Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Boric Acid

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

CLH-O-0000003738-64-03

Adopted

14 March 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BORIC ACID

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.
All attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). Non-confidential attachments that have not been copied into or underneath the RCOM table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website.

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Substance name: **Boric acid**
EC number: **233-139-2 [1], 234-343-4 [2]**
CAS number: **10043-35-3 [1], 11113-50-1 [2]**
Dossier submitter: **Poland**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	France	FUCHS LUBRIFIANT FRANCE	BehalfOfAnOrganisation	1
Comment received				
Fuchs Lubrifiant France is a downstream user of boric acid or elated sodium borates. 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, Fuchs Lubrifiant France fully supports and endorses the comments submitted to this consultation by EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Poland	Nordiska Ekofiber Poland	BehalfOfAnOrganisation	2
Comment received				
Nordiska Ekofiber Poland is a downstream user of boric acid or related sodium borates. 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, Nordiska Ekofiber Poland fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and				

fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Belgium	Ineos NV	BehalfOfAnOrganisation	3
Comment received				
Ineos NV is a downstream user of boric acid or related sodium borates. 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, Ineos NV fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Czech Republic		BehalfOfAnOrganisation	4
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany		Company-Downstream user	5
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the				

conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany	EUKALIN special adhesives	BehalfOfAnOrganisation	6
Comment received				
EUKALIN is using borates for production of adhesives. 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, EUKALIN fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Spain	Ferro Spain, S.A.	BehalfOfAnOrganisation	7
Comment received				
Ferro Spain, S.A. is a downstream user of boric acid or related sodium borates. 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, Ferro Spain, S.A. fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany		Company-Downstream user	8
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				

RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany	EUKALIN special adhesives	BehalfOfAnOrganisation	9
Comment received				
EUKALIN is using borates for production of adhesives. 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, EUKALIN fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Iceland		Company-Importer	10
Comment received				
We are an importer/downstream user of boric acid or related sodium borates. 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, we as an organisation fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Spain		Company-downstream user	11
Comment received				
Our company a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				

Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
23.06.2013	Belgium	PCIM	BehalfOfAnOrganisation	12
Comment received				
PCIM is a downstream user of boric acid or related sodium borates. 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, PCIM fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Germany	isofloc Wärmedämmtechnik GmbH	BehalfOfAnOrganisation	13
Comment received				
Isofloc Wärmedämmtechnik GmbH is a downstream user of boric acid or related sodium borates. 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, Isofloc Wärmedämmtechnik GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Netherlands	Nedri Spanstaal BV	BehalfOfAnOrganisation	14
Comment received				
Nedri Spanstaal is a downstream user of boric acid or related sodium borates. 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, Nedri Spanstaal fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Estonia		BehalfOfAnOrganisation	15
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Germany		Company-Downstream user	16
Comment received				
As a "Downstream user" involved in development and manufacturing of boric acid base protective paints for heat treated steel parts for more than 60 years - without having faced any problems regarding boric acid hazards, neither in respect of our workers nor our customers - we strongly support the considered re-classification of boric acid to Category 2. In fact we think it was overdue to introduce the investigations carried out on human beings exposed to the chemical in question for longer periods of time. The studies carried out in U.S.A., Turkey and China clearly show that even in the case of mine workers heavily exposed to boric acid for decades, the hazards were much lower than suspected based on the overdose animal tests which lead to the present classification. That is why we plea for either reclassification to Class 2 or even too non-hazardous. No doubt, hazardous chemicals must be classified, labelled and handled with utmost care according to their characteristics. On the other hand it makes no sense to classify substances which even after thorough and repeated investigations did show only low to no hazardous potential for human beings – even if there was an adverse effect in animal tests with severely overdose exposition. An inflationary hazards classification and use of respective symbols must be avoided if the				

CLP regulation shall be a trustworthy reliable and informative system allowing the people involved to decide from the labelling, if a substance is hazardous and if yes how it can be handled safely in order to protect people and the environment. Moreover, according to our opinion, preparations containing a hazardous chemical in a way that no direct exposition is thinkable during use of the final product (in the case of boric acid such final products might be for instance glasses based on boron silicates or protective paints for steel hardening), there should be no labelling required, whatsoever – particularly if they are distributed only for industrial use. As a matter of fact boric acid is in some physical and chemical aspects unique. In the case of protective paints for steel hardening it cannot just be substituted by other chemicals. So severely restricting its use by stringent hazards classification / making it a SVHC etc. would enforce big industries (manufacturers of cars, tractors, trucks, gears/transmissions, heavy machinery) to develop completely new and very costly technologies. To avoid this, hazards classification and labelling should be made based not just on assumption or suspicion but strictly based on proven facts.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. It is a fact that all mammals investigated are sensitive to the testicular toxicity of Boron, and there is no reason to believe that humans are not. The epidemiological studies might just indicate that there is no testicular toxicity at human exposure levels much lower than those affecting experimental animals. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Germany	DÄMMSTATT W.E.R.F. GmbH	BehalfOfAnOrganisation	17
Comment received				
DÄMMSTATT W.E.R.F. GmbH is a downstream user of boric acid or related sodium borates. 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, DÄMMSTATT W.E.R.FD. GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France	Arch Water Products France, group Lonza	BehalfOfAnOrganisation	18
Comment received				
Arch water Products France is a downstream user of boric acid or related sodium borates.				

