Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling
at EU level of

Boric acid,
Diboron trioxide,
Tetraboron disodium heptaoxide hydrate,
Disodium tetraborate anhydrous,
Orthoboric acid sodium salt,
Disodium tetraborate decahydrate and
Disodium tetraborate pentahydrate

CLH-O-0000001412-86-300/F

Adopted

20 September 2019

20 September 2019

CLH-O-0000001412-86-300/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 names, EC/CAS numbers:

Boric acid [1] [2]: EC 233-139-2 [1], EC 234-343-4 [2]; CAS 10043-35-3 [1], CAS 11113-50-1 [2]
Diboron trioxide: EC 215-125-8; CAS 1303-86-2
Tetraboron disodium heptaoxide hydrate [1], disodium tetraborate anhydrous [2], orthoboric acid, sodium salt [3]: EC 235-541-3 [1], 215-540-4 [2], 237-560-2 [3]; CAS 12267-73-1 [1], 1330-43-4 [2], 13840-56-7 [3]
Disodium tetraborate decahydrate: EC 215-540-4; CAS 1303-96-4
Disodium tetraborate pentahydrate: EC 215-540-4; CAS 12179-04-3

The proposal was submitted by **Sweden** and received by RAC on **2 November 2018.**

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 **10 December 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 February 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Betty Hakkert**

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 **20 September 2019** by **consensus**.

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

	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	005-007-00-2	boric acid [1] boric acid [2]	233-139-2 [1] 234-343-4 [2]	10043-35-3 [1] 11113-50-1 [2]	Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: C ≥ 5,5%	
Dossier submitters proposal	005-007-00-2	boric acid [1] boric acid [2]	233-139-2 [1] 234-343-4 [2]	10043-35-3 [1] 11113-50-1 [2]	**Retain** Repr. 1B	**Retain** H360FD	**Retain** GHS08 Dgr	**Retain** H360FD		**Remove** Repr. 1B; H360FD: C ≥ 5,5%	
Resulting Annex VI entry if agreed by RAC and COM	005-007-00-2	boric acid [1] boric acid [2]	233-139-2 [1] 234-343-4 [2]	10043-35-3 [1] 11113-50-1 [2]	Repr. 1B	H360FD	GHS08 Dgr	H360FD		*	

*The generic concentration limit of 0,3% will apply

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

	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	005-008-00-8	diboron trioxide	215-125-8	1303-86-2	Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: C ≥ 3,1%	
Dossier submitters proposal	005-008-00-8	diboron trioxide	215-125-8	1303-86-2	**Retain** Repr. 1B	**Retain** H360FD	**Retain** GHS08 Dgr	**Retain** H360FD		**Remove** Repr. 1B; H360FD: C ≥ 3,1%	
Resulting Annex VI entry if agreed by RAC and COM	005-008-00-8	diboron trioxide	215-125-8	1303-86-2	Repr. 1B	H360FD	GHS08 Dgr	H360FD		*	

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

	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	005-011-00-4	tetraboron disodium heptaoxide, hydrate [1] disodium tetraborate, anhydrous [2] orthoboric acid, sodium salt [3]	235-541-3 [1] 215-540-4 [2] 237-560-2 [3]	12267-73-1 [1] 1330-43-4 [2] 13840-56-7 [3]	Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: ≥ 4,5%	
Dossier submitters proposal	005-011-00-4	tetraboron disodium heptaoxide, hydrate [1] disodium tetraborate, anhydrous [2] orthoboric acid, sodium salt [3]	235-541-3 [1] 215-540-4 [2] 237-560-2 [3]	12267-73-1 [1] 1330-43-4 [2] 13840-56-7 [3]	**Retain** Repr. 1B	**Retain** H360FD	**Retain** GHS08 Dgr	**Retain** H360FD		**Remove** Repr. 1B; H360FD: ≥ 4,5%	
Resulting Annex VI entry if agreed by RAC and COM	005-011-00-4	tetraboron disodium heptaoxide, hydrate [1] disodium tetraborate, anhydrous [2] orthoboric acid, sodium salt [3]	235-541-3 [1] 215-540-4 [2] 237-560-2 [3]	12267-73-1 [1] 1330-43-4 [2] 13840-56-7 [3]	Repr. 1B	H360FD	GHS08 Dgr	H360FD		*	

