Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON DISODIUM OCTABORATE, ANHYDRATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

ECHA accepts no responsibility or liability for the content of this table.

ECHA has received confidential comments or attachments during public consultation. They have been responded by the dossier submitter and the RAC and have been taken into account for the opinion development. However, they will not be published on ECHA website after the adoption of the opinion and background documents.

Substance name: disodium octaborate, anhydrate
EC number: 234-541-0
CAS number: 12008-41-2
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2013	United Kingdom		MemberState	1
Comment received				
We believe that it is currently inappropriate to develop a harmonised classification for disodium octaborate anhydrous whilst the dataset on boric acid is also under consideration in the harmonised classification and labelling process.				
Dossier Submitter's Response				
We agree that the classification for disodium octaborate anhydrous should be discussed together with the classification for boric acid.				
RAC's response				
The evaluation of Boric Acid was made in parallel with the DOT and DOA by RAC. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Norway		MemberState	2
Comment received				
Norway would like to thank the Netherlands for the proposal for harmonised classification and labeling of Disodiumoctaborate, anhydrate, cas no. 12008-41-2 We support the proposal to classify Disodiumoctaborate, anhydrate for reproductive toxicity with Repr. 1B - H360FD based on a read across to boric acid. Disodium octaborate anhydrate will predominantly exist as undissociated boric acid in physiological conditions. Therefore, the toxicological properties of borates are expected to be similar and a read across approach would be justified. This proposal is also in line with already existing classifications of borates included in Annex VI.				
Dossier Submitter's Response				
Thank you for the support				

RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	Belgium	Fertilizers Europe	Industry or trade association	3
Comment received				
Fertilizers Europe represents the downstream users of boron compounds. Boron is an important micro-nutrient, essential for plant growth. Boron can be added to fertilizers to sustain growth. The European Borates Association (EBA) has provided a consolidated response on behalf of the European borate manufacturers and importers and on behalf of the REACH consortium for borates. As a consequence, Fertilizers Europe fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
See response to comment 19				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	France		Industry or trade association	4
Comment received				
This Industry or trade association is a downstream user of boron compounds. The European Borates Association (EBA) has provided a consolidated response on behalf of the European borate Manufacturers and Importers and on behalf of the REACH consortium for borates. As a consequence, this Industry or trade association fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
See response to comment 19				
RAC's response				
RAC evaluated all the data available for reproductive toxicity. 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 give reasons to challenge the relevance of the animal toxicity data to humans at similar dose levels as causing toxicity in experimental animals. The human data does not contradict the animal data. Therefore, there is no evidence that the effects observed in animals are not relevant to humans. In conclusion, based on the adverse developmental and fertility effects of borates in rats and rabbits RAC agreed with the dossier submitter (the Netherlands) to assign a harmonised classification as a substance which may damage fertility and the unborn child (Repr. 1B; H360FD), according to Regulation EC 1272/2008. The RAC opinion includes the derivation of the 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, as the substance is a medium potency reproductive toxicant, the generic concentration limit of 0.3% (w/w) is				

applicable and there is thus no need for a SCL. The Committee also concluded that classification into other hazard classes was not warranted.
For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	Belgium	European Borates Association (EBA)	Industry or trade association	5

Comment received

About the European Borates Association (EBA): The EBA is the representative body of the European borates industry and is a member of IMA-Europe, the Industrial Minerals Association. The EBA membership represents all of manufactures and importers of disodium octaborate tetrahydrate in Europe. The IMA-Europe Secretariat is the Borates REACH Consortium Coordinator for disodium octaborate tetrahydrate as well as boric acid (EC 233-139-2). These comments represent the view of member companies.

1. Throughout the CLH Report the substance is referred to as "Disodiumoctaborate anhydrate". The correct substance name is "Disodium octaborate, anhydrous".

2. p10, Part A: Section 1.3, Table 3: "5.1 Hazardous to the ozone 'data lacking'"
The REACH registration dossier for this substance states the reason for no classification is "conclusive but not sufficient for classification".

3. p14, Part B: Section 1.1: the structure of disodium octaborate is incorrect
Anhydrous disodium octaborate is an amorphous substance; consequently it has no well-defined molecular structure. Its structure consists of an extended random network of boron-oxygen bonds in which one fourth of the boron atoms are tetrahedral and the remainder trigonal, with a repeating unit of B8O13. Each tetrahedral boron atom possesses a negative charge and is associated with an interstitial sodium cation, giving an overall repeating unit of Na2B8O13.

4. p17, Part B, Section 2.2: The Report states there is no identified use of disodium octaborate anhydrate. This is correct as the anhydrous substance is not manufactured or placed on the market. The hydrated substance, disodium octaborate tetrahydrate, is manufactured and placed on the market. Is it appropriate to consider a harmonised classification for disodium octaborate anhydrous?

Dossier Submitter's Response

1. Noted.
2. Noted
3. Noted
4. Since there is a REACH registration dossier and several notifications for disodium octaborate anhydrous, a harmonised classification is considered appropriate. Further, as described in chapter 1.1.1.5 of Annex VI, entries in table 3.1 and 3.2 of Annex VI cover both the anhydrous and the hydrous forms and according to chapter 1.1.1.3 normally the CAS number for the anhydrous form is included. However, as there is a difference in SCL between both forms, two proposals were submitted.

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number

11.06.2013	Denmark	Osmose Denmark A/S	Company-Downstream user	6
Comment received				
Osmose is a downstream user of boron compounds. The European Borates Association (EBA) has provided a consolidated response on behalf of the European borate Manufacturers and Importers and on behalf of the REACH consortium for borates. As a consequence, Osmose fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
See response to comment 19				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	7
Comment received				
FR agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for the support				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	United Kingdom	REACH Boron Consortium	Industry or trade association	8
Comment received				
The REACH Boron Consortium represents the manufacturers/importers of metallic boron and its alloys. The European Borates Association (EBA) has provided a consolidated response on behalf of the European borate Manufacturers and Importers and on behalf of the REACH consortium for borates. As a consequence, the REACH Boron Consortium fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
See response to comment 19				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
12.06.2013	Belgium		Company-Downstream user	9
Comment received				
We believe it is currently inappropriate to develop a harmonised classification for disodium octaborate anhydrate/tetrahydrate whilst a different classification of boric acid is also under consideration and is based on new information.				
Dossier Submitter's Response				
We agree that the classification for disodium octaborate anhydrous should be discussed together with the classification for boric acid.				
RAC's response				

Please see response to comment 1

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Germany		Company-Downstream user	10
Comment received				
Dossier does not consider information on epidemiological studies of workers in China and Turkey exposed to Boric Acid. Read Across approach to Boric acid has been considered to be valid due to similar properties of substances. Therefore the decision on the harmonised classification on disodium octaborate, anhydrate should be put on hold, until decision on re-classification dossier for Boric acid has been taken.				
Dossier Submitter's Response				
We did (although shortly) consider the epidemiological studies, however, since the results of these studies are not contradictive to the results of the animal studies, we see no reason to downgrade the classification to Repr. 2. The workers are exposed to concentrations that are lower than the doses that cause reproductive effects in laboratory animals. It can therefore not be excluded that in humans higher doses would also result in reproductive effects. For a more elaborate discussion of the epidemiological studies, see response to comment 19. In addition, we agree that the classification for disodium octaborate anhydrous should be discussed together with the classification for boric acid.				
RAC's response				
Please see response to comment 4				

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2013	United Kingdom		Company-Downstream user	11
Comment received				
There is recent high-quality research which supports a lower classification for reproductive toxicity.				
Dossier Submitter's Response				
We do not agree. See response to comment 19.				
RAC's response				
Please see response to comment 4				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Germany		MemberState	12
Comment received				
The classification and SCL proposed for disodiumoctaborate anhydrate reflects that of the related borates according to Commission Regulation (EC) No 790/2009 of 10 August 2009 and the conversion table provided in the CLH report. The proposal is fully supported. Currently there is also a proposal for reduced C&L of boric acid as Repr. 2, H361d rather than Repr. 1B, H360FD (version 2, 23/04/2013) by PL. We do, however, not think that a decision about harmonized classification for DOA should be delayed until an opinion is adopted about reduced classification for boric acid.				
Dossier Submitter's Response				
Thank you for the support				

RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Austria		MemberState	13
Comment received				
The Austrian CA supports the Dutch classification proposal of disodium octaborate, anhydrate as Repr 1B H360FD.				
Dossier Submitter's Response				
Thank you for the support				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
05.06.2013	Germany		Company-Downstream user	14
Comment received				

(ECHA note: The comment below has been submitted as a separate attachment. Document name: "The case for a Category 2 Toxic to Reproduction classification for Borates. New and Previously Not Considered Scientific Data Justify Reclassification. Position Paper of the European Borates Association 4 June 2013")

The case for a Category 2 Toxic to Reproduction classification for Borates

New and Previously Not Considered Scientific Data Justify Reclassification

Position Paper of the European Borates Association

4 June 2013

Introduction

The European Chemicals Agency (ECHA) has invited interested parties to comment on a dossier proposing the re-classification of boric acid as a Category 2 reproductive toxicant under the EU's Classification, Labelling and Packaging Regulation (CLP). The proposal, which was submitted by Poland and cleared ECHA's customary accordance check, is based on scientific evidence from studies conducted on Chinese and Turkish borate mine workers with the highest exposures, which have yet to be considered by ECHA's Risk Assessment Committee. The dossier proposes to remove the classification for fertility effects and down-grade the current Category 1B classification of boric acid to Category 2 for developmental effects. The Polish proposal is supported by the European Borates Association (EBA).

ECHA has also requested comments on a proposal to classify disodium octaborate and disodium octaborate tetrahydrate (DOT) as a Category 1B reproductive toxicant. The reason for this proposal follows the inclusion of DOT as an active substance in Annex I of the Biocidal Products Directive (1998/8/EC) and the rules set out in CLP. The EBA does not support this proposal and is of the opinion that the data and evidence that justify a re-classification of boric acid to Category 2 apply equally to DOT which therefore leads to the logical conclusion that DOT should also be classified as a Category 2 reproductive toxicant.

The EBA anticipates that re-classification dossiers shall be submitted by Poland in due course for diboron trioxide and disodium tetraborates in accordance with the information in the ECHA Registry of Intentions. As with boric acid, these borates are currently classified as Category 1B reproductive toxicants and the forthcoming proposals to down-grade them to Category 2 would achieve a regulatory alignment for all relevant borates. As such, these future re-classifications would also be supported by the EBA.

Chinese and Turkish Worker Studies - new and previously not considered data

Chinese Study

Potential adverse male reproductive health effects among boron mine industry workers in the province of Liaoning in northeast China were investigated by a Chinese and US research team[i]. The project was led by principal investigators W.A. Robbins and Fusheng Wei, with funding from the U.S. National Institute of Occupational Safety and Health (NIOSH) and the China National Environmental Monitoring Station. Although the study was conducted in the period 2002-2004, it was not readily accessible, given that a large amount of the results had only been published in Chinese language journals. Consequently, the peer-reviewed and translated results of the study only became available in one place for review after the EU's 2008 decision published as the 30th ATP[ii] to classify borates as Category 1B reproductive toxicants. Indeed the 30th ATP recognizes this fact as it contains a Recital which states that '*special attention should be paid to further results of epidemiological studies on the Borates concerned by this Directive including the ongoing study conducted in China.*'

Boron measurements included concentrations in the workplace, soil, water, food, urine, blood and semen. The boron workers experienced very high boron exposures, exceeding the WHO recommended upper safe limit (13 mg B/day) by more than three-times and the highest exposed group was exposed to over 100-times more than the average daily exposure of the general European population. Despite these high exposures, no adverse reproductive effects were found.

Turkish study

A study of workers in Turkey[iii] was conducted in 2009 by a Turkish and German research team to investigate the reproductive effects of boron exposure in workers employed in a boric acid production plant in Bandirma, Turkey. The project was led by principal investigator Prof. Dr., Yalçın Duydu, Ankara University, Department of Toxicology with funding from the National Boron Research Institute (BOREN) and Eti Mine Works.

Boron concentrations were determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. The mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. As with the Chinese study, there were no negative effects observed for boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone).

Recognising the weight of evidence for Category 2

CLP describes the weight of evidence determination where all available information relating to hazard is considered together, including relevant animal data, information on mechanism and human data. The importance of applying expert judgement in such weight of evidence cases is also conveyed for determining the most realistic conclusion on the hazard category.

For boric acid, it is known that the studies on laboratory animals clearly demonstrate fertility and developmental effects. However other available information relating to intrinsic properties considered as part of a weight of evidence assessment is summarised by the bullets below.

Human studies

- The China and Turkey worker studies represent the most sensitive studies that have been carried out on humans to date. They included sperm analysis, which is the most sensitive test for testicular toxicity in humans. These studies found no adverse reproductive toxic effects from high exposures to boron. The exposure of the workers in China is 100-times higher than the general European population.
- The Chinese and Turkish workers studies further support the argument that humans are not more sensitive to the effects of boric acid than laboratory animals demonstrated by the low rat NOAEL[iv] (17.5 mg B/kg/day) to human NOAEL (2.08 mg B/kg) ratio of 8.75. This ratio is over 10 times lower than the default safety factor of 100 often used in risk assessments.
- There is no evidence of developmental effects in humans attributable to boron. Three epidemiological studies evaluating high environmental exposures to boron and developmental effects in humans have been conducted and have shown an absence of effects.

- The highly exposed male Turkish workers did not show any adverse effects on hormone levels (FSH levels, LH levels and total testosterone). These results are in agreement with tests on laboratory animals that boric acid does not have an endocrine-related mechanism for the fertility and developmental effects because boric acid and its compounds are not Endocrine Disruptors. Furthermore, the U.S. Environmental Protection Agency (US EPA) did an evaluation of the endocrine disrupting potential of compounds where boric acid received the lowest score among the 309 chemicals evaluated indicating extremely low potential for endocrine-related toxicity[v].

Mode of action

- Recent studies provide possible mechanisms of boric acid related developmental effects in laboratory animals, including histone deacetylase inhibition (HDACi)[vi] and effects of boric acid on expression of Hox genes[vii]. A major difference between laboratory animals and humans is the large zinc stores in bone and soft tissues in humans compared to laboratory animals. Zinc has been shown to be protective against the acute toxicity and male fertility effects of boron[viii].

- Studies that are underway that will provide more information on the role zinc plays in developmental and fertility effects of boric acid include:
    - Embryonic stem cell test (June 2013),
    - *In vitro* spermatogenesis assay (June 2013),
    - Developmental toxicity dose range finder study of zinc borate (June 2013),
    - 90-day oral toxicity study of zinc borate (October 2013),
    - Developmental toxicity study of zinc borate (to be completed in 2014).

Nutrient essentiality

- Boron is regarded as an essential nutrient to maintaining optimal human health and has demonstrated beneficial effects in several animal models. In 2001, the U.S. Food and Nutrition Board published a Tolerable Upper Intake Level for boron of 20mg per day, confirming its biological importance. In 2002, the U.K. Expert group on Vitamins and Minerals also ratified boron's benefits. Other epidemiological studies indicate that increased dietary boron exposure is associated with lower incidences of prostate, lung, cervical and esophageal cancer[ix].

In accordance with the CLP legislation and guidance, EBA considers that based on a weight of evidence evaluation of these studies, other investigations and considerations, there is sufficient evidence leading to the conclusion that it is improbable that boric acid will cause reproductive or developmental effects in humans, thereby questioning the relevance of the animal studies to humans.

Read across

The classification of boric acid as a Category 2 toxic for reproduction should also apply to the other classified borates and DOT. This is because in aqueous solutions at physiological and acidic pH, low concentrations of simple inorganic borates such as boric acid, disodium tetraborates, diboron trioxide and DOT will predominantly exist as undissociated boric acid. Accordingly, the boric acid data is also relevant to these other borates as they too can be considered to exist as undissociated boric acid under the same conditions. It would therefore be appropriate for the classification of these borates to be aligned.

Existing regulatory controls

The borate industry acknowledges that the proposed Category 2 classification would still require hazard communication for products containing boric acid. Further, compliance with EU legislation for classified substances would ensure humans are adequately protected.