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, Arch Water Products France fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	United Kingdom	Excel Industries Limited	BehalfOfAnOrganisation	19
Comment received				
ExcelIndustries Limited is a downstream user of boric acid or related sodium borates. 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, Excel Industries Limited fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France		Industry or trade association	20
Comment received				
Our industry or trade association is a downstream user of boric acid or related sodium borates. 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, we fully support and endorse the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Belgium	Fertilizers Europe	Industry or trade	21

			association	
Comment received				
Boron is an important micronutrient for plants, which is needed to support crop growth and development. Addition of boron in fertilizers is thus important for agriculture. Fertilizers Europe fully supports and endorses the comments submitted to this consultation by the European Borates Association (EBA).				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France	IGLOO FRANCE CELLULOSE SAS	BehalfOfAnOrganisation	22
Comment received				
Igloo France Cellulose is a downstream user of boric acid or related sodium borates. 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, Igloo France Cellulose fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France	OUATTITUDE	BehalfOfAnOrganisation	23
Comment received				
OUATTITUDE is a downstream user of boric acid or related sodium borates. 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, OUATTITUDE fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number

21.06.2013	Austria	Isocell	BehalfOfAnOrganisation	24
Comment received				
Isocell is a downstream user of boric acid or related sodium borates. 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, Isocell fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France	CELLAOUATE	BehalfOfAnOrganisation	25
Comment received				
CELLAOUATE is a downstream user of boric acid or related sodium borates. 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, CELLAOUATE fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Spain	INQUIDE	BehalfOfAnOrganisation	26
Comment received				
INQUIDE is a downstream user & importer of boric acid. 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, INQUIDE fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number

21.06.2013	Belgium	European Federation of Corrugated Board Manufacturers	Industry or trade association	27
Comment received				
The European Federation of Corrugated Board Manufacturers (FEFCO) is a downstream user of boric acid or related sodium borates. 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, FEFCO fully supports and endorses the comments submitted to this consultation by the EBA. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: CLH report on Boric acid, EBA's comments submitted to ECHA, EXECUTIVE SUMMARY, 20 JUNE 2013)				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	France	AIR LIQUIDE WELDING	BehalfOfAnOrganisation	28
Comment received				
AIR LIQUIDE WELDING is a downstream user of boric acid or related sodium borates. 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, AIR LIQUIDE WELDING fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Germany		Company-Downstream user	29
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Netherlands		Company-Downstream user	30
Comment received				
Our company is a downstream user and was using boric acid or related sodium borates until 2011. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Czech Republic	Bochemie a.s.	BehalfOfAnOrganisation	31
Comment received				
Bochemie a.s. is a downstream user of boric acid or related sodium borates. 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, Bochemie a.s. fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Germany		Company-Downstream user	32
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the				

conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Belgium	European Borates Association (EBA)	Industry or trade association	33

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 manufacturers and importers placing about 95% of the boric acid volume on the market in Europe. These comments represent the view of member companies.

The European Borates Association supports the proposed Category 2, H361d classification. A summary of our position is provided in the Specific comments under Reproductive toxicity and a full discussion with reference to the appropriate sections within the CLH Report is attached with this submission.

Boric acid and other simple soluble inorganic borates predominantly exist under physiological conditions as undissociated boric acid. It is therefore widely accepted that read across to boric acid is relevant for other simple soluble inorganic borates when assessing their toxicological properties. In addition, the CLH report on boric acid is the most up-to-date dataset. Taking these two points into account, EBA recommends ECHA to first consider the boric acid dossier and to assess the disodium octaborate (anhydrous and tetrahydrate) dossiers according to the conclusions made for boric acid.

(ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: Detailed Comments on Boric Acid, CLH Report, 20 June 2013; and 8 confidential attachments submitted, see the list of Confidential attachments received: A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats (draft report); A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats (executive summary); An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate 2335 in Rats (draft report); An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate 2335 in Rats (executive summary); In vitro Embryonic Stem Cell Test with Zinc Chloride and Boric Acid (draft report); In Vitro Embryonic Stem Cell Test With Zinc Chloride And Boric Acid (executive summary); TESTICULAR TOXICITY EVALUTATION OF THE COMBINED EFFECT OF BORIC ACID WITH ZINC CHLORIDE USING BIO-ALTER TECHNOLOGY (STUDY PHASE 2) (draft report); Testicular Toxicity Evaluation of the Combined Effect Of Boric Acid With Zinc Chloride Using Bio-Alter Technology (executive summary))

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. The additional information provided by EBA does not warrant a revision either. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number

20.06.2013	Germany		Company-Downstream user	34
Comment received				
Boric acid is essential for use in medicinal products as eye care solutions, and has been used safely for long time. Attached cytotoxicity studies (agar overlay)for 0.6% boric acid formulations show no detectable reactivity, and the biocompatibility studies proof, that the formulation containing 0.6% boric acid are compatible with biological tissues. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: Report for cyto toxicity and biocompatibility testing of boric acid solution in eye care products; and 1 confidential attachment submitted, see the list of Confidential attachments received: Report for cyto toxicity and biocompatibility of boric acid solution in eye care products - confidential version)				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
Boric acid is clearly a very useful disinfectant. As regards the classification, the RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	Spain		Academic institution	35
Comment received				
We consider that it would be reasonable to review and unify the classification of borates, taking into consideration the last results obtained from the tests run on humans, included in the CLP report submitted by the Bureau for Chemical Substances from Poland "Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Boric Acid				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	France		MemberState	36
Comment received				
We do not support the revision of classification for toxicity to reproduction of boric acid. Detailed arguments are given below in the corresponding section (see comment 138).				
Dossier Submitter's Response				
See comment No 138				
RAC's response				
See response to comment nr 138				