*The generic concentration limit of 0,3% will apply

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

	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	005-011-01-1	disodium tetraborate decahydrate	215-540-4	1303-96-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: ≥ 8,5%	
Dossier submitters proposal	005-011-01-1	disodium tetraborate decahydrate	215-540-4	1303-96-4	**Retain** Repr. 1B	**Retain** H360FD	**Retain** GHS08 Dgr	**Retain** H360FD		**Remove** Repr. 1B; H360FD: ≥ 8,5%	
Resulting Annex VI entry if agreed by RAC and COM	005-011-01-1	disodium tetraborate decahydrate	215-540-4	1303-96-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD		*	

*The generic concentration limit of 0,3% will apply

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

	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	005-011-02-9	disodium tetraborate pentahydrate	215-540-4	12179-04-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: ≥ 6,5%	
Dossier submitters proposal	005-011-02-9	disodium tetraborate pentahydrate	215-540-4	12179-04-3	**Retain** Repr. 1B	**Retain** H360FD	**Retain** GHS08 Dgr	**Retain** H360FD		**Remove** Repr. 1B; H360FD: ≥ 6,5%	
Resulting Annex VI entry if agreed by RAC and COM	005-011-02-9	disodium tetraborate pentahydrate	215-540-4	12179-04-3	Repr. 1B	H360FD	GHS08 Dgr	H360FD		*	

*The generic concentration limit of 0,3% will apply

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The proposal submitted by Sweden concerns several borates with existing entries in Annex VI of the Regulation (EC) No 1272/2008 (CLP Regulation). As shown in the Table below, these borates are currently harmonised as toxic to reproduction for both developmental and fertility effects, i.e. Repr. 1B (H360FD). They also have various specific concentration limits (SCLs) which were set 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**: Borates covered by this RAC opinion*

Entry in CLP (Index number)	Chemical name(s)	CAS	EC	Existing specific concentration limit (SCL) (% w/w)	Proposed generic concentration limit (GCL) (% w/w)
005-007-00-2	boric acid	10043-35-3 11113-50-1	233-139-2 234-343-4	5,5	0,3
005-008-00-8	diboron trioxide	1303-86-2	215-125-8	3,1	0,3
005-011-00-4	disodium tetraborate, anhydrous; boric acid, disodium salt	1330-43-4	215-540-4	4,5	0,3
	tetraboron disodium heptaoxide, hydrate	12267-73-1	235-541-3	4,5	0,3
	orthoboric acid, sodium salt	13840-56-7	237-560-2	4,5	0,3
005-011-01-1	disodium tetraborate decahydrate; borax decahydrate	1303-96-4	215-540-4	8,5	0,3
005-011-02-9	disodium tetraborate pentahydrate; borax pentahydrate	12179-04-3	215-540-4	6,5	0,3

RAC concluded in March 2014 on the classification of two disodium octaborates (EC 234-541-0 and 234-541-0) as Repr. 1B (H360FD) with a GCL of 0.3% w/w (Commission Regulation (EU) 2016/1179 of 19 July 2016). A proposal for a revised harmonised classification of boric acid submitted in September 2013 did not include a suggestion to revise the SCL and it was therefore not addressed by RAC. However, in the opinion for boric acid RAC noted that a GCL of 0.3% would apply if the concentration limit had been addressed. Table 3.7.2 of Annex I to the CLP Regulation contains generic concentration limits (GCLs) above which classification for reproductive toxicity is required for mixtures. The GCL of 0.3% (w/w) applies to reproductive toxicants in Category 1A and 1B.