Conclusion

The EBA recognises there is a reproductive effect of boron compounds in laboratory animals under test conditions. However, the latest studies and scientific evidence demonstrate that such effects are not found in humans, even when exposed to high levels. Therefore considering all available information, EBA supports the proposed Category 2 classification for boric acid.

The EBA urges all stakeholders, scientific experts and regulatory officials in ECHA, the European Commission and the Member States to support these facts as the re-classification proposals are debated and progress through the EU's regulatory process.

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[i] Scialli AR, Bonde JP, Brüske-Hohlfeld, Culver DB, Li Y & Sullivan FM. (2010). An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reproductive Toxicology 29: 10 – 24

[ii] COMMISSION DIRECTIVE 2008/58/EC of 21 August 2008 amending, for the purpose of its adaptation to technical progress, for the 30th time, Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

[iii] Duydu Y, Başaran N, Ustündağ A, Aydın S, Undeğer U, Ataman OY, Aydos K, Düker Y, Ickstadt K, Waltrup BS, Golka K, Bolt HM. (2011). Reproductive toxicity parameters and biological monitoring in occupationally and environmentally boron-exposed persons in Bandırma, Turkey. Arch Toxicol. 2011 Jun;85(6):589-600. PMID:21424392.

[iv] No Observed Adverse Effect Level

[v] Reif DM, Martin MT, Tan SW, Houck KA, Judson RS, Richard AM, Knudsen TB, Dix DJ, Davlock RJ (2010) Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data. Environ Health Perspect 118:1714–1720.

[vi] Di Renzo et al. (2007). Boric acid inhibits embryonic histone deacetylases: A suggested mechanism to explain boric acid-related teratogenicity. Tox. and Applied Pharm. 220:178-185.

[vii] Narotsky MG, Wery N, Hamby BT, Best DS, Pacico N, Picard JJ, Gofflot F, and Kavlock J (2004). Effects of Boric Acid on Hox Gene Expression and the Axial Skeleton in the Developing Rat. From: The Skeleton: Biochemical, Genetic, and Molecular Interactions in Development and Homeostasis Edited by: E. J. Massaro and J. M. Rogers, Humana Press Inc., Totowa, NJ, pp 361-372.

[viii] Ball, W and Harrass, M (2013) Weight of Evidence Considerations for Developmental Toxicity Classification of Boric Acid. The Toxicologist. PS:1021, p.218..

[ix] Nielsen, FH, and Meacham, SL. (2011) Growing Evidence for Human Health Benefits of Boron. J Evidence-Based Complementary & Alternative Medicine. 9 May 2011 [Epub ahead of print].

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Dossier Submitter's Response
See response to comment 19
RAC's response
Please see response to comment 4

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	15
Comment received				
Fertility : Studies in rats, mice and dogs show that boric acid and tetraborates target the male reproductive system. The effects, which manifest as histological changes in the testes, impaired spermiation and sperm quality, result in a partial reduction in fertility or complete sterility, depending on the dose administered. Moreover, these effects occur at doses that do not induce any strong signs of toxicity. In the epidemiological studies on exposed human workers, no robust effect was identified on the male reproduction. However, these studies suffer methodological weaknesses such as imprecise or absent definition of fertility criteria (Chang 2006), socioeconomic factors not adjusted or different between groups (Sayli 2003 and 2004, Chang 2006), absence of consideration of potential co-exposure (Chang 2006, Sayli 2003 and 2004, Duydu 2011)				

and analysis of mean sperm parameters that do not reflect heterogeneity of individual sperm count (Robbins 2008 and 2010). Besides, the small size of the cohorts resulted in a limited statistical power. Only large impact could be identified, in the range of a 30 to 40% reduction in sperm concentration in Robbins 2008 and 2010 and in the range of a 50 to 60% reduction in sperm cell concentration in Duydu 2011. These studies were unable to rule out potential, less subtle effects that may contribute to low fertility in humans. Besides, it is noted that due to differences in exposure levels, the human data do not contradict with animal data and do not allow concluding that humans are not sensitive to the toxicity of borates on the male reproductive system that was identified in rats, mice and dogs.

FR therefore supports the proposal to classify disodiumoctaborate (anhydrate and tetrahydrate) in category 1B for fertility consistently with the classification of boric acid and tetraborates.

Development:
Exposure to boric acid during gestation causes reduced foetal weight, and malformations of the cardiovascular system, ribs and brain in rats, mice and rabbits. The rat is the most sensitive species and developmental effects are observed at a dose that induces only limited maternal toxicity and which cannot explain the effects observed in offspring..
A few epidemiological studies are available for assessing the effects of boric acid on fertility in exposed workers. Some indicators measured in these studies may be relevant for identifying effects on development (e.g., miscarriages) but in addition to their methodological deficiencies, these studies were conducted on groups of exposed workers mainly composed of men and are not considered to be relevant for an adequate assessment of the developmental effects of boric acid. The case-control study on congenital abnormalities by Acs (2006) reports an association between treatment with boric acid during pregnancy and neural tube defects as well as skeletal system abnormalities. This result was however based on a very small number of exposed controls and cases and exposure was imprecisely characterised. This study is therefore considered insufficiently robust to draw a firm conclusion but overall, human data do not provide an evidence of an absence of effect in humans nor challenge the human relevance for the effects identified in animals.
FR therefore supports the proposal to classify disodiumoctaborate (anhydrate and tetrahydrate) in category 1B for development consistently with the classification of boric acid and tetraborates.

Dossier Submitter's Response
Thank you for the support
RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Germany		Company-Downstream user	16
Comment received				
New human studies of workers in China and Turkey exposed to Boric Acid are available and provide new and previously not considered data. In addition to that, further studies on the developmental and fertility effects of boric acid are underway and should be used for read-across purpose. Read Across approach to Boric acid has been considered to be valid due to similar properties of substances. Therefore the decision on the harmonised classification on disodium octaborate, anhydrate should be put on hold, until decision on re-classification				

dossier for Boric acid has been taken.
Dossier Submitter's Response
Since the results of these studies are not contradictive to the results of the animal studies, we see no reason to downgrade the classification to Repr. 2. The workers are exposed to concentrations that are lower than the doses that cause reproductive effects in laboratory animals. It can therefore not be excluded that in humans higher doses would also result in reproductive effects. For a more elaborate discussion of the epidemiological studies, see response to comment 19. In addition, we agree that the classification for disodium octaborate anhydrous should be discussed together with the classification for boric acid.
RAC's response
Please see response to comment 4

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2013	United Kingdom		Company-Downstream user	17
Comment received				
Chinese Study Potential adverse male reproductive health effects among boron mine industry workers in the province of Liaoning in northeast China were investigated by a Chinese and US research team . The project was led by principal investigators W.A. Robbins and Fusheng Wei, with funding from the U.S. National Institute of Occupational Safety and Health (NIOSH) and the China National Environmental Monitoring Station. Although the study was conducted in the period 2002-2004, it was not readily accessible, given that a large amount of the results had only been published in Chinese language journals. Consequently, the peer-reviewed and translated results of the study only became available in one place for review after the EU's 2008 decision published as the 30th ATP to classify borates as Category 1B reproductive toxicants. Indeed the 30th ATP recognizes this fact as it contains a Recital which states that 'special attention should be paid to further results of epidemiological studies on the Borates concerned by this Directive including the ongoing study conducted in China.' Boron measurements included concentrations in the workplace, soil, water, food, urine, blood and semen. The boron workers experienced very high boron exposures, exceeding the WHO recommended upper safe limit (13 mg B/day) by more than three-times and the highest exposed group was exposed to over 100-times more than the average daily exposure of the general European population. Despite these high exposures, no adverse reproductive effects were found. Turkish study A study of workers in Turkey was conducted in 2009 by a Turkish and German research team to investigate the reproductive effects of boron exposure in workers employed in a boric acid production plant in Bandirma, Turkey. The project was led by principal investigator Prof. Dr., Yalçın Duydu, Ankara University, Department of Toxicology with funding from the National Boron Research Institute (BOREN) and Eti Mine Works. Boron concentrations were determined in biological samples (blood, urine, semen), in workplace air, in food, and in water sources. The mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. As with the Chinese study, there were no negative effects observed for boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone).				