Date	Country	Organisation	Type of Organisation	Comment

				number
14.06.2013	United Kingdom	Advanced Chemical Specialties Ltd	BehalfOfAnOrganisation	37
Comment received				
Advanced Chemical Specialties Ltd 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, Advanced Chemical Specialties Ltd fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Netherlands		Company-manufacturer	38
Comment received				
There is recent high-quality research which supports a lower classification for reproductive toxicity. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: Final report Boric acid and Exposure Inspection at Factory 1 Location; and 1 confidential attachment submitted, see the list of Confidential attachments received: Comments on REACH Annex XV considering boric acid (EC# 233-139-2))				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	France	European Domestic Glass Committee	BehalfOfAnOrganisation	39
Comment received				
Companies members of EDG, the European Domestic Glass Committee, are downstream users 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, EDG fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and				

fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Belgium	Glass Alliance Europe	BehalfOfAnOrganisation	40

Comment received

Glass manufacturers support the REACH Regulation and believe that a control of the risk associated with worker exposure and environmental impact of dangerous substances is welcome in the EU Market.
Glass Alliance Europe welcomes the opportunity to provide its contribution to the public consultation on the proposed re-classification of boric acid as a Category 2 toxic for reproduction substance under the EU's Classification, Labelling and Packaging Regulation (CLP).
Recital (2) of the 30th ATP (Commission Directive 2008/58/EC of 21 August 2008), which added certain borates to the Dangerous Substances Directive as toxic to reproduction category 2 (now 1B) and which was inserted by the European Commission, 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" underlining that uncertainty still existed on the exact classification.
The new proposal, which was submitted by Poland, is based on scientific evidence from studies conducted on Chinese and Turkish borate mine workers with the highest known exposure levels. 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).
GAE cannot provide any further scientific evidence on the issue. However, the latest studies seem to demonstrate clearly that reproductive effects of boron compounds, still evident in laboratory animals under test conditions, are not found in humans even when exposed to high levels.
Considering all available information, GAE supports the proposed Category 2 classification for boric acid. Moreover GAE believes that the classification of boric acid as a Category 2 toxic for reproduction should apply also to the other classified borates and DOT.
Finally GAE would like to underline that boron is of great importance for the glass industries and that boron compounds/raw materials are completely consumed in the glass production process and are no longer present as such in the final article. These final products are definitely safe. Borosilicate glass articles, as for example, pharmaceutical and laboratory ware, which are produced using boron compounds, are considered as to be amongst the most inert materials from a chemical point of view.

(ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachment received: Consultation on the reclassification of boric acid as Category 2 Toxic for reproduction)

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion. It is a fact that all mammals investigated are sensitive to the testicular toxicity of Boron, and there is no reason to believe that humans are not. The epidemiological studies might just indicate that there are no testicular toxicity at human

exposure levels much lower than those affecting experimental animals.

Date	Country	Organisation	Type of Organisation	Comment number
13.06.2013	Slovenia		BehalfOfAnOrganisation	41
Comment received				
Our company 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, our company fully supports and endorses the comments submitted to this consultation by the EBA				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
12.06.2013	United States		Company-manufacturer	42
Comment received				
Just read that the hazard classification of boric acid is being considered for downgrade. If this is under consideration for boric acid, would not the same be considered for diboron trioxide, which is simply the anhydrous form of boric acid? Perhaps this is already being discussed. Diboron trioxide is relatively hygroscopic, and will quickly hydrate in the presence of water to form boric acid. So from an environmental, health and safety perspective, I would think the classification of boric acid and diboron trioxide would be very similar. Diboron trioxide is also included in the SVHC list under CAS # 1303-86-2. As a non-EU entity, I understand we are not entitled to register with the EU, but would like to understand this classification to aid our customers understanding of our product.				
Dossier Submitter's Response				
In our CLH dossier we only concentrate on boric acid. Boric acid and other simple soluble inorganic borates predominantly exist under physiological conditions as undissociated boric acid. It is therefore widely accepted that read across to boric acid is relevant for other simple soluble inorganic borates when assessing their toxicological properties.				
RAC's response				
RAC agrees with the dossier submitter.				

Date	Country	Organisation	Type of Organisation	Comment number
12.06.2013	Germany		Company-Downstream user	43
Comment received				
Borate minerals have been extracted and used commercially for over 100 years. In metal working fluids boric acid is used successfully since more than 40 years. In all these years no case of illness is known to us that would have been due to the use of boric acid. If the classification of boric acid remains repr. tox 1B – H360FD, it will remain on the SVHC candidate list. Consequently, being a substance of very high concern boric acid could be				

banned of use in the EU. Due to the big variety of function within the metal working fluids there is no adequate substitution. Thus, the metal working fluids producers would have to take other substances that fulfil the requirements of being a good corrosion inhibitor, having a good buffer system and having broad spectrum biocidal effects. But, those materials, especially biocides, can pose a greater danger then boric acid.