Hence, the objective of the CLH proposal was to harmonise the GCL value for the seven borates to 0.3% w/w. The reason given by the dossier submitter (DS) for combining the borates in one CLH report is that the data and argumentation are the same for all the substances.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The dossier submitter provided summaries of the available reproductive studies in animals with borates and identified the key studies for determination of the dose corresponding to a 10% increase in an adverse effect, relative to the control response (ED_{10} value) for effects on sexual function and fertility and for effects on development. ED_{10} and LOAEL values were derived for the seven borates using the conversion factor for equivalent dose of boron as the effects observed for the tested borates can be extrapolated to the non-tested borates as all the borates will convert into un-dissociated boric acid at physiological conditions. An ED_{10} of 17.5 mg/kg bw/day boron equivalent (B) for effects on sexual function and fertility and a LOAEL of 13.3 mg/kg bw/day boron equivalent for effects on development were derived using the method described in the CLP guidance (Guidance on the application of the CLP criteria, v.5 July 2017) and in line with the previous assessment by RAC of the two octaborates (RAC, 2014). In addition, summaries of the available epidemiological studies were provided. It was concluded that the absence of observed effects in humans does not contradict the effects observed in animals because the human exposure levels were below the NOAEL in animals.

The ED_{10} for effects on sexual function and fertility for each of the seven borates (Table below) were between 4 and 400 mg/kg bw/day (medium potency group). The LOAEL for effects on development for each of the seven borates (Table below) were also between 4 and 400 mg/kg bw/day (medium potency group). In addition, none of the modifying factors were applicable according to the DS. Therefore, the GCL would be applicable and the SCL should be removed for the seven borates.

***Table**: Derivation of ED_{10} values and concentration limits for borate compounds based on boron contents*

Substance	**Formula**	**EC**	**CAS**	**Molecular weight (g/mol)**	**Conversion factor for equivalent dose of boron[1]**	**ED_{10} for fertility corrected for boron-content** (mg/kg bw/day)	**LOAEL for development corrected for boron-content** (mg/kg bw/day)	**Proposed generic concentration limit (GCL, % w/w), fertility**	**Proposed generic concentration limit (GCL, % w/w), development**
Boric acid	H_3BO_3	233-139-2; 234-343-4	10043-35-3; 11113-50-1	61.83	0.17	17.5/0.17 = 103	13.3/0.17 = 78	0.3	0.3
Diboron trioxide	B_2O_3	215-125-8	1303-86-2	69.62	0.31	17.5/0.31 = 56	13.3/0.31 = 43	0.3	0.3
Tetraboron disodium heptaoxide, hydrate	$Na_2B_4O_7 \bullet H_2O$	215-540-4	12267-73-1	219.24	0.20	17.5/0.20 = 88	13.3/0.20 = 67	0.3	0.3
Disodium tetraborate anhydrous	$Na_2B_4O_7$	235-541-3	1330-43-4	201.22	0.21	17.5/0.21 = 83	13.3/0.21 = 63	0.3	0.3
Orthoboric acid, sodium salt	Na_3BO_3	237-560-2	13840-56-7	127.80	0.08	17.5/0.08 = 219	13.3/0.08 = 166	0.3	0.3
Disodium tetraborate decahydrate	$Na_2B_4O_7 \bullet 10H_2O$	215-540-4	1303-96-4	381.38	0.11	17.5/0.11 = 159	13.3/0.11 = 121	0.3	0.3
Disodium tetraborate pentahydrate	$Na_2B_4O_7 \bullet 5H_2O$	215-540-4	12179-04-3	291.35	0.15	17.5/0.15 = 117	13.3/0.15 = 89	0.3	0.3

[1] Molecular weight of boron equals 10.8 g/mol

Comments received during public consultation

Comments were received from Member States Competent Authorities (MSCA), industry or trade associations, companies or downstream users, individuals and academic institutions. Several MSCA agreed to the proposed removal of the SCLs for the seven borates. However, the other commenters did not agree with the proposed removal and brought forward a number of arguments challenging the justification provided by the DS. These comments can be grouped into the following main arguments:

- The absence of an observed increase in effects on reproduction in the epidemiological studies supports a very low potency hazard for boron substances (modifying factor);
- A GCL of 0.3% or 3% based on boron content should be applied and would be in line with other European legislation;
- Comments regarding the methodology for deriving the SCL;
- The effects used to derive the ED_{10}/LOAEL for developmental effects were considered variations and not malformations and would therefore not be used for the derivation of the ED_{10}/LOAEL;
- Alternative ED_{10} values should be applied which are close to the border for low potency and therefore, applying the low potency group should be considered;
- The strong impact of the removal of the SCLs on the borates supply chain;
- It is not justified that a reduction of the concentration limit in mixtures will improve safety and therefore the proposed change is unnecessary.