CLP describes the weight of evidence determination where all available information relating to hazard is considered together, including relevant animal data, information on mechanism and human data. The importance of applying expert judgement in such weight of evidence cases is also conveyed for determining the most realistic conclusion on the hazard category. For boric acid, it is known that the studies on laboratory animals clearly demonstrate fertility and developmental effects. However other available information relating to intrinsic properties considered as part of a weight of evidence assessment is summarised by the bullets below.

Human studies

• The China and Turkey worker studies represent the most sensitive studies that have been carried out on humans to date. They included sperm analysis, which is the most sensitive test for testicular toxicity in humans. These studies found no adverse reproductive toxic effects from high exposures to boron. The exposure of the workers in China is 100-times higher than the general European population.

• The Chinese and Turkish workers studies further support the argument that humans are not more sensitive to the effects of boric acid than laboratory animals demonstrated by the low rat NOAEL (17.5 mg B/kg/day) to human NOAEL (2.08 mg B/kg) ratio of 8.75. This ratio is over 10 times lower than the default safety factor of 100 often used in risk assessments.

• There is no evidence of developmental effects in humans attributable to boron. Three epidemiological studies evaluating high environmental exposures to boron and developmental effects in humans have been conducted and have shown an absence of effects.

• The highly exposed male Turkish workers did not show any adverse effects on hormone levels (FSH levels, LH levels and total testosterone). These results are in agreement with tests on laboratory animals that boric acid does not have an endocrine-related mechanism for the fertility and developmental effects because boric acid and its compounds are not Endocrine Disruptors. Furthermore, the U.S. Environmental Protection Agency (US EPA) did an evaluation of the endocrine disrupting potential of compounds where boric acid received the lowest score among the 309 chemicals evaluated indicating extremely low potential for endocrine-related toxicity .

Mode of action

• Recent studies provide possible mechanisms of boric acid related developmental effects in laboratory animals, including histone deacetylase inhibition (HDACi) and effects of boric acid on expression of Hox genes . A major difference between laboratory animals and humans is the large zinc stores in bone and soft tissues in humans compared to laboratory animals. Zinc has been shown to be protective against the acute toxicity and male fertility effects of boron .

• Studies that are underway that will provide more information on the role zinc plays in developmental and fertility effects of boric acid include:

o Embryonic stem cell test (June 2013),

o In vitro spermatogenesis assay (June 2013),

o Developmental toxicity dose range finder study of zinc borate (June 2013),

o 90-day oral toxicity study of zinc borate (October 2013),

o Developmental toxicity study of zinc borate (to be completed in 2014).

Nutrient essentiality

• Boron is regarded as an essential nutrient to maintaining optimal human health and has demonstrated beneficial effects in several animal models. In 2001, the U.S. Food and Nutrition Board published a Tolerable Upper Intake Level for boron of 20mg per day, confirming its biological importance. In 2002, the U.K. Expert group on Vitamins and Minerals also ratified boron's benefits. Other epidemiological studies indicate that increased dietary boron exposure is associated with lower incidences of prostate, lung, cervical and

esophageal cancer .
In accordance with the CLP legislation and guidance, EBA considers that based on a weight of evidence evaluation of these studies, other investigations and considerations, there is sufficient evidence leading to the conclusion that it is improbable that boric acid will cause reproductive or developmental effects in humans, thereby questioning the relevance of the animal studies to humans.

Read across
The classification of boric acid as a Category 2 toxic for reproduction should also apply to the other classified borates and DOT. This is because in aqueous solutions at physiological and acidic pH, low concentrations of simple inorganic borates such as boric acid, disodium tetraborates, diboron trioxide and DOT will predominantly exist as undissociated boric acid. Accordingly, the boric acid data is also relevant to these other borates as they too can be considered to exist as undissociated boric acid under the same conditions. It would therefore be appropriate for the classification of these borates to be aligned.

Existing regulatory controls
The borate industry acknowledges that the proposed Category 2 classification would still require hazard communication for products containing boric acid. Further, compliance with EU legislation for classified substances would ensure humans are adequately protected.

Conclusion
The EBA recognises there is a reproductive effect of boron compounds in laboratory animals under test conditions. However, the latest studies and scientific evidence demonstrate that such effects are not found in humans, even when exposed to high levels. Therefore considering all available information, EBA supports the proposed Category 2 classification for boric acid.
The EBA urges all stakeholders, scientific experts and regulatory officials in ECHA, the European Commission and the Member States to support these facts as the re-classification proposals are debated and progress through the EU's regulatory process.

Dossier Submitter's Response
See response to comment 19
RAC's response
Please see response to comment 4

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Poland		MemberState	18

Comment received

The proposed classification and labelling of disodium octaborate anhydrate for reproductive toxicity is based on read-across from other tested borates e.g. boric acid.

PL CA accepts that there is a reproductive effect of boron compounds in laboratory animals under test conditions; however, it questions the relevancy of these data to consider disodium octaborate anhydrate as meeting the classification and labeling criteria of Category 1B as is proposed in this CLH Report.

Although the CLH Report has given some consideration to data not previously reviewed at the time of the original harmonized classification of boric acid in 2008, some key information has been omitted. Secondly, the CLP Regulation acknowledges that weight of

evidence can be used to determine the category of classification.

A weight-of-evidence evaluation of numerous independent epidemiology, worker exposure and mechanistic studies raises doubt about the relevance in humans of the developmental and reproductive effects of boric acid observed in laboratory animals:

No evidence of developmental effects in humans attributable to boron has been observed in studies of populations in China, Turkey and Chile with high exposures to boron. While boron has been shown to adversely affect male reproduction in laboratory animals, studies of highly exposed boron industry workers consistently show no reproductive effects attributable to boron. Workers in boron mining and processing industries represent the maximum possible human exposure.
- The highest exposed workers in China were exposed to about 5 mg B/kg/day, which is more than 100 times greater than the average daily exposure of the general population.
- In the Turkish studies, the mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. As with the Chinese study, there were no negative effects observed for boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone).
- The Chinese and Turkish semen studies in highly exposed workers are a major source of information as to human reproductive toxicity. Not only are these the most exposed workers with exposures measured directly from food, drink and inhalation, but the Chinese and Turkish workers studies are the most sensitive studies that have been carried out as semen analysis was performed, a very sensitive detection system for testicular damage.
- These studies show that humans are not more sensitive to fertility toxic effects than rodents.

Based on the total weight of evidence, the data show that it is improbable that boric acid will cause reproductive or developmental effects in humans. Repr. Category 2 H361d: suspected of damaging the unborn child, is considered the appropriate classification for the following reasons: Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility justifying the removal of the fertility classification; and no developmental effects have been seen in highly exposed populations. However, epidemiological studies of developmental effects are not as robust as the fertility studies, warranting the Category 2 H361d. This classification accommodates for both the positive findings in laboratory animals and the absence of significant effects in humans.

Dossier Submitter's Response

We did (although shortly) consider the epidemiological studies, however, since the results of these studies are not contradictive to the results of the animal studies, we see no reason to downgrade the classification to Repr. 2. The workers are exposed to concentrations that are lower than the doses that cause reproductive effects in laboratory animals. It can therefore not be excluded that in humans higher doses would also result in reproductive effects.It should be noted that classification should be based on hazard, not on risk. Maximal exposure (under normal circumstances) in workers is therefore no criterium for downgrading the classification. For a more elaborate discussion of the epidemiological studies, see response to comment 19.