However, boric acid has contributed to a better health and safety of humans and the environment. The resistance against microbial degradation leads to a significant decrease of biocides in the metal working industry. A ban of boric acid form the market (possible as long as it is on the candidate list) would lead to the opposite trend.

Considering the fact that initial measurements have shown that even when handling crystalline boric acid during the manufacture of MWF concentrates, the AGW (exposure limit) threshold is not exceeded, due the above mentioned facts, and due to our long time experience we strongly encourage the proposed harmonized classification and labelling. The risk to employees from boric acid's toxic effects on reproduction can be ruled out, if risk management measures are considered.

(ECHA's comment: 1 non-confidential attachments submitted, see the list of Attachments received: Public consultation – boric acid (CAS 10043-35-3); and 1 confidential attachment submitted, see the list of Confidential attachments received: Public consultation – boric acid (CAS 10043-35-3), confidential version)

Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
Boron substances are clearly very useful. The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	Denmark	Osmose Denmark A/S	BehalfOfAnOrganisation	44
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				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	Czech Republic	Fosfa akciova spolecnost Breclav	BehalfOfAnOrganisation	45

Comment received
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, Fosfa as a downstream user of boric acid fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
05.06.2013	Germany		Company-Downstream user	46
Comment received				
(ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: 1. 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)				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2013	United Kingdom		Company-Downstream user	47
Comment received				
There is recent high-quality research which supports a lower classification for reproductive toxicity.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2013	Austria		Individual	48
Comment received				

I have been involved in the borates discussions between European institutions and industry from 1990 onwards, in which we (the industry) argued that extreme animal tests were not representative for human exposure. Furthermore we requested to give more weight to risk versus hazard. Those arguments however were not taken into consideration by the classifying bodies. Industry representatives (toxicologists) were not permitted to attend the discussions of "specialized experts".
Dossier Submitter's Response
Thank you for that information.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2013	Italy	IGDT Srl	BehalfOfAnOrganisation	49
Comment received				
I'm very glad to know that the benefits of Boron and in Particular of boric Acid are now recognized by the studies done in Poland. I support the results of these studies.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification. For clarification: the study were not performed in Poland. Polish CA only has collected all the available information and has prepared CLH dossier for boric acid.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Hungary	GE Hungary Kft.	BehalfOfAnOrganisation	50
Comment received				
GE Hungary Kft is a downstream user of boric acid or related sodium borates. 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, GE Hungary Kft fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Belgium	A.I.S.E.	BehalfOfAnOrganisation	51
Comment received				

A.I.S.E. representing the detergent industry is (and was more widely in the past) a downstream user of boric acid and its salt. We are supporting effort to classify boric acid appropriately and are supporting the proposal made by Poland to have it reclassified Category 2 (H361d: Suspected of damaging the unborn child) according to CLP. 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. A.I.S.E. fully supports and endorses the comments submitted to this consultation by the EBA. Indeed, the studies showing not effect in humans even when exposed to high levels should be considered and therefore using all available information based on a the weight of evidence approach boric acid should be classified as category 2.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	United States		Company-Downstream user	52
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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. Our company fully supports to the conclusions from the current scientific weight of evidence presented by the Boric Acid CLH Report and the EBA comments.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Italy	Lamberti S.p.A.	BehalfOfAnOrganisation	53
Comment received				
The boric acid is one of the chemical used in the chemical industry, as varnishes, fertilizers, adhesives (mostly for paper industry) , industrial fluids (lubricant and coolant fluids), abrasive products, ceramics, cleaning products, cosmetics and the tanning industry, and is also used as additive in different processes to produce specialty chemicals.				
Dossier Submitter's Response				
Thank you for that information.				
RAC's response				
The information is noted.				

Date	Country	Organisation	Type of Organisation	Comment

				number
28.06.2013	Belgium		BehalfOfAnOrganisation	54
Comment received				
Our company is a downstream user of boric acid or related sodium borates (PROC 15). 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	United Kingdom		Company-Downstream user	55
Comment received				
Our company is a downstream user of boric acid. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Belgium		Individual	56
Comment received				
Pemco Brugge Bvba is a downstream user of boric acid or related sodium borates. 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, Pemco Brugge Bvba fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Sweden	Swedish Adhesive and Sealants Association	BehalfOfAnOrganisation	57
Comment received				
Swedish Adhesive and Sealant Association is a downstream user of boric acid or related sodium borates. 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, Swedish Adhesive and Sealant Association fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	France	Arc International Coockware	BehalfOfAnOrganisation	58
Comment received				
Arc International Cookware is a downstream user of borates for glass manufacturing. EBA gave a consolidate answer of the borate manufacturers on behalf of the REACH consortium for borates. Arc International Cookware supports the comments submitted to this consultation by EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Belgium		MemberState	59
Comment received				
We would like to thank Poland for the classification proposal. We cannot support the new classification proposal based on the rational detailed in the uploaded attachment. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: PUBLIC CONSULTATION, Harmonised Classification & Labelling, Comments on the classification proposal on Boric Acid)				
Dossier Submitter's Response				
MS Comments *Fertility*				

In the Scialli et al. study (2010) (reported as the key study in the dossier), one preliminary and one main studies have been carried out. It is concluded that no impairment on testicular function following Boron exposure is observed in the main study. However,

- in the preliminary study, the semen sample of 60 boron workers and 10 remote background controls had been analysed. A large proportion of these boron workers presented semen not meeting WHO criteria for normal semen analysis:
  - 4 on 58 boron-exposed workers had < 20 million sperm/ml,
  - 26 on 58 failed to have ≥ 50% forwardly motile sperm,
  - 8 on 58 failed to have ≥ 25% rapidly progressive sperm.