Most of these arguments will be taken into account in the RAC assessment and in the comparison with the classification criteria. The exceptions are made with the arguments of the impact of the proposed change on the borates supply chain and the relevance of the proposed changes for risk assessment. It should be noted that a socio-economic impact/analysis is not part of the CLP criteria used for the assessment of the classifications and the related SCL or GCL.

In addition, specific comments were provided on the summary of the study by Igra *et al*., 2016. In this prospective epidemiology study, a decrease in birth length was determined for the offspring of mothers with a serum boron concentration above 80 µg/L. The DS considered the results as additional information that does not contradict the animal data. The industry provided comments concerning the co-exposure to other substances, the effect of altitude on birth parameters and other limitations. This study and these comments were not assessed as the interpretation of the results of this study does not affect the derivation of the GCL or SCL.

Assessment and comparison with the classification criteria

Method for deriving potency classes for substances inducing reproductive effects

Industry (European Borates Association, EBA) questioned the approach as included in the CLP guidance. It was stated that the method used to differentiate substances into potency classes is questionable because it takes into account only the dose level at which effects on reproduction are observed but not the difference in severity of the reproductive effects between substances. Therefore, a case by case assessment would be necessary. RAC agrees that for certain effects, such as the difference in adversity between a reduction in sperm counts and a reduction in the number of offspring, this difference could be taken into account for potency setting as it is likely that the ED_{10} for both effects for the same substance could be different. For this reason, a minimal level of severity is already required according to the guidance. Furthermore, the severity of the effects should be taken into account as a modifying factor (CLP guidance paragraph 3.7.2.6.5.1).

Additionally, it was suggested by industry to take the difference between animal studies and epidemiological studies, including human relevance as a modifying factor, into consideration (Annex I to comments received from EBA). RAC agrees that effects observed in animals that have shown not to be relevant for humans should not be taken into account. However, absolute or quantitative differences between animals and humans should already be taken into account within the modifying factor 'Mode or mechanism of action' (CLP guidance 3.7.2.6.5.4).

Overall, RAC considers the current approach as described in the CLP guidance, using three broad classes, reasonable for assigning substances to the appropriate potency classes and associated SCLs or GCLs.

Derivation of the ED_{10} values for effects on sexual function and fertility and development

No new reproductive studies in animals were available for the evaluation of the seven borates. Therefore, the same data as previously used by RAC for the disodium octaborates were used to derive the ED_{10} (or LOAEL) value(s).

Reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that borates impair fertility through atrophy and seminiferous tubule degeneration in the testes. The effects observed in the different species are similar in nature. Based on the data from the 2-year feeding study on boric acid in rats (Weir, 1996a), the overall NOAEL for fertility is 100 mg/kg bw/day, equivalent to 17.5 mg /kg bw/day of boron. This conclusion on the testicular effects and the overall NOAEL is also supported by the study conducted with disodium tetraborate decahydrate (Weir, 1996b). As the incidence of the animals with testis atrophy was increased by 10% at the NOAEL, this value is also the ED_{10} (100 mg/kg bw/day, equivalent to 17.5 mg /kg bw/day of boron) for this effect (see Table below).