RAC's response

Please see response to comment 4

Date	Country	Organisation	Type of Organisation	Comment

				number
11.06.2013	Belgium	European Borates Association (EBA)	Industry or trade association	19
Comment received				
See confidential RCOM				
Dossier Submitter's Response				
See confidential RCOM				
RAC's response				
See confidential RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Denmark		MemberState	20
Comment received				
Denmark supports the proposal for classification with Repr. 1B; H360FD and agrees that read-across to boric acid and other tested borates is fully justified. This is based on the well-established reproductive toxicity of the boron ion in different species and the fact that disodiumoctaborate anhydrate primarily exists as undissociated boric acid in aqueous solution at physiological and acidic pH. As mentioned in the CLH report, read-across for borate substances has also recently been deemed acceptable by the European Court of Justice. The epidemiological studies in humans have not demonstrated effects on either fertility or development. However, the exposure levels in these studies did not reach the levels leading to adverse effects in animal studies. The toxicokinetics of boric acid are similar for animals and humans and there is no mechanistic information supporting that humans should be less susceptible to borates than the animal models used. Furthermore, it can be questioned whether the human data are adequate and representative. Hence, the epidemiological studies in humans are considered insufficient to demonstrate an absence of adverse effects on reproduction. With regard to the suggested SCL we can accept the approach for the reason of consistency in relation to the already established SCL for boric acid and several other borates. As the Guidance to the CLP regulation recently has introduced a novel approach to assess the potency of reproductive toxicants based on the ED10 value, we however suggest that the SCLs for all the borates in CLP Annex VI should be looked over and re-evaluated at a given opportunity.				
Dossier Submitter's Response				
Thank you for the support. We agree that, considering the novel approach for SCLs, the SCLs for all borates should be re-considered.				
RAC's response				
Please see response to comment 4				

Date	Country	Organisation	Type of Organisation	Comment

				number
06.06.2013	United Kingdom		MemberState	21
Comment received				
We believe that it is currently inappropriate to develop a harmonised classification for disodium octaborate anhydrous whilst the dataset on boric acid is also under consideration in the harmonised classification and labelling process.				
Dossier Submitter's Response				
We agree that the classification for disodium octaborate anhydrous should be discussed together with the classification for boric acid.				
RAC's response				
Please see response to comment 1				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France		MemberState	22
Comment received				
We agree with the current proposal for consideration by rac: CLP regulation: Disodium octaborate anhydrate does not need to be classified with respect to hazards to the aquatic environment according to Regulation EC no 1272/2008. DSD: N; R52-53 – Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.				
Dossier Submitter's Response				
Thank you for your support. However, we no longer consider that disodium octaborate anhydrate should be classified under DSD due to the applicability of the escape clause for the classification R52-53. For further information please see response to comment number 26.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Germany		Company-Downstream user	23
Comment received				
Boric acid and borates do not pose a chronic risk to aquatic environment because they are minerals.				
Dossier Submitter's Response				
Comment is noted.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment

				number
13.06.2013	Germany		MemberState	24
Comment received				
p. 57ff: The German CA supports the proposal to classify disodium octaborate anhydrate. However, we would like to mention, that the Competent Authority Report (CAR) for this substance according to Directive 98/8 EEC was finalized in June 2008. The data referenced in the CLH dossier refer to the draft CAR from 2006. Thus, not all key studies for aquatic toxicity identified in the final CAR from 2008 are referenced in the CLH Dossier (e.g. Brachydanio rerio: ELS-test; 34d-NOECgrowth = 1.8 mg B/L)). It would be helpful to add the final CAR from June 2008 to the CLH dossier.				
Dossier Submitter's Response				
Thank you for your support and comments. However, we no longer consider that disodium octaborate anhydrate should be classified under DSD due to the applicability of the escape clause for the classification R52-53. For further information please see response to comment number 26. As suggested, the finalized CAR of Disodium octaborate tetrahydrate (2008) has been taken into account (Product-type 8 (Wood preservative) Annex I, 20 February 2009, NL). As for the ELS study in *Brachydanio rerio* (34d-$NOEC_{growth}$ = 1.8 mg B/L), the established NOEC value is higher than the NOEC value of 0.7 mg B/L obtained in Oncorhynchus mykiss and will not change the outcome of the assessment.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Sweden		MemberState	25
Comment received				
SE supports the environmental classification of Disodium octaborate, anhydrate (CAS No 12008-41-2) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations. CLP- Acute aquatic hazards The lowest L(E)C50 obtained in acute aquatic toxicity studies is 25.05 mg B/L, equivalent to 98.7 mg/L disodium octaborate anhydrate, in the invertebrate Litopenaeus vannamei. This value is above the classification threshold value of 1 mg/L. Disodium octaborate anhydrate does therefore not fulfill the criteria for classification as acute hazard to the aquatic environment. CLP- Chronic aquatic hazards Disodium octaborate anhydrate is considered not rapidly degradable in the environment. Chronic aquatic toxicity information is available for all trophic levels. The lowest NOEC available is 0.7 mg B/L, equivalent to 2.6 mg/L disodium octaborate anhydrate, obtained in fish. This value is above the classification threshold value of 1 mg/L. Disodium octaborate anhydrate does therefore not fulfill the criteria for classification as a chronic hazard to the aquatic environment. Directive 67/548/EEC				

Disodium octaborate anhydrate is considered not readily degradable in the environment. Experimental BCFvalues are low (up to 1.5 L/kg based on boron). Taking into account the available data and the physical form of disodium octaborate anhydrate, the bioconcentration and bioaccumulation potential is considered low. The lowest L(E)C50 obtained in acute aquatic toxicity studies is 25.05 mg B/L, equivalent to 98.7 mg/L disodium octaborate anhydrate, in the invertebrate Litopenaeus vannamei. This value falls in the range of 10 mg/L < L(E)C50 ≤ 100 mg/L .

Disodium octaborate anhydrate therefore fulfills the criteria for classification with R52/R53.

OTHER INFORMATION
This proposal for harmonized classification and labelling is based on the data provided for the registration of disodium octaborate tetrahydrate according to Directive 98/8/EEC. The summaries included in this proposal are partly copied for the CAR and CAR document IIA. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the CAR and its document IIA.

Dossier Submitter's Response

Thank you for your support. However, we no longer consider that disodium octaborate anhydrate should be classified under DSD due to the applicability of the escape clause for the classification R52-53. For further information please see response to comment number 26.

RAC's response

Noted

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	Belgium	European Borates Association (EBA)	Industry or trade association	26

Comment received

Data selection from the extensive database of ecotoxicological studies on boric acid and other borates appears to be based on the classical techniques applied for data-poor organic chemicals and not the specific metal guidance presented in Chapter 4 of the CLP guidance. For example, it seeks the lowest value among studies rated with Klimisch scores 1 and 2. Where multiple studies with the same species were available, the CLH Report provides only the single lowest value. For data-rich chemicals, such as inorganics and metals, means of the test results with the same species or a species-sensitivity-distribution (SSD) are widely used, as is done in REACH as well as CLP. The CLH Report does not appear to have involved any independent review of the original study reports or publications to ascertain the relevance to classification and labeling.

Most relevant is that acute marine data were used to conduct a long-term hazard assessment, ignoring the availability of long-term hazard data for freshwater organisms. Other accepted practices for assessing metal and inorganic substances were also ignored, such as correction for background and application of a weight-of-evidence approach.

With the exception of the proposed environmental classification under Directive 67/548/EEC, and within the limitations of the approach taken, the Report's conclusions are consistent with other European reviews, i.e., that borates are stable in the environment (not biodegraded nor photodegraded), are not bioaccumulated in aquatic food chains, and are generally of low toxicity to aquatic organisms.

Several issues of significance have been noted regarding the proposed R52/53 classification under Directive 67/548/EEC. This proposed R52/53 classification is considered incorrect for the following main reasons. Additional information and further comments supporting this opinion are given in the attachment.

(1) The screen for applicable data included studies of marine organisms although abundant data for freshwater organisms are available. This contrasts with the typical guidance that looks at freshwater organisms for which standard test guidelines have been developed. Table 22 identifies the "relevant" data as being an acute study of a marine fish (Limanda limanda), an acute study of a marine invertebrate (Litopenaeus vannamei), and a chronic marine alga study (Emiliania huxleyi). Freshwater studies for each of these endpoints are available and stated in Tables 23-27. This issue has been debated in the past when other metals were assessed for environmental hazard classification, concluding that for data rich substances, standard freshwater data should preferably be used if extensive freshwater data sets are available, therefore limiting the need for read across from salt water data. The same approach should be applied to disodium octaborate.

(2) The key study used to propose the chronic classification is an acute marine invertebrate for which no standard test guideline is available. The reference for this study (Li et al. (2008), "Acute toxicity of boron to juvenile white shrimp, Litopenaeus vannamei, at two salinities" Aquaculture 278: 175-178) was evaluated as "reliable with restriction". This rating reflects that the study, as reported in the publication, is consistent with typical ecotoxicity test designs and principles, but that there are limitations. The publication presents two endpoints, one at a normal salinity (20 ppt) and one at a low salinity (3 ppt). The low-salinity test actually imposed a second stress, and therefore by itself must be considered unacceptable for purposes of classification (see attachment). This is additionally problematic because there are tests with the standard aquatic species (Daphnia magna) that are of equivalent reliability but higher relevance.