Due to the outcome of this preliminary study, the authors reported that *"there were statistically significant decrements in boron workers in percet sperm with forward motility, rapidly progressive sperm, …, and conclude that boron exposure had adverse effects on sperm viability and sperm motion endpoints."* However, this conclusion is not reported in the dossier.

Response

As stated, this was only a preliminary study. Because it was only a preliminary study to be used in the design of the definitive study, the preliminary data was not presented.

The research was conducted in three phases. Recruitment was conducted separately for each phase. In all three phases eligibility was based on age, employment in the same industry for at least the previous year, not currently under treatment for chronic disease, and no history of vasectomy. Boron workers were recruited at five boron industry sites and controls were recruited from a town ~30 miles away with no boron mining or industry and low-environmental boron. Phase three added an additional community control group of non-boron workers who lived in the vicinity of the boron industry sites with high environmental boron.

Phase one was conducted in 2002. This phase aimed to collect information on industry, workers, lifestyles, and health in this part of the world in order to inform subsequent study design. Interviews with environmental and boron industry representatives were conducted. An interview guide was developed in collaboration with local representatives. Interviews were conducted with boron workers (n=936) and control workers (n=251). Important information was learned about the organization of boron work plus worker health and safety. No biological samples were collected.

Phase two was conducted in 2003. Phase two aimed to establish exposure ranges for boron workers and feasibility of biological sampling SOPs. Recruitment for this phase was targeted to different work stations. Sixty boron workers and nine controls provided biological samples and were monitored in the workplace. Important information was learned about daily boron exposure/dose and health outcomes. Data were used for the design /power calculations for the definitive study, phase three.

Phase three was conducted in 2004. This was a longitudinal, intensive repeated measures sampling design. Workers were monitored for three months to capture boron exposure data for one full cycle of spermatogenesis. Over-enrollment was built in to compensate for expected attrition over repeated sampling. Only men with complete exposure assessment sampling over three months (blood, urine, workplace inhalable dust) were included in the final analysis. Because sperm-FISH assay is expensive and time intensive, a randomly selected subset per group based on previous sample size calculations was analyzed for Y:X ratio in sperm (n=146).

The panel (Scialli et al. 2010) goes on to state: "Although the preliminary study came to the conclusion that boron exposure may be associated with impaired semen quality, this conclusion was not supported by the larger and more complete main study."

MS Comment

- In the main study, an interview on the reproductive experience of men and their wives were conducted in 957 boron workers and 251 remote background controls. Findings of this study are higher prevalence of miscarriage, delayed pregnancy and a lower sex ratio in the boron workers. Besides, it is also mentioned that men exposed to boron had a decrease in live births.

Response

The expert panel (Scialli et al. 2010) concluded the following: "The delayed pregnancy end point showed a statistically significant difference between groups that disappeared on multivariate analysis, suggesting that confounding could explain the apparent difference. The report of fewer live births in boron workers than controls was based on univariate analysis; adjustment for potential confounders was not reported. The small difference between the groups (0.09 live births per subject) and the lack of adjustment for potential confounders or for multiple comparisons detract from the reliability of the reported difference. The authors' conclusions that boron workers have

an increase in miscarriage and a deficit in boy children are not supported by the data presented in these papers. In addition, the reliability of sex ratio data may be severely compromised in societies such as China where selective abortion of female fetuses is practiced, although we do not have information on the prevalence of this practice in Liaoning province at the time of this study. The review panel found that these reports do not add reliable data on male reproductive success associated with boron exposure in humans."

MS Comment
In another key study in the dossier, Robbins WA et al. (2010), the p-value of the original sale of normal morphology is 0,04 which means that the difference is statistically significant compared to the control group. After adjustment for age, abstinence interval, smoking, alcohol, pesticide exposure and Mg, the p-value rose 0,06. This value is still quite low and just above the reference value p-0.05.

Response
Although the p-value for morphology was relatively low, all the other p-values (total sperm count, sperm concentration, % motile sperm, straight line velocity, curvilinear velocity, linearity, sperm head defects, sperm neck and mid-piece defects, tail defects, cytoplasmic droplets) were high, ranging from 0.17 to 0.97; clearly showing no effects.

The authors concluded (Robbins et al. 2010): "Boron workers in our study experienced chronic exposure to boron over one complete cycle of spermatogenesis. When compared to healthy working men living in an area of low environmental boron and healthy working men living near or on the boron ore beds but not employed in the boron industry, we found no adverse association between exposure group and conventional semen parameters (total sperm count, sperm concentration, motility and morphology) or sperm DNA integrity measures (aneuploidy, DNA strand breakage and apoptosis). We specifically looked in our human subjects for toxicologic endpoints reported in animal chronic dosing experiments but did not find evidence to suggest human sensitivity at the exposure levels encountered by our study population that averaged 42mg boron per day (standard deviation 58 mg boron per day)." Scialli et al. (2010) concluded: "The data do not indicate that boron exposure under the conditions described impairs testicular function with respect to sperm concentration, motility, morphology, or chromatin denaturability."