***Table**. Incidence of testis atrophy after chronic exposure to boric acid (Study report, 1966)*

Dose (B) mg/kg bw/day	0 (0)	33 (5.9)	100 (17.5)	334 (58.5)
No of animals	3/10	1/10	4/10	10/10

For effects on development, the overall NOAEL for embryotoxic/teratogenic effects was 9.6 mg /kg bw/day boron equivalent, based on a reduction in mean foetal body weight/litter and an increased incidence in short rib XIII malformation at 76 mg/kg bw/day (13.3 mg /kg bw/day boron equivalent) (Price *et al*., 1996). The foetal incidence of short rib XIII malformation was 1.2 % and 1.5% at the LOAEL (13.3 mg /kg bw/day boron equivalent) and the highest dose tested (25 mg /kg bw/day boron equivalent) respectively (Price *et al*., 1996). As the incidences are low, it is not possible to derive an ED_{10}. In line with the guidance, in such cases the LOAEL of 13.3 mg/kg bw/day boron equivalent should be used for setting the SCL. This value is in accordance with the previous RAC assessment for disodium octaborates (RAC, 2014).

In the public comments it was stated that the effects used to ascertain the LOAEL for developmental effects, namely reduced foetal body weight, increased incidence of short rib XIII, wavy rib and decreased incidence of extra rib on lumbar I, should be considered as variations. Therefore, these effects should not be taken into account for deriving the potency group and the SCL/GCL. According to RAC and in line with the previous RAC opinion on the disodium octaborates the effects on the ribs should be considered as malformations as there are several related effects on the ribs which were not fully reversible. A low level agreement (grey zone, value 38.5) was reached on the classification of short rib as a malformation or variation upon assessment and

discussion by a large group of teratologists (Solecki *et al*, 2001). In addition, a strong increase in foetuses with cardiovascular defects per litter (72% vs 3% in controls) was observed in the developmental study in rabbits (Price *et al*, 1996) at 25 mg B/kg bw/day. The ED_{10} for this effect is estimated at approximately 150 mg/kg bw/day for boric acid and 26 mg/kg bw/day for boron. This results in an ED_{10} value for all borates within the medium potency group.

Also, for effects on sexual function and fertility, it was suggested to use the LOAEL instead of the ED_{10}. In line with the guidance, RAC is of the opinion that an ED_{10} is a better descriptor of the potency than a LOAEL and whenever possible this should be used. Furthermore, it is noted that the LOAEL would still be within the medium potency range. It was also argued to use the ED_{10} values for effects on sexual function and fertility (123.5 mg/kg bw/day) and for effects on development (195 mg/kg bw/day) for boric acid as derived by Muller *et al*. (2012). RAC does not agree with the proposed suggestion as for effects on development an LOAEL approach should be applied. The ED_{10} value for effects on fertility differ only to a very limited extent and was based on another study. The reason for this difference cannot be determined by RAC. Therefore, no changes are applicable. Further, it is noted that both suggested alternative ED_{10} values are still within the range for medium potency.

In an analysis of the distribution of the ED_{10} values for boric acid for effects on sexual function and fertility (123.5 mg/kg bw/day) and for effects on development (195 mg/kg bw/day) compared to the distribution of ED_{10} values from Muller *et al*. (2012), it is stated that ED_{10} values are close to the border for low potency (Annex I of the EBA comments). The same comment stated that only 13% (development) and 22% (fertility) of the substances are within the medium group have a higher ED_{10} value (between the ED_{10} for boric acid and the border of 400 mg/kg bw/day). Since RAC does not agree with the use of an ED_{10} value for effects on development, this issue on the ED_{10} is not considered relevant. For effects on fertility RAC applies a marginally lower ED_{10} value. Therefore, RAC does not agree that the data show that the ED_{10} for boric acid is close to the border for low potency.

Overall, RAC sees no justification to deviate from the previous assessment of the ED_{10}/LOAEL for borates. Even if a higher LOAEL or ED_{10} would be applicable for developmental effects, the ED_{10} value for effects on sexual function and fertility would still result in a medium potency class and be determinative for the overall GCL or SCL for effects on reproduction. Based on the values for boron derived above, the comparable values for the individual boron compounds were calculated (see Table above). This results in a medium potency group for all seven borates.

Derivation of the potency group taking into account the modifying factors

Type and severity of the effect

The type of effects observed in reproductive toxicity studies following exposure to borates and used to determine the ED_{10} included malformations were considered as severe. The same applies to the increase in testis atrophy. Therefore, this does not change the potency group.

