Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Boric Acid

EC numbers: 233-139-2 [1], 234-343-4 [2]

CAS numbers: 10043-35-3 [1], 11113-50-1 [2]

CLH-O-0000003738-64-03

Adopted

14 March 2014

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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CLH-O-0000003738-64-03

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:

Chemicals name: **Boric Acid**
EC numbers: **233-139-2 [1], 234-343-4 [2]**
CAS numbers: **10043-35-3 [1], 11113-50-1 [2]**

The proposal was submitted by **Poland** and received by the RAC on **26 April 2013.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS), the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

Poland 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 **14 May 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **28 June 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Normunds Kadikis**

Co- rapporteur, appointed by RAC: **Paola di Prospero Fanghella**

To ensure the consistency of the opinions for boric acidand disodium octaborate anhydrate as well as disodium octaborate tetrahydrate (dossier submitter: The Netherlands), the Rapporteur appointed for the latter dossiers, **Bert-Ove Lund**, collaborated closely in support of the current opinion.

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **14 March 2014.** The RAC Opinion was adopted by **consensus**.

OPINION OF RAC

RAC adopted the opinion that **Boric Acid** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment 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]	**Modify:** Repr. 2	**Modify:** H361d	GHS08 Wng	**Modify:** H361d		
RAC opinion					Repr. 1B	H360FD	GHS08 Dgr	H360FD		*
Resulting Annex VI entry if agreed by COM					Repr. 1B	H360FD	GHS08 Dgr	H360FD		Repr. 1B; H360FD: C ≥ 5,5 %

* A change of the SCL was not proposed for discussion by the Dossier Submitter, therefore the current RAC opinion does not include a recommendation on the SCL. It is nevertheless noted by RAC that applying the new Guidance on the Application of the CLP Criteria (Version 4.0 – November 2013) would result in a value of 0.3%, thus identical to the GCL; these calculations are provided below at the end of the opinion.

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The Dossier Submitter (DS) proposed to revise the current harmonised Repr. 1B classification of boric acid (H360FD; index number 005-007-00-2 in Annex VI to CLP[1]). The proposal was to remove the classification for fertility effects and to downgrade the classification for developmental effects from category 1B to 2 (Repr. 2, H361d).

According to the DS, extensive evaluations of sperm parameters in highly exposed workers demonstrated no effects on male fertility, justifying no classification. While no developmental effects were seen in highly exposed populations, the epidemiological studies of developmental effects were not considered to be as robust as the fertility studies, and would therefore warrant classification in reproductive toxicity category 2 (H361d).

The DS concluded that based on adverse developmental effects of boron in rats and rabbits, boric acid should be classified with Repr. 2, H361d 'Suspected of damaging the unborn child' according to CLP. According to Directive 67/548/EEC (DSD), the DS proposed to classify boric acid with reproductive toxicity category 3 and assign the risk phrase R63 'Possible risk of harm to the unborn child'. While not proposed for discussion by RAC, the specific concentration limit (SCL) for these effects inserted in the CLH report by the DS is in line with the current SCL for boric acid already included in Annex VI.

Comments received during public consultation

A total of 141 comments were received during the public consultation (PC) on boric acid. None of the 8 member states competent authorities (MSCAs) who commented during the PC supported the revision of the classification for toxicity to reproduction of boric acid. By contrast, the European Borates Association (EBA) and other companies or industry associations supported the proposal from the Polish MSCA.

The comments received during PC covered a number of aspects including:

- the results obtained in epidemiological studies that may or may not be used to overrule positive results from animal studies with respect to reproductive and developmental toxicity
- the concept of exposure and risk in the context of classification and labelling which may or may not be taken into consideration
- the mechanistic or Mode of Action (MoA) studies that may or may not be relevant for humans
- the hypothesis that zinc stores in the human body may or may not protect against testicular toxicity of boric acid. Several studies on zinc borate were announced and/or submitted by EBA during or after public consultation of boric acid. The full study reports and non-confidential executive summaries received on 15 January 2014 were made available through CIRCA BC to the RAC (Hofman-Huther, 2013, Durand, 2013, Kirkpatrick, 2013a, Kirkpatrick, 2013b, Edwards, 2013 and Edwards, 2014).

A detailed response to these comments from the Polish MSCA is available in the RCOM.

Assessment and comparison with the classification criteria

Studies of reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that boron (B) impairs fertility through an effect on the testes. The effects observed in the different species are similar in nature. Based on data from the 2 years feeding study with boric acid in rats (Weir, 1996), the overall NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. This conclusion is supported by the study with

disodium tetraborate decahydrate (Weir, 1996). There are no indications that the impaired fertility is secondary to other toxic effects.

Developmental toxicity (malformations) was clearly observed in studies in rats and rabbits, the rat being the most sensitive species, with an overall NOAEL of 9.6 mg B/kg bw/day. Malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system, and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. There were no indications that the developmental effects were secondary to other toxic effects. In addition, the teratogenicity was possibly caused by an altered hox gene expression, caused by inhibition of histone deacetylases, a mechanism that is likely to be also relevant for humans (see below).

There are a number of cross sectional epidemiological studies available on cohorts of workers studies available from China, Turkey and the US on the potential effects of boron exposure on parameters mainly related to fertility among workers occupationally exposed to B. The average daily boron exposure for the high exposure groups in these studies were estimated to be 1.8 mg B/kg/day (n=16), 0.2 mg B/kg/day (n=39) and 0.4 mg B/kg/day (n=109) (Scialli *et al.,* 2010, Duydu *et al.,* 2011, and Whorton *et al.,* 1994, respectively). Average daily exposure values in these workers were one to two orders of magnitude below the lowest observed adverse effect levels (LOAEL) for fertility in mice (Fail *et al*., 1991, 1998), and for developmental toxicity in rats (Price *et al.*, 1994, 1996).

The Chinese studies (reviewed in Scialli *et al*., 2010) showed the highest B exposure levels, with a small subset (n= 16) of the highly exposed group having an average intake of 1.8 mg B/kg bw/day. The analysis was also conducted on a larger group having an average exposure of 0.45 mg B/kg bw/day (n= 75). Parameters included semen analysis, reproductive outcomes and sperm X:Y ratio: no statistically significant effects were observed in either group compared to controls. It is noted that most study groups contained a rather low number of participants, as illustrated by a local and a regional control group of 15 and 23 persons, respectively, thus decreasing the power of the studies. Some of the parameters showed a large variation (e.g. the total sperm count (±S.D.) in controls was 218±124 million), making it difficult to identify potential effects. Furthermore, the selection of participants in the Chinese study was unclear, as it was not explained how 75 workers were selected out of the 957 interviewed workers. Also, it was not explained why 21 out of 60 workers from a pilot study were selected to participate in the full study, but not the other workers. Overall, it is acknowledged that no effects were found, but it is considered that the power of the studies could have been higher and that there are questions regarding the selection of participants (Scialli *et al*., 2010).

The Turkish studies (Duydu *et al.*, 2011, 2012; Başaran *et al.*, 2012) were initially set up based on the assumption that different occupational categories would give groups with quantitatively different exposure to B. However, high B concentrations in drinking water resulted in high exposure also in the controls (without occupational exposure), and a very poor correlation between occupational air exposure and blood concentrations of B was observed. Therefore, participants were grouped according to blood concentrations of B rather than based on occupational exposure. It is not clear how well these new groups were matched. Also, the participation rate was very low (about 24%). The estimated average daily B exposure for the high exposure group was 14.45 mg B/day, which can be calculated into an external daily dose of 0.2 mg B/kg bw/day based on an assumed body weight of 70 kg. No adverse effects of B exposure on sperm analysis parameters were found, but the group size (n=39 in the high exposure group) was limited, leading to low statistical power. The B exposure level was still approximately two orders of magnitude lower compared to the rat NOAEL for reproductive and developmental effects; moreover the difference in exposure level between the groups was relatively low.

No epidemiological studies on possible adverse pregnancy outcomes in female workers are available.

In addition to the non-occupational exposure data presented in the Boric Acid CLH Report (Page 110), the highest non-occupational exposures were found in communities from Northern Chile in which the estimated intake of boron was 21 to 27 mg B/day, which correlated to naturally high B concentrations in local rivers (Barr *et al*. 1993). In a recent study

of populations in Chile, exposure levels of B in drinking water and urine was measured from volunteers in Arica, an area in the North of Chile with high levels of naturally occurring B (Cortes *et al*. 2011). The concentration of boron in urine varied between 0.45 and 17.4 mg/l, with a median of 4.28 mg/l and was found to be correlated with tap water sampled from the homes of the volunteers (r=0.64). Espinoza-Navaro *et al*. (2010) analysed sperm for total sperm count, sperm concentration, volume, vitality, pH, morphology, overall motility and grade A for motility in a sample of 102 healthy young males aged 18 to 30 years residing in Arica, Chile. The volunteers also completed a questionnaire about fertility, habits and andrologic diseases. Males sampled in Arica had normal sperm values in comparison with international reports (Espinoza-Navarro *et al*. 2010). No analysis was apparently performed on potential developmental effects of high environmental B exposure.

The overall negative epidemiological studies on male fertility effects of B should be considered as additional information, due to several limitations in design as pointed out by Scialli *et al*. (2010). The available human studies show no clear evidence of adverse effects on male fertility at these exposure levels, which is quite different than showing no evidence for such effects. In contrast experimental studies in animals showed clear and significant reproductive toxicity in four different species. For effects on fertility, the lowest effect level (LOAEL) was 27 mg B/kg/day in mice (Fail *et al.*, 1991, 1998), and for developmental toxicity 13.3 mg B/kg/day in rats (Price *et al.,* 1994, 1996). The highest occupational exposure levels in the two occupational cohorts and in the environmental exposed cohort were, thus, 15-135 times lower than the animal LOAEL for fertility effects and 7-66 times lower than the animal LOAEL for developmental toxicity. Assuming a similar sensitivity of humans as in the four laboratory species studied, it would have been unlikely to observe any adverse effects on human male fertility at those exposure levels. Also, effects on female fertility and prenatal development were not investigated in the epidemiological studies, which anyway had human exposure levels far below the animal LOAELs for these effects. In line with CLP, Annex 1, Section 1.1.1.4, RAC concluded that human data showing no clear evidence do not contradict the animal data.

Several studies on zinc borate were announced and/or submitted by EBA during or after public consultation on boric acid. Non-confidential executive summaries were submitted by EBA for Hofman-Huther, 2013; Durand, 2013; Kirkpatrick, 2013a; Kirkpatrick, 2013b; Edwards, 2013 and Edwards, 2014). It is stated by EBA (European Borate Association; see RCOM) that zinc interacts with boric acid in the body, reducing the toxicity of boric acid. A reason for this assumption is that zinc borate is less toxic than other borates in experimental studies. EBA further proposed that higher zinc stores in humans than in the experimental animals will provide some protection in humans against the toxic effects of boron, and that this species difference raises doubt about the human relevance of the reproductive toxicity seen in animals.

The RAC acknowledged that zinc borate *in vivo* in rats appears to have a higher LOAEL than other borates, but did not find the argumentation for the protective nature of zinc convincing. Firstly, there is no proposed mechanism for this zinc/borate interaction. Secondly, the unpublished *in vitro* study by Durand (2013), referred to in the RCOM and submitted after public consultation as evidence for a protective effect of zinc, suffers from not showing any negative effects of boric acid that zinc can protect against. Thirdly, if tissue levels of zinc affect the toxicity of borates, it is difficult to explain rather similar LOAELs in the experimental animals (in the range of 13-79 mg B/kg/day in mice, rats, rabbits and dogs) despite e.g. perhaps 40-fold higher zinc concentrations in dog liver than in mouse liver (see RCOM). It is also noted that the lethal dose of boric acid is much lower in humans than in rats, so apparently humans are more sensitive than rats to acute exposure despite the alleged protection from zinc in humans. A specific protective action of zinc against reproductive/developmental effects might not be ruled out, but the evidence is still limited. It is possible that zinc quantitatively affects the toxicity of borates at some conditions, as well as boron might impair the physiological functions of zinc, an essential trace element involved in fertility and development in both animals and humans. These statements bring about a certain scientific interest but there is at present not sufficient evidence to generally support them; most importantly, there is no reason to challenge the relevance for humans of the toxicity of borates observed in experimental animals.

EBA stated that the mechanism of action (MoA) for developmental toxicity of borates involves histone deacetylase inhibition (HDACi) and affected expression of the Hox genes, and that

these effects are high dose phenomena in animals making the likelihood of similar effects in humans low. The evidence comes from studies with single exposure of pregnant mice to 1000 mg/kg boric acid on gestation day 8, causing a high incidence of malformations and showing evidence of inhibition of histone deacetylase and a shifted expression of Hoxc6 and Hoxa6. The RAC noted that this MoA might be plausible, but there is no proof that the altered histone deacetylase is only a high dose effect. On the other hand, if these effects only occur at high exposure levels, they may not represent the most sensitive and relevant MoA for the developmental toxicity of borates. Lower exposure levels were not tested so it is unclear to what extent these effects are relevant MoAs for the borates. Even if these effects are indeed the relevant MoA, it is not clear why they would not be relevant for humans. Finally, it is noted that this MoA is proposed for developmental toxicity, but not for adverse effects on fertility.

The EBA also highlighted that B is likely to be an essential mineral in mammals, and that homeostatic control of B concentrations in the cells will decrease the risk of toxic effects. The RAC noted that in its opinion on the upper tolerable intake level of B, the European Food Safety Authority concluded that, although it may have a beneficial effect on bone calcification and maintenance, B has not been established to be an essential nutrient for humans and no specific biochemical function has been identified in higher animals or man (EFSA, 2004). Therefore, the statement on the essentiality of B appears unsupported. In the unlikely situation that essentiality at very low intake levels will be demonstrated, the RAC further notes that B is still toxic to reproduction and development in experimental animals above certain exposure levels, and cannot see how the essentiality will affect the inherent toxicological properties of B.

It is stated in the EBA comments that the studied workers (in B mining and processing industries) represent the maximum possible human exposure, and that the data show that it is improbable that borates will cause effects on fertility or development in humans. The RAC had no possibility to assess the exposure potential for the different B substances in different uses, but noted that the classification criteria do not consider exposure assessments. Rather, it is the inherent toxicological properties of the substances that lead to classification. Finally, the available epidemiological investigations dealt with male fertility only, with several methodological limitations; they did not cover developmental effects at all.

Based on the total weight of evidence, toxicity data from four different species (mice, rats, rabbits and dogs) provide clear evidence of an adverse effect on sexual function, fertility, and development 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. Therefore, the epidemiological studies do not lead to doubt as to the relevance of the animal toxicity data to humans at similar dose levels as causing toxicity in experimental animals. In line with CLP, Annex 1, Section 1.1.1.4, it was concluded overall 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.

The SCL for boric acid was not addressed in detail by the RAC as it was not proposed by the DS. However, the RAC noted that the current SCL of 5.5% (w/w) in Annex VI to CLP for reproductive toxicity is calculated based on the German method (BAuA, 1998) and not according to the new guidance for the setting of specific concentration limits proposed by an EU expert group (version 4.0 - November 2013). The SCLs for boric acid and other borates were derived from the overall NOAEL for embryotoxic/teratogenic effects of 9.6 mg B/kg bw/day, based on a reduction in mean fetal body weight/litter and an increased incidence in short rib XIII at 76 mg/kg bw/day (13.3 mg B/kg bw/day) (Price at al., 1996).

The fetal incidence of short rib XIII malformation was 1.2 and 1.5% at the LOAEL (13.3 mg B/kg bw/day) and the highest dose tested (25 mg B/kg bw/day) respectively (Price et al., 1996). As the incidences are low, it is not possible to derive an ED_{10}. In this instance the LOAEL should be used for setting the SCL, according to the guidance. Correcting for the percentage of boron (w/w), the LOAEL of 13.3 mg B/kg bw/day corresponds to a LOAEL of 76.1 mg/kg bw/day (17.48% B in boric acid). Boric acid thus belongs to the medium potency group (4 mg/kg bw/day < ED_{10} (LOAEL) < 400 mg/kg bw/day). None of the modifying factors apply. As borates are classified in category 1B, an SCL of 0.3% applies. This SCL is therefore equivalent to the generic concentration limits (GCL) for reproductive toxicants classified in category 1B (see Table 3.7.2 of CLP). For the sake of maintaining consistency for the SCLs listed for other borates in Annex VI to CLP, the revised SCL is not part of this opinion. RAC noted that the

preparation of a CLH dossier proposing the update of the SCLs using the new method for all boron compounds with a harmonised classification would ensure consistency in the future.

Conclusion

In conclusion, based on the adverse developmental and fertility effects of boric acid in different species, RAC does not support the proposal from the DS to revise the current harmonised classification of boric acid (index number 005-007-00-2 in Annex VI to the CLP Regulation (EC) No 1272/2008). Boric acid should be classified with Repr. 1B, H360FD 'May damage fertility. May damagethe unborn child.' according to Regulation (EC) No 1272/2008. The RAC has reassessed the current SCL according to the new Guidance on the application of the CLP criteria (version 4.0 – November 2013) but the current RAC opinion does not include a proposal to change the SCL as this was not proposed for discussion by the DS. Thus, for the sake of maintaining consistency for the SCLs listed for other borates in Annex VI to CLP, the revised SCL is not part of this opinion. It is nevertheless noted by RAC that it would result in a value of 0.3%, thus identical to the GCL according to the new Guidance.

Additional references

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Price CJ, Strong PL, Marr MC, Myers CB and Murray FJ, 1996. Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. *Fundam Appl Toxicol*, **32**, 179-193.

The EFSA Journal (2004), **80**, 1-22. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid), Request N° EFSA-Q-2003-018. Adopted on 8 July 2004.

ANNEXES:

Annex 1 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 by RAC (excl. confidential information).