It was reported in Wei and Robbins (2008) that there were no significant effects of worker group status on sperm morphology or on the sperm chromatin structure assay, an assessment of chromatin denaturability." (Wei F, Robbins WA, editors. The effects of boron pollution on male reproductive health, Chapter 9. Beijing: China Environmental Science Publisher; 2008.)

MS Comment
<u>*Development*</u>

We cannot consider the Tuccar *et al* (1998) and Col et al (2000) studies as supportive studies to assess the effect of boron on human reproductive parameters due to the lack of data.

In the Tuccar et al (1998), it is not clear which exposure is taken into account as the study mentions "the drinking water" – people environmentally exposed- and the questionnaires were sent to the workers at borate plant - occupationally exposed. Besides, no information on the occupational exposure level neither on the criteria selection of the families in each region are presented.

Another concern is the Boron exposure level in the drinking water in 3 chosen regions. The concentration of boron is not measured in the named "Region III". The estimated level of exposure of this population living in this region is unknown and therefore the comparison between the different region cannot be carried out. We consider that no conclusion on the level of exposure and the potential adverse effects observed in human can be drawn. On page 93 in the dossier, it mentioned that the named "Region II" is the *low boron level*. Does it mean that "Region III" present boron level in between? The DS referred also to another study (Korkmaz et al. 2007) to assess the daily exposures "*in the boron rich region"* but it is not clear if it is referring to the corresponding "Region III" and if the drinking water has been assessed. Besides, the data are presented in different units (ppm in the Tuccar study and kg/day in the korkmaz study). Korkmaz study also mentioned the exposure of the control but no detailed data is provided regarding this control group (which region of Turkey, size of the sample, lifestyle, workers at plant, workers in the office, general population,…)

Response
Because of the ecolological study design, these studies have clear limitations. However, these studies contribute to a weight-of-evidence evaluation that requires the integration of multiple lines of evidence before conclusions may be reached.

Tuccar et al (1998) study was carried out by home visits. Workers and others related individuals were contacted at

borate plants and mines. No concentrations are reported by the authors for Region III, only stating that "B contents are not too high." Boron concentrations in water for Regions I and II were reported in Tuccar et al. and Korkmaz et al. (2007). Boron dose determinations that included boron concentrations in drinking water supplies and in urine samples from women living in Regions I and II are presented in Korkmaz et al. (2006). Based on urine concentrations, daily boron intake for women in Regions I and II are 8.41 and 1.26 mg B/day, respectively. Regions I and II in Tuccar et al. (1998) correspond to the same regions in Korkmaz et al. (2007).
(Korkmaz M., Uzgoren E., Bakirdere S., Aydin F, Ataman O.Y.. Effects of dietary boron on cerival cytopathology and on micronucleus frequency in exfoliated buccal cells. *Environ Toxicol* 22:17-25 (2007)).

MS Comment
Regarding the Col et al (2000) study, we also have some concerns about the level of exposure in the 3 different regions. The boron level in drinking water ranges from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 ppm in Region III. The level of exposure in the Region II is already covered by the level of exposure in the Region I and we cannot distinguish those both regions in term of Boron exposure level. We have the same remark regarding the dust concentrations in production departments where the Boron exposure level in Region I is covered by the level exposure in Region II (it varied from 1.11 to 2.96 mg/m³ in Region I, 0.69 to 9.25 mg/m³ in Region II and 0.39 to 9.47 mg/m³ in Region III). For occupational exposure, we question the possible occupational personal protective method in place at the plant (personal protective equipment, risk management measure,…), so that the real worker exposure is lower than the measured exposure. Any information would be helpful to assess the real exposure.

Regarding the boron exposure level of the wives, we disagree with the following statement: "*No boron exposure measurements were available for the spouses of the workers during the pregnancies , **however their exposure were likely lower than the male workers who were also exposed to boron at the production facilities***". We understand the rationale behind this statement however, without no measured blood sample, no relevant conclusion can be drawn on the difference of exposure level between the spouses and the workers.

Regarding those both studies, we finally have a general remark concerning the protocol of those studies. We have doubt on the reliability of those studies only based on personal interview (standardised birth ratio, no spermogram data, lifestyle,…).
We consider that a study based on a questionnaire cannot be used as supportive evidence due to the social and cultural issues that can bring bias to the study and cannot reflect the real adverse effects. How is it possible to establish the correlation between levels of inhaled boron dust/ingested boron, the concentration level in the body and the adverse effects observed?

Response
The authors do not provide information on the use of personal protective equipment by workers, and no individual blood or urine boron measurements were taken. Use of questionnaires is a common data collection method for ecologic epidemiology studies. This study was conducted by experienced independent researchers from the departments of Public Health, Genetic, and Biostatistics at the Medical School of Ankara University. The bias associated with questionnaires used in this study is not expected to be greater than similar ecologic epidemiologic studies. These studies provide a qualitative evaluation of long term exposures to relatively high levels of boron and select fertility and developmental outcomes. Although the occupational exposure assessments are limited in this study, the occupational studies of Robbins et al. (2008, 2010) and Duydu et al. (2011) are considered the definitive studies that were well conducted studies with high statistical power that establishes the correlation between level of inhaled borate dust and ingested boron, the concentration level in the body and potential adverse effects.