Data availability

The available data for the borates was considered adequate compared to the REACH requirements and does not justify adaptation of the potency group.

Dose-response relationship

Borates showed a normal dose-response relationship for effects on sexual function and fertility and no adaptation of the potency group was considered necessary. For effects on development a LOAEL is used to derive the potency group and the incidence of effects at the LOAEL is only

0.5% above the control value (0.7% in controls and 1.2% at 13.3 mg /kg bw/day boron equivalents). Calculation of an ED_{10} value is not possible as this would require extrapolation beyond the tested dose levels. However, the ED_{10} value would be much higher than the LOAEL and potentially resulting in an ED_{10} value corresponding to a lower potency group. However, according to the guidance, in such situations the higher potency group based on the LOAEL should be used.

Mode or mechanism of action

No conclusive information was available on the mode or mechanism of action of borates for the induction of malformations or effects on sexual function. Several epidemiological studies are available showing no increase in effects on sexual function or fertility or on developmental effects at mean boron blood levels considerably below the blood levels estimated for the NOAEL for observed effects in rats. Therefore, this comparison does not demonstrate an absolute or quantitative difference between humans and animals and modification of the potency group is not justified.

Toxicokinetics

There were no data available that indicate that borate toxicokinetics from animals would not be relevant for humans and no adaption to the potency group is needed.

Bio-accumulation of substance

Borates are not considered to be bio-accumulating substances from the data available.

Conclusion on modifying factors and potency group

No modifying factors were identified that would affect the potency group. Therefore, RAC concludes that the final potency group for the seven borates is 'medium'.

Derivation of a GCL or SCL

Several commenters suggested assigning a GCL or SCL based on the boron content as only borates mixtures containing the same percentage of boron are equipotent. This is supported by the use of a boron based approach also in other EU legislation and opinions of EU scientific committees. RAC notes that Annex VI of CLP contains the option to apply Note 1 to a substance stating "*The concentration stated or, in the absence of such concentrations, the generic concentrations set out in this Regulation are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture*". This Note is applied to several metal containing compounds classified as Repr. 1B and/or Carc. 1B including cobalt dichloride, cadmium sulphide and lead compounds. In addition, for chromates Note 3 is available stating "*The concentration stated is the percentage by weight of chromate ions dissolved in water calculated with reference to the total weight of the mixture*". This Note is applicable to potassium chromate. Since these Notes only apply to metals and metal compounds, RAC is of the opinion that it does not apply to boron. The GCL would be applicable to all seven borates as they all fall into the medium potency group and the differences in potency between these borates based on the amount of boric acid that can be formed is only small (see table above). In view of that, RAC agrees with the proposal of the DS in setting a GCL of 0.3% for all seven borates, which is also in line with the previous conclusion of RAC on the two disodium octaborates in 2014.

Regarding the medium potency group for reproductive toxicity, determined according to the CLP Guidance, no modifying factors were identified that could have an impact. Therefore, in agreement with the DS's proposal, the final potency group for the seven borates is concluded by

RAC as being medium potency (boundaries: 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day) (Table 3.13 and Section 3.7.2.6.8.5 of the CLP Guidance).

RAC agrees with the DS that the SCLs of the seven borates should be removed from the existing entries in CLP as they are not in line with the approach according to the CLP guidance. RAC agrees with DS that in line with the CLP guidance on the medium potency group, **a GCL of 0.3% applies**, which is in accordance with the previous evaluation of RAC (RAC 2014).

Conclusion

All relevant scientific data related to the reproductive toxicity of boron has previously been assessed by RAC. The available (recent) human data collectively show no effects on fertility and sexual function. However, there is no evidence that the effects observed in animals are not relevant to humans (RAC, 2014).

Additional references

Solecki et al (2000) Harmonisation of rat foetal skeletal terminology and classification. Report of the third workshop on the terminology in developmental toxicology. Reproductive Toxicology 15: 713-721.

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).