(3) The key study was conducted under conditions (low salinity) known to stress the marine test organism, the white shrimp Litopenaeus vannamei. At normal salinity, effects were significantly less severe (96-hr LC50 80.06 mg B/L) than when combined with stress from low salinity (96-hr LC50 25.05 mg B/L). The authors acknowledged that low salinity is a serious stress for L. vannamei. So this study was a test of multiple toxic stressors, which is not the typical test design and is avoided in standard test methods. The low-salinity endpoint should therefore not be considered as a reliable or relevant study, and unacceptable for use in classification.

(4) Studies on freshwater organisms of preferred and standard aquatic species (Daphnia magna, Pimepheles promelas and Selenastrum capricornutum) are available and are of equivalent reliability to the key studies proposed. These freshwater studies were not considered in the assessment of the classification proposal. This is counter to Annex VI of Directive 67/548/EEC as replaced by Directive 2001/59/EC.

(5) The Report identifies both acute and long-term studies for standard freshwater organisms that are acceptable for hazard evaluation. The studies are presented in Tables 22-27 and the single study with lowest endpoint value is presented below together with the calculated result for disodium octaborate:

Method Results (mg B/L) Result (mg Na2B8O13/L) Reference
Acute fish: Pimepheles promelas 96-hr LC50 = 74 314 Study report 005 (2010)a
Chronic fish: Oncorhynchus mykiss (embryo and sac-fry stage) 28-d LC10 = 0.7 (mortality) 2.7 Dyer (2001)

Acute invertebrate: Daphnia magna 48-hr LC50 = 133 524 Gersich (1984)
Chronic invertebrate: Daphnia magna 21-d NOEC = 6 (reproduction) 24 Lewis and Valentine (1981)
Algae: Selenastrum capricornutum 74.5-hr EC50 = 44.6
74.5-hr NOEC = 17.5 176
69 Hanstveit and Oldersma (2000)
a Summarized in the REACH registration for disodium octaborate, accessed on October 25, 2012. These same data have also been published by Soucek, DJ, A Dickinson, BT Koch, 2011, "Acute and chronic toxicity of boron to a variety of freshwater organisms", Environ Toxicol Chem 30(8): 1906-1914.

Based on these standard freshwater organism results, no acute test shows toxicity less than 100 mg/L and no long-term (chronic) test shows a result less than 1 mg/L. Hence no environmental classification is justified (Annex VI of 67/548/EEC as last replaced by Directive 2001/59/EC, section 5.2.1).

(ECHA note: The attachment "Detailed comments on Disodium octaborate anhydrate CLH Report - Environment (hazardous to the aquatic organisms)" is copied below)

Detailed comments on Disodium octaborate anhydrate CLH Report$
Environment (hazardous to the aquatic organisms
Five significant issues were identified concerning the aquatic hazard evaluation in the CLH Report. The review selected tests of marine organisms, even though abundant freshwater organism tests are available for each endpoint. The key study used a marine species (*Litopenaeus vannamei)* for which no standard test method is available (discussed more fully below). The endpoint selected from this study actually represented a multi-stressor test design (based on low salinity) which must be considered "not reliable" and unsuitable for use in the classification determination. Studies of equivalent (or better) quality and more relevance are available in the database and appropriate single studies can be identified from those presented in the Report.
Acute toxicity of boric acid to white shrimp, *Litopenaeus vannamei.*
The conclusion of the CLH Report is that the low-salinity endpoint from the *Litopenaeus* study was the single critical study that leads to a R52/53 classification as Dangerous to the Environment under Directive 67/548/EEC, but not under the CLP regulation. Since this organism is not routinely included in ecotoxicity test guidelines, a review of the limitations of the study are provided below.
Section 5.4.2.1 of the CLH Report identified the endpoint from a study using the white shrimp, *Litpenaeus vannemei* at low salinity conditions (3 ppt) as the key study. This study (published by Li et al. (2008)) was assessed as "reliable with restrictions". Therefore, the restrictions should be considered before accepting it as the key study. Significant restrictions for its use in determining the classification and labeling include:
1. The procedure specifies that classification is to be preferably based on *Daphnia magna* (preferred species) or *Daphnia pulex*. Such data are available and should be used. (Annex VI of Directive 67/548/EEC as replaced by Directive 2001/59/EC.)
2. The shrimp *Litopenaeus vannamei* is a marine species. The classification procedures (guidelines) were based on freshwater organisms. Data on the preferred freshwater species, *Daphnia magna* are available, which suggests those data should be used.
3. The study is an acute (short-term) study, but there are chronic (long-term) studies available for the preferred freshwater invertebrate species, *Daphnia magna* (see Table 26). The use of acute data may be justified if no chronic data are available. As indicated in Annex VI of Directive 67/548/EEC (as replaced by Directive 2001/59/EC), that chronic data can be considered more reliable for a chronic classification and therefore supplant extrapolations from acute study data.
4. *Litopenaeus vannamei* has not been used as a routine assay organism. Because of its extensive use in aquaculture, there is a large literature on temperature, salinity and age-related tolerances (see Annex A). However, these have not been evaluated to either describe a reliable laboratory ecotoxicity test, or to demonstrate that test results are consistent and readily interpreted. Therefore, no accepted criteria are available for conducting an acceptable test. These often include parameters for organism culture and health, age of organisms, acceptable temperature and oxygen ranges, test duration, control survival, and results of reference toxicants. These are

among the necessary restrictions that limit the reliability of the study.
5. The publication includes many details which suggest the study was similar to standard ecotoxicological test designs. Hence, it was rated as "reliable with restrictions." Important items that would be included in a guideline type test are missing. Specific comments about the limitations of the reported information include:
a. The age of the individuals at test initiation was not stated. Mean weights were provided, but the literature on *Litopenaeus*' tolerance to salinity usually refers to post-larval age.
b. Purity of the test material was not specified.
c. Test concentrations are not reported. Nominal concentrations are used, based on the authors' statement that "Actual concentrations of boron in test solutions are basically accordant with nominal concentrations". Unfortunately, the extent to which values are "accordant" cannot be evaluated.
d. Seawater naturally contains boron and it cannot be determined whether the results are expressed as total boron or added boron, i.e. were treatment concentrations adjusted by boron concentrations in the control? This is a common criterion for relevance of studies with naturally-occurring substances such as metals (e.g. zinc).
e. Calculation of the LC50 endpoints considered the data as three separate tests with unreplicated exposures, and then computed the average of the 3 studies. The more common approach is to include all replicates in a single calculation of the LC50, which allows calculation of the 95% confidence intervals of the LC50. In the absence of data, alternative statistics cannot be determined.
f. The test duration was chosen as 96 hr. The duration for the recommended *Daphnia* acute test is 48 hr. Because there is no standard guideline for testing *Litopenaeus*, the appropriate duration is not established. Although Li et al. (2008) used 96 hr, other researchers have used 48 hr tests (e.g., Davis et al. (2002)). This becomes significant when noting that the 48 hr mean LC50 from Li et al. (153 mg B/L) would not have led to a conclusion of classification under 67/548/EEC.
6. The low salinity is recognized as an additional stress on *Litopenaeus*, as noted by the study authors and discussed in Annex A. Optimal salinity was reported by the authors to be around 20 ppt. Consequently, the results at 3 ppt reflect a test of two stressors, which is a less-thandesirable study design, and lower than the European standard test methods for determining hazard classification. Given that the appropriate evaluation for this endpoint should be Klimisch 3, not reliable, the study is not relevant for classification purposes and should not be used.
Other comments on CLH Report.
A number of relatively minor inaccuracies in citations and experimental information have also been identified. Specific comments are made below with reference to the relevant section and table.
1. Section 5.1.3: The evaluation of persistence/degradation is generally correct and consistent with the sources. However, no information is presented to support the rate of dissociation of disodium octaborate to boric acid. Thus the accurate statement would be: "*Based on the available information, anhydrous disodium octaborate dissociates to form boric acid."* (p. 55)
2. Section 5.4, Table 22: The acute fish species selected as the critical value is a marine organism. Freshwater organisms are the usual species, and there are high-quality acute fish tests with freshwater species available, such as the *Pimephales promelas* test shown in Table 23. Use of freshwater-based values are more appropriate and relevant.
3. Section 5.4, Table 22: The description of the acute *Litopenaeus* test is incorrect, as the test was never considered "reliable without restriction." The test was not done in freshwater. As discussed in detail later, the endpoint used in Table 22 should be considered not acceptable for hazard assessment review as it was conducted under multi-stress conditions which are avoided in standard test methods.
4. Section 5.4, Table 22: The acute invertebrate species selected as the critical value is a marine species that is not a daphnia as specified in Annex VI of Directive 67/548/EEC (as replaced by Directive 2001/59/EC). There are several acute *Daphnia magna* tests (the preferred species) shown in Table 25. Further comments on the limitations on reliability and relevancy of this study (*Litopenaeus*) are stated separately.
5. Section 5.4, Table 22: The study authors for the *Selenastrum* work are not Antia and Cheng (see Table 27). The duration of the *Selenastrum* study is slightly more than 3 days. This type of study is multi-generational for the algae, so can be considered a chronic (long-term) study and a NOEC value was reported (see table 27).
6. Section 5.4, Table 22: The *Emiliania* study selected as the critical value is a marine organism.