MS Comment
<u>Animal/In vitro studies</u>
The Lanoue et al. (1998) assessed the effects of low boron diets on embryonic and fetal development in Rodents in four studies.

In the first study, rat dams were fed either a low (0,04µg B/g) or an adequate (2,00µg/g) B diet. No marked effects on fetal growth or development are reported. However, the authors point out that "Low" and "Adequate" do not **<u>imply deficiency or adequacy</u>** : " *0.04µg/g of diet is an amount that certainly represented a very low level of intake. 2µg/g of diet also resulted in a significant reduction in blood B concentration in weanling rats previously fed a commercial rodent diet (these diet typically contain 12.0 – 14.0 µgB/g. So whether 2 µg/g represents an adequate B intake is an issue that **<u>needs further research</u>***."

Concerning the reproductive outcome with low B diet, the study reported no differences in fetal BW and length, or in the external morphology and skeletal structures of the foetuses. As stated in the study, " *one interpretation of this study could be that B is not essential for mammalian reproduction.*"
Based on the conclusion of the first study, we cannot therefore agree with the statement on page 91 in the dossier

that "*Early embryonic development was impaired in rodents fed boron deficient diet*".

Response
The dossier summarizes the Lanoue et al. (1998) publication (1) in a single sentence on page 91 of the text and (2) in greater detail in Table 15 on page 81. The statement cited on page 91 is the dossier's overall conclusion for the Lanoue et al. (1998) article. It is not a conclusion specific to the first of the four experiments performed by Lanoue et al., and we agree that the first experiment did not show that early embryonic development was impaired in rodents fed a low boron diet. However, other experiments, particularly the fourth experiment, support the summary statement on page 91. Further, this statement is consistent with the overall conclusions of the authors:

"Collectively, these studies [the four experiments] support the concept that B deficiency impairs early embryonic development in rodents."

Importantly, the four experiments evaluated different endpoints of embryotoxicity using different test systems. In order to conclude that early embryonic development was impaired, it is not necessary to show that every endpoint in every experiment was adversely affected.

The first of four experiments was designed to evaluate fetal development *in vivo* among the offspring of rats fed diets with two different concentrations of B. No significant difference in fetal growth or development was observed in this first experiment. In discussing the results of the first experiment, the full statement from the study authors should be considered:

"Although one interpretation of this study could be that B is not essential for mammalian reproduction, an alternative explanation is that a longer period of deficiency is needed before having consequences on fetal development. In addition, it should be emphasized that postnatal survival and development were not evaluated in this study."

The authors were pointing out that the first experiment's results, although negative, do not prove that B is not essential. In fact, according to the authors, the collective results of the four experiments support a conclusion that "B deficiency impairs early embryonic development in rodents."

MS Comment
In the third study carried out in the Lanoue et al (1998) article, the effects of Boric Acid exposure on the *in vitro* preimplantation development of mouse embryos have been investigated. Preimplantation development was evaluated by determining the number of embryos reaching the blastocyst stage after 72h of culture and by counting the number of cells in fixed blastocysts. The figure below indicates the frequency of blastocyst formation expressed as percent of baseline T6 medium: addition of low amount of BA to the medium (6-12µM) increased the frequency of blastocyst formation but it was reduced by 25% at 2000µM and by 75% at 4000µM BA (statistically significant).

The study further reported that "*Blastocyst cell number, an indicator of embryonic cell proliferation, was more susceptible to the effects of BA and may be a better marker for determining toxicity threshold levels. When expressed as percent of control, 50-1000µM boric acid decreased blastocyst cell number by 25% and 2000-4000 µM by 50 %; blastocysts did not form at concentration of BA > 8000 µM"*(see figure below).

Although we recognize the limit of the *in vitro* studies, the outcome of the Lanoue et al (1998) study indicates BA-induced embryotoxicity which is not negligible. We would request DS to mention explicitly the findings observed in each study.

Response
Many of the results of this study were summarized in Table 15 on page 81. However, the results of the third study did not appear in Table 15. We agree that the dossier would be improved if the results of each experiment were mentioned. The following additional language should be included in Table 15 to describe the results of the third and fourth experiments in the Lanoue et al. publication as follows:

"In two-cell mouse embryos cultured in media containing various levels of boric acid (from 6 to 10,000 uM), impaired embryonic differentiation and proliferation were observed only when embryos were exposed to high concentrations of boric acid (>2000 uM and ≥200 uM, respectively), reflecting a relatively low level of toxicity of BA on early mouse embryonic development compared to other substances, such as zinc and copper."

"Maternal exposure to the low B diet for 10, 12 and 16 weeks combined with low B culture medium was associated with reductions in blastocyst formation and blastocyst cell number (proliferation), as well as increased numbers of degenerate embryos (57%)."

MS Comment

Endocrine disrupting properties

The Duydu et al. study (2011) indicates a significant higher mean FSH and LH levels at the high exposure group. The mean FSH level is significantly higher than the control group and the mean LH level is significantly higher than the medium group.

