Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Disodium Octaborate Anhydrate

EC number: 234-541-0
CAS number: 12008-41-2

CLH-O-0000003654-72-03/F

Adopted

14 March 2014

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CLH-O-0000003654-72-03/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 (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: Disodium Octaborate Anhydrate
EC number: 234-541-0
CAS number: 12008-41-2

The proposal was submitted by **the Netherlands** and received by the RAC on **5 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

The Netherlands 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 **30 April 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **14 June 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Bert-Ove Lund**

To ensure the consistency of the opinions for disodium octaborate anhydrate and boric acid (dossier submitter: Poland), the (co-)Rapporteurs appointed for boric acid, **Normunds Kadikis** and **Paola Di Prospero Fanghella**, 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 RAC opinion on the proposed harmonised classification and labelling was reached on **14 March 2014** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **Disodium Octaborate Anhydrate** 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	No current annex VI entry									
Dossier submitters proposal	005-020-00-3	disodium octaborate anhydrate	234-541-0	12008-41-2	Repr. 1B	H360FD	GHS08 Dgr			Repr. 1B; H360FD: C ≥ 3,7%
RAC opinion					Repr. 1B	H360FD	GHS08 Dgr			*
Resulting Annex VI entry if agreed by COM					Repr. 1B	H360FD	GHS08 Dgr			

* The RAC opinion includes the derivation of the generic concentration limit (GCL) based on the new Guidance (Version 4.0 – November 2013, section 3.7.2.5. Setting of specific concentration limits). Using the new guidance, the GCL of 0.3% should apply and there is thus no need for an SCL.

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The DS proposed to classify DOA for reproductive toxicity with Repr. 1B, H360FD ('May damage fertility. May damage the unborn child.'), based on read-across from other tested borates (e.g. boric acid) and borate salts (borax or disodium tetraborate decahydrate). Hydrolysis of borates results in the formation of the same chemical entities (boron, B). The resulting classification is comparable to that of the other borates in Annex VI of CLP.

The DS assessed the available epidemiological studies, and noted that the estimated exposure levels in the human studies were lower than the overall NOAELs for testis effects in experimental animals. Thus, the DS argued that human data do not contradict the animal data. Furthermore, an SCL of 3.7% w/w for this classification was proposed using a calculation method which is in line with the other borates already included in Annex VI.

Comments received during public consultation

A total of 27 comments were received during the public consultation on DOA. Most Member states who participated in the public consultation agreed with the proposal to classify DOA as Repr. 1B (H360FD) accordingly to the CLP criteria.

The Polish CA recognised that there are reproductive effects of B compounds in laboratory animals under test conditions, but it questioned if these data met the criteria for Category 1B classification as argued in the CLH Report submitted to ECHA for boric acid. Based on the total weight of evidence, the Polish CA was of the opinion that the data showed that it is improbable that boric acid will cause reproductive or developmental effects in humans. Therefore, they considered Repr. 2 (H361d: 'Suspected of damaging the unborn child') as the most appropriate classification.

Moreover, the European Borates Association (EBA) and other industry organisations including downstream users (all referred to as EBA below) opposed the proposed classification. EBA stated that there is no evidence of reproductive or developmental effects in humans attributable to B in epidemiology studies with cohorts in China, Turkey and Chile with high exposures to B. According to EBA, workers in B mining and processing industries represent the maximum possible human exposure and a key difference between humans and laboratory animals relative to boric acid toxicity is the large zinc stores in humans compared to laboratory animals. According to EBA, the protective effect of the large zinc stores in the human body may explain the absence of toxicity in humans exposed to high levels of B. Supporting studies conducted with zinc borate were submitted during the boric acid public consultation to support this hypothesis. They were shared with the DS of DOA and commented on in due course (see the RCOM). Additionally, mechanistic data showed that the action of boric acid on histone deacetylase inhibition (HDACi) and Hox genes occurs at a high dose (1000 mg boric acid/kg bw) and during a very narrow window of gestation (gestation days 8-9) in laboratory animals. According to EBA, these effects were not likely to be relevant to humans, since the dose of 1000 mg/kg bw in humans would be lethal. Based on the total weight of evidence, EBA argued that it is improbable that boric acid will affect fertility in humans. However, they recognised that epidemiological studies of developmental effects being not as robust as the fertility studies, a classification in Category 2 (H361d: 'Suspected of damaging the unborn child') was warranted.

A detailed response to these comments is provided by The Netherlands 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 B impairs fertility through an effect on the testes including testicular atrophy and seminiferous tubule degeneration. The effects observed in the different species are similar in nature. Based on the data from the 2 years feeding study on boric acid in rats (Weir, 1996a), the overall NOAEL for fertility is 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. This conclusion on

the testicular effects and the overall NOAEL is also supported by the study conducted with disodium tetraborate decahydrate (Weir, 1996b). There are no indications that the impaired fertility is secondary to other toxic effects (CAR, 2006).

Developmental toxicity of B 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 are no indications that the developmental effects are secondary to other toxic effects. In addition, the teratogenicity is 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 B 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, the 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 B in urine varied between 0.45 and 17.4 mg/l, with a median of 4.28 mg/l and it was found to correlate 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 their 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 the study 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, it is overall 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 of boric acid. They were shared with the DS of DOA and commented (see the RCOM). The study reports (final or drafts) were made available through CIRCA BC to the RAC. Non-confidential executive summaries for Hofman-Huther, 2013; Durand, 2013; Kirkpatrick, 2013a; Kirkpatrick, 2013b; Edwards, 2013 and Edwards, 2014 were provided by EBA. It was stated by EBA (see the 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 the 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.

The 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. 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. 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. 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 of B (and consequently of DOA) 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.

Regarding SCLs, the DS proposed an SCL of 3.7% in line with the method used to determine SCLs for several other borates (the so-called 'German' method; BAuA, 1998) in Annex VI of CLP. 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).

However, RAC concluded that the SCL for DOA should be determined according to the new guidance for the setting of specific concentration limits proposed by an EU expert group (Guidance on the application of the CLP criteria, version 4.0. November 2013). 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 B (w/w), the LOAEL of 13.3 mg B/kg bw/day corresponds to a LOAEL of 51.5 mg/kg bw/day for DOA as it contains 25.83% B. DOA thus belongs to the medium potency groups (4 mg/kg bw/day < ED_{10} (LOAEL) < 400 mg/kg bw/day). None of the modifying factors apply. For medium potency substances, the general concentration limit (GCL) applies. As borates are classified in category 1B, the GCL is 0.3% w/w (see Table 3.7.2 of CLP).

Conclusion

In conclusion, based on the adverse developmental and fertility effects of borates (B) in rats and rabbits, RAC concluded that DOA should be classified with Repr. 1B, H360FD ('May damage fertility. May damage the unborn child.') according to CLP with no specific concentration limits.

Additional references

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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.

US EPA (2006). Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Eligibility Decision (TRED) for Boric Acid - Sodium Borate Salts (PDF) - July 2006 http://www.epa.gov/oppsrrd1/REDs/boric_acid_tred.pdf (accessed on 24 April 2014).

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 rapporteurs' comments (excl. confidential information).