Freshwater organisms are the usual species, and there is a high-quality test with the recommended freshwater species available for hazard classification (see Table 27).
7. Section 5.4, Table 23: The correct species spelling is *Pimephales promelas*. The Study report 005 from the 2010 REACH registration is now part of a technical publication by DJ Soucek, A Dickinson and BT Koch, 2011, Acute and chronic toxicity of boron to a variety of freshwater organisms, Environ Toxicol Chem 30(8): 1906-1914.
8. Section 5.4.1.2, Table 24: The endpoint reported by Dyer 2001 for *Oncorhynchus mykiss* embryo-larval test was the LC10, not the NOEC (per table 1 in Dyer). The underlying data (also shown in table 1 in Dyer) shows a highly non-monotonic pattern of mortality, suggesting this study is difficult to interpret.
9. Section 5.4.1.2, Table 24: The entry for *Pimephales promelas* is confusing, as Dyer (2001) does not list data for this fish. Soucek et al. (2011) report a chronic NOEC of 11.2 mg/L for this species, which would not have been available for the CAR or EU RAR, but was included in the REACH registration dossiers (see Table 42 in the Joint Chemical Safety Report for disodium octaborate, dated 2012-06-13).
10. Section 5.4.1.2, Table 24: The *Brachydanio rerio* test result cited is not in Dyer (2001). The reference should be the unpublished study report from Hooftman et al. (2000).
11. Section 5.4.1.2, Table 24: The Black et al. (1993) study of *Micropterus salmoides* was an 11-day study. While Dyer referenced this publication, he did not include the endpoint. His value and LC10 for *Micropterus* of 6 mg/L was based on an earlier study by Birge and Black (1977).
12. Section 5.4.2.1, Table 25: The Directive 67/548/EEC specifies that an acute test with *Daphnia magna* (preferred species) or *Daphnia pulex* be conducted and used for classification. The lowest *Daphna magna* value is from Gersich (1984), with an LC50 of 133 mg B/L.
13. Section 5.4.2.1, Table 25: The tests with *Hyalella azteca* and *Ceriodaphnia dubia* are also part of the Soucek et al. (2011) publication.
14. Section 5.4.2.1, Table 26: The chronic test with *Hyalella azteca* is included in the Soucek et al. (2011) publication.
15. Section 5.4.3, Table 27: The table is titled "Freshwater toxicity data for green algae…." However, all the studies by Antia and Cheng (1975) (note spelling) are of marine algae and so are probably not appropriate for this table or for an evaluation for classification and labeling. *Spirodella polyrrihiza* is not an algae but rather a multicellular duckweed and should not be considered relevant. The study by Hanstveit and Oldersma (2000) is a GLP-compliant study using a recommended standard freshwater species and should be the relevant key study.
16. Section 5.5, Comparison with criteria for environmental hazards: The studies of the lowest acute values include marine species for the acute fish, acute daphnid, and chronic algal categories (Table 22). As noted above, the use of marine species is inconsistent with practices for classification and labeling of inorganics and metals when extensive freshwater organism evidence is available. Studies of acceptable quality with recommended freshwater species are available for each category. These would require revision of the text in Section 5.5.
17. Section 6. Other Information: Mention is made that the proposal is based on disodium octaborate tetrahydrate. However, an anhydrous form is the specific topic of this Report. The report acknowledges that the anhydrous material is not marketed, so one wonders at the need to consider classification of a non-marketed substance and how the proposal will benefit evaluations of other borates.

Annex A. Background information – *Litopenaeus vannamei*

The white or whiteleg shrimp, *Litopeneaus vannamei* (formerly *Peneaus vannamei*), is a marine species cultured in the warmer areas of North, Central and South America and Asia. It is native to the eastern Pacific coast in areas where water temperatures exceed 20 C throughout the year. Adults live and spawn in the open ocean while postlarvae migrate inshore and juveniles migrate back offshore (FAO, 2013).[1] Aquaculture of *Litopenaeus vannamei* dominates shrimp cultivation in the Western hemisphere (Jiang et al. (2000)) and has grown in Asian areas as well (Li et al. (2008); FAO (2013)). Global production is reaching 2,800,000 tonnes/yr (FAO, 2013).

Litopenaeus vannamei is tolerant of a range of salinities, which has made it an attractive species for inland low salinity farming. The tolerance range is often cited as 1 to 50 ppt (Li et al., 2008), but a number of studies show that the optimal range is smaller and varies during the life stages (Jiang et al., 2000). Ponce-Palafox et al (1997)[2] reported optimal survival and growth at salinites of 33 to 40 ppt, and temperatures of 28 to 30 C for PL18 (post larval stage, 18 days old) organisms over a 40 day test. However, results from other studies have been inconclusive, with some reporting better growth at lower salinities (Jiang et al., 2000).

The window of tolerance to wide salinity fluctuations was considered to be PL10 to PL40 (op. cit. Davis et al., 2002). PL are not tolerant to large salinity fluctuations when very young (Davis et al., 2002)[3]. McGraw et al (2002)[4] reported the tolerance to acclimation changed with age: survival of PL10 was reduced at 0, 1 or 2 ppt, whereas PL15 and PL20 could be acclimated to 1 ppt. In addition, the ionic composition of the culture water can affect the survival and growth. Roy et al. (2011)[5] found potassium and magnesium effective in improving growth, survival and osmoregulatory capacity. Saoud et al (2002)[6] suggested that manganese and sulfate also affected survival.

Low salinity conditions (less than 15 ppt) appear to adversely affect survival, growth and other indicators of organism condition. Blanc (2012)[7] reported that salinity of 15 ppt and higher resulted in better growth, survival and immune conditions during a 24 week test. Laramore et al (2001)[8] reported that survival and growth of PL (100 mg weight) cultured at 2 and 3 ppt was significantly less than those cultured at 30 ppt for 18-40 days at 30 C. Temperature and PL size also affected growth, but very low salinities (2 ppt or less) led to complete mortality. Li et al. (2008) do not report the age of the PL used in their study, but report a mean weight of 46 mg, suggesting these organisms were younger than those tested by Laramore at al. (2001) and so likely to experience osmoregulatory stress.

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1 See http://www.fao.org/fishery/culturedspecies/Litopenaeus_vannamei/en. Accessed 15 May 2013.

2 Ponce-Palafox, J, CA Martinex-Palacios, LG Ross (1997) The effects of salinity and temperature on the growth and survival rates of juvenile white shrimp, Penaeus vannamei, Boone, 1931. Aquaculture 157: 107-115

3 Davis, D. A., Saoud, I. P., McGraw, W. J., Rouse, D. B., 2002. Considerations for *Litopenaeus vannamei* reared in inland low salinity waters. In: Cruz-Suárez, L. E., Ricque-Marie, D., Tapia-Salazar, M., Gaxiola-Cortés, M. G., Simoes, N. (Eds.). Avances en Nutrición Acuícola VI. Memorias del VI Simposium Internacional de Nutrición Acuícola. 3 al 6 de Septiembre del 2002. Cancún, Quintana Roo, México.