Response
For FSH (follicle stimulating hormone) the global null hypothesis that all group means are equal was rejected. The significant pair wise differences are between Control-Medium and Medium-High. Neither a clear dose response nor a significant correlation was found. A statistically significant correlation was seen between urine boron concentrations and LH (lutenising hormone) levels. Nevertheless this correlation is very weak (correlation factor = 0.244). No other statistically significant effects or correlations between boron levels in body fluids and semen parameters or hormone levels were found. The only statistically signifcant difference ($P < 0.05$) observed for the mean LH levels was between medium and high-exposure groups. However, a steady increase in mean LH levels was not observed throughout the exposure groups. In spite of the presence of the person with the highest LH value (20 mIU/mL) in the high-exposure group, the difference of mean LH values between control and high-exposure group was statistically not significant ($P > 0.05$). Additionally, the correlation between the LH levels and blood boron levels was very low (Pearson corr. coeff.: 0.164).

The weak effects that were seen are not indicative for a reproductive toxicity potential of boric acid but are considered incidental. The absence of clear correlations between urine or semen boron levels and adverse effects in semen parameters strengthens the position made in Duydu et al. (2011) that boron does not have an adverse effect on the male reproductive system at typical exposure conditions.

MS Comment
Besides, Acid Boric is listed in the Danish Environmental Protection Agency's list of Undesirable Substances: the substance is classified as Category 1, substance for which evidence of endocrine-disrupting properties has been found in at least one live organism.

We would ask to the DS if the potential Endocrine properties have been assessed and which rationale has been taken into account for not mentioning those properties in the dossier.

Response
It is not clear what studies or data is the basis of the Danish listing of boric acid as an endocrine-disrupting properties.

The potential endocrine properties of boric acid were assessed. Absence of endocrine active properties is mentioned on page 11 and 109 in the Boric Acid CLH dossier and was considered as part of the CLH report submission.

MS Comment
Beneficial effects
On page 104 of the dossier, it is stated that "*A recent review of evidence for the essentiality of dietary boron shows that boron meets the criteria for* ***essentiality in humans*** *(Hunt 2007, 2012)…2) it is present in healthy tissues of different animals* ***at comparable concentrations****; 3) toxicity results only* ***at relatively high intakes*** *; 4)* ***tissue concentrations during short term variations*** *in intake are maintained by homeostatic mechanisms…*". We cannot support this statement without any valuable data. More detailed data from the Hunt studies are requested in order to assess the beneficial effects of dietary boron in humans.

Response
Detail data on essentiality of boron can be found in the attached publications by Curtiss Hunt (2007, 2012).

MS Comment
Editorial comments
- Page 51 : In the study of Korkmaz et al. (2006), the average age of women into the control group is 35.83 ± 83. Then the most elderly women take into account had nearly 120 years largely the age of menopause.

Response: The SD for the control group age is a typographical error, the correct age and SD presented in Table 2 of the paper is 35.83 ± 1.47, minimum of 23 and maximum age of 54.

- Page 59 : In the study Yazbeck C & Huel G (2006), it is mentioned that a negative association between blood delta-aminolevulinic acid dehydratase activity and placental boron was discovered and a potential boron threshold for this association was estimated. However, this threshold is not indicated.

Response: The threshold placental boron content at about 0.08 mg/g is reported in Huel et al. (2004). (Huel G, Yazbeck C, Burnel D, Missy P, Kloppmann W. 2004 Environmental boron exposure and activity of delta-aminolevulinic acid dehydratase (ALA-D) in a newborn population. *Toxicol Sci* 80, 304-309.Toxicol Sci. 2004; 80:304-309).

- Page 67 : In the study of Duydu Y et al. (2011), the result mentioned for semen boron concentrations in the high exposure group is 1875.68~~.2255.07~~ ± 2255.07.

Response: This was a typographical error.

- Page 121 : Volume and page are lacking in the article of Sayli BS (2003), Low frequency of infertility among workers in a borate processing facility, Biological Trace Element research.

Response: Vol. 93, pp 19-29

The Hunt publications are attached.

Hunt 2007 Hunt 2012

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Italy	Federchimica	BehalfOfAnOrganisation	60

Comment received

Federchimica is the Italian Federation of the Chemical Industry. Currently more than 1.400 companies (mostly SMEs) are part of it, with a total of 90.000 employees. Member companies are grouped into 17 Associations, which in turn are articulated into 40 Product Groups.

Major uses of boric acid
The boric acid is mainly used, by the members of Federchimica, in varnishes, fertilizers, adhesives (mostly for paper industry), industrial fluids (lubricant and coolant fluids), abrasive products, cleaning products, cosmetics, in the tanning industry, frits and is also used as additive in different process to produce specialty chemicals.

Essentiality and Nutritional Importance of boric acid
Boron is naturally present and widely distributed in the environment and is essential for the healthy development of all higher plants (Butterwick et al., 1989, Eisler, 2000). Shorrocks (1997) documented the use of boron applications for 132 crops in over 80 countries, demonstrating the widespread nature of agricultural use of boron. Boron has also been found to be an essential element to a variety of aquatic species. These include some fungi and bacteria (Saiki et al., 1993, Fernandez et al., 1984), some diatoms and algae (Smyth and Dugger, 1981), and macrophytes (Eisler, 2000).
Boron is essential also for normal reproduction and embryonic development in frogs and fish

(Fort et al., 1999, 2002; Rowe et al., 1998), and mechanisms for this essentiality are beginning to be revealed (Fort 2002). Additional studies on effects of low boron diets to embryonic development and embryo membrane function in rats, mice, and frogs are currently being conducted. Between those it has been demonstrated that in rats, maternal exposure to a low boron diet was associated with a reduction in embryