13.6 in the control group) was reported. A lower post-natal survival was observed at both 300 mg/kg bw/d and at 125 mg/kg bw/d and a substance-related lower mean male and female pup body weight and body weight gain were also seen in these two dose groups. At necropsy of pups found dead at 300 mg/kg bw/d malformations (2 pups with anasarca, 1 cleft palate, 2 hydrocephaly, 3 microphthalmia, 1 lack of one rib pair, 1 displaced aortic arch and 1 with affected sternal bands) and variations were detected. The dams had lower body weights occasionally reaching 21.7 % at the highest dose of 300 mg/kg bw/d. The DS regarded the developmental

findings reported relevant for classification and not considered to be a secondary non-specific consequence of other toxic effects, as supportive to the previous assessment.

Human data

No new studies related to developmental toxicity from epidemiology studies were published since the CLH opinion on barium diboron tetraoxide (2020). However, the conclusion from the previous RAC opinions was that the epidemiological studies related to developmental toxicity did not show clear adverse effects on pregnancy outcomes, including birth weight from boron exposure. RAC concluded that the human data should be seen as additional information. The human information on developmental effects does not contradict the animal data and gives no evidence that the effects observed in animals are not relevant to humans.

RAC conclusion on classification for developmental toxicity

In agreement with the previous evaluation on borates, RAC considers that classification in Category 1B for development is justified based on read across to studies in several species showing malformations and lower weights of the offspring, e.g. the PNDT study in the rat with boric acid, by Heindel *et al.* (1992), which showed markedly increased incidence of agenesis of rib XIII from 58 mg B/kg bw/d. The available reproduction toxicity screening study on magnesium tetraborate also demonstrated developmental effects and is used as supportive evidence. RAC notes the guidance on the use of human evidence under the CLP Regulation Annex I, section 1.1.1.4 and the CLP guidance on criteria, point 3.7.2.3.3. The available epidemiological data for borates, indicating no or minimal developmental effects, are not considered to contradict the animal data due to low exposure levels and due to methodological limitations in some of the studies.

Concentration limits

The DS proposed to base the calculation of a concentration limit on the missing/short XIII rib (Heindel et al, 1992), in accordance with the evaluation in previous RAC opinions on borates. As no ED_{10} could be derived due to low incidences of the effect and the absence of a NOAEL the LOAEL of 13.3 mg B/kg bw/d was used, in accordance with the criteria, leading to placing the 10 inorganic boron salts in the medium potency group (4 < LOAEL < 400 mg/kg bw/d). No modifying factors related to type or severity of effect, data availability, dose-response relationship, mode/mechanism of action, toxicokinetics or bioaccumulation apply.

RAC agrees with this calculation and resulting use of the GCLs of 0.3 % for Repr. 1B; H360D.

Effect on or via lactation

Information on adverse effects on or via lactation from animal studies are inconclusive, as described in previous opinions. In the reproduction toxicity screening study on magnesium metaborate, mortality of pups in the high dose group (60 mg B/kg bw/d) at post-natal day (PND) 0 or 1 precluded the possibility to assess effects under or during lactation. At the second highest dose level (5 mg B/kg bw/d) body weight decreases were continued from PNDT 1. Thus, the causality of the effect was not clearly attributable to lactation as relation to prenatal or postnatal exposure cannot be separated. Studies are available for boric acid and borate salts, where diffusion of boron from maternal serum to breast milk was shown in humans. The available information does not allow to conclude whether these boron levels in breast milk are potentially toxic.

RAC conclusion on effect on or via lactation

RAC concludes that classification for effects on or via lactation is not warranted to any of the ten inorganic borates due to inconclusive data.

Overall RAC conclusion on reproductive toxicity

RAC concludes, in agreement with the DS, that **classification for fertility as Repr. 1B H360F** is warranted for all ten inorganic borates, based on read across from boric acid and borax, for which severe effects on testes and spermatogenesis have been reported in several animal species. In the case of magnesium metaborate, the similar effects seen in the rat screening toxicity study support the classification.

RAC concludes, in agreement with the DS, that **classification for developmental toxicity as Repr. 1B H360D** is warranted for the ten inorganic borates based on read across from boric acid and borax. Skeletal malformations and visceral malformations and anomalies in the rat have been identified as the most relevant effects for developmental toxicity classification of borates. The recent screening study on magnesium metaborate demonstrated similar developmental toxicity and supports the previous evaluations on borates and classification.

RAC further concludes that the available epidemiological data on borates which report no adverse effects on sexual function and fertility and no or minimal developmental effects, are not considered to contradict the animal data due to low exposure levels and due to methodological limitations in some of the studies.

RAC also agrees with the DS's proposal of **no classification for effects on or via lactation** for the ten inorganic borates in this opinion.

Overall, in agreement with previous opinions on borates, RAC concludes that the ten inorganic borates listed below warrant classification as **Repr. 1B H360FD together with applying the generic concentration limits and Note 11:**

1) magnesium metaborate;
2) sodium metaborate, anhydrous [1]; boric acid (HBO_2), sodium salt, tetrahydrate [2]; and any other hydrated form;
3) potassium pentaborate;
4) potassium metaborate;
5) dipotassium tetraborate;
6) dipotassium octaborate;
7) diammonium decaborate;
8) calcium tetraborate;
9) calcium metaborate ($Ca(BO_2)_2$) and calcium tetraborate (CaB_4O_7), amorphous reaction products of boric acid with lime;
10) pentaboron sodium octaoxide.

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.

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