4 McGraw, WJ, DA Davis, D Teichert-Coddington, DB Rouse. 2002. Acclimation of Litopenaeus vannamei postlarve to low salinity: influence of age, salinity endpoint and rate of salinity reduction. J World Aquaculture Society 33(1): 78-84.

5 Roy, LA, DA Davis, I P Saoud, CA Boyd, HJ Pine, CE Boyd. 2010. Shrimp culture in inland low salinity waters. Reviews in Aquaculture 2: 191-208

6 Saoud, IP, DA Davis, DB Rouse. 2003. Suitability studies of inland well waters for Litopenaeus vannamei culture. Aquacultre 217: 373-383.

7 Blanc, M. 2012 Performance of White shrimp Litopenaeus vannamei after long term culture at different salinity levels and its immune response. Accessed at: http://share.pdfonline.com/aedadb49c4f24d2baff07f0e0ee83762/2012TaiwanICDF%20Paper_Moramade%20BLANC.htm

8 Laramore, S, C R Laramore, J Scarpa, 2001. Effect of low salinity on growth and survival of postlarvae and juvenile Litopenaeus vannamei. J World Aquaculture Society 32(4) 385-392.

---End of attachment ---

Dossier Submitter's Response

Thank you for your comments.

<u>*Specific response to comments related to the environmental classification under DSD*</u>
During the public consultion many comments were received, both supporting the proposed classification as well as suggesting that the substance should not be classified for the environment under Directive 67/548/EEC. The Dutch CA has reconsidered its position and decided to change it proposal for disodium octoborate anhydrate and propose no classification for the environment based on the following reasoning:

The effect assessment reports a 96-h EC_{50} of 25.05 mg B/L (equivalent to 98.7 mg/L disodium octaborate anhydrate, in the invertebrate, *Litopenaeus vannamei*, as the lowest valid value for acute toxicity. This value falls in the range of 10 mg/L < L(E)C50 ≤ 100 mg/L. As disodium octaborate anhydrate is considered not readily degradable, it therefore fulfils the criteria for classification with R52-R53.

However, Annex VI of Directive 67/548/EEC specifies that the R52-53 critarion should apply *"unless there exists additional scientific evidence concerning degradation and/or toxicity*

sufficient to provide an adequate assurance that neither the substance nor its degradation products will constitute a potential long-term and/or delayed danger to the aquatic environment. Such additional scientific evidence should normally be based on the studies required at Level 1 (Annex VIII), or studies of equivalent value, and could include:
(i) a proven potential to degrade rapidly in the aquatic environment,
(ii) an absence of chronic toxicity effects at a concentration of 1.0 mg/litre, e.g. a no-observed effect concentration of greater than 1.0 mg/litre determined in a prolonged toxicity study with fish or Daphnia."

Disodium octaborate anhydrate is a inorganic compound that rapily dissociates in water to form a highly water soluble degradation product. Chronic aquatic toxicity information is available for all trophic levels. All available NOEC values are above the trigger value of 1 mg/L (see Table 1 below). Based on this, the Dutch CA has decided to change the proposal and not classify disodium octaborate anhydrate as dangerous to the environment.

Table 1: Summary of the lowest aquatic chronic toxicity results for each trophic level

Method	**Test substance, test conditions and reliability**	**Results [mg B/L]**	**Result [mg$Na_2B_8O_{13}$/L]**	**Reference**
Chronic fish: *Oncorhynchus mykiss* (embryo and sac-fry stage)	Boric acid, peer-reviewd study, fresh water, 188 mg/L hardness, reliable without restriction.	28 days LC10 for mortality = 0.7	2.7	Dyer, 2001 [a c]
Chronic invertebrate: *Daphnia magna*,	Boric acid, comparable to guideline study, fresh water, 170 mg/L hardness, reliable without restriction	21 days NOEC for reproduction = 6	24	Lewis and Valentine, 1981 [c]
Algae (chronic) Emiliania huxleyi	Boric acid, guideline study, fresh water, reliable without restriction.	NOE_rC = 5	NOE_rC: 20	Antia and Cheng (1975) [c]

[a] As summarised in the CAR (Doc. IIA) Effects and Exposure Assessment Active Substance, June 2006.
[c] As summarised in the EU RAR: Disodium tetraborate, anhydrous; Boric acid; Boric acid, crude natural (1). Risk assessment Environment draft version 2.0. (2007).

Specific response to issues raised by EBA:

We are of the opinion that the studies provided in the CLH, are all relevant for the classification and labelling of the substance. As stated in the CLH report, only studies indicated in the CAR as being reliable have been included in this CLH report. Additional good quality aquatic toxicity studies (equivalent to Klimisch score 1 and 2) and reported in the EU RAR and the REACH registration dossier were included if the results obtained in these studies were lower than those reported in the CAR. The only study which required an independent review was the Li et al. (2008) study. We still consider the results of the Li et al. (2008) study to be relevant for the hazard assessment and classification and labelling. However, in light of the revised classification, a further discussion is unlikely to change the outcome of the classification. We also note that CLP (e.g. Annex I 4.1.1.2.2) allows use of marine species for hazard assessment as the goal of the Regulation is to protect the entire aquatic environment. Although the DSD is less explicit on this issue, we consider that DSD (e.g. Annex VI sections 1.6.1 (b) and 1.7.2) also allows "non-standard" species and "non-standard" tests.

RAC's response

The RAC agrees that the escape clause has to be considered, and as the chronic NOAECs are all above 1 mg/l there are no reasons to classify disodium octaborate anhydrate according to the DSD. Furthermore, the RAC notes that classification under Directive 67/548/EEC (DSD) will not be addressed by RAC anymore.

Regarding the other issues, the RAC notes that boron is a metalloid that has properties in between those of metals and non-metals. The DS choose not to use the specific metal guidance of the CLP when assessing the need to classify for environmental effects. RAC agrees to this approach. The RAC notes that all borate compounds dissociate to boric acid, an inorganic substance for which the degradation criteria do not apply, and supports the conclusion that DOT should be considered not readily/rapidly degradable. The interpretation of the Li *et al*. (2008) study is difficult in light of the use of low salinity conditions for a marine species. The data obtained at a normal salinity seems more reliable. However, independently of how this study is interpreted, there is no basis for an environmental classification of DOT. It is noted that some of these studies uses marine species. The RAC supports the use of reliable marine toxicity data, and the CLP also endorse this (CLP 4.1.1.2.2).

Date	Country	Organisation	Type of Organisation	Comment number
10.05.2013	Spain		MemberState	27
Comment received				
The Dutch environmental classification proposal is classified R52/53 under the Directive 67/548/EEC and not classified under the CLP Regulation. However we consider that the substance should not be classified for the environment also for Directive 67/548/EEC based on the application of the escape clause since the NOECs are above 1 mg/L for the three trophic levels.				
Dossier Submitter's Response				
Thank you for your comment. We agree that sodium octaborate anhydrate does not need to be classified based on the escape clause. For further information, please see response to comment number 26.				
RAC's response				
The RAC agrees with the Spanish comment.				

ATTACHMENTS RECEIVED

1. **Detailed comments on Disodium octaborate, anhydrous CLH Report - Reproductive Toxicity** (Filename: DO CLH report_EBA detailed comments_HH.pdf), submitted on 11.06.2013 by the European Borates Association (EBA) *(ECHA note: This attachment is copied under comment number 19)*

2. **Detailed comments on Disodium octaborate anhydrate CLH Report - Environment (hazardous to the aquatic organisms)** (Filename: DO CLH report_EBA detailed comments_Environment.pdf), submitted on 11.06.2013 by the European Borates Association (EBA) (*ECHA note: This attachment is copied under Comment number 26)*

3. **The case for a Category 2 Toxic to Reproduction classification for Borates. New and Previously Not Considered Scientific Data Justify Reclassification. Position Paper of the European Borates Association 4 June 2013** (Filename: EBA position paper reclassification_3 June2013.docx), submitted on 05.06.2013 by a Company-Downstream user from Germany. (*ECHA note: This attachment is copied under Comment number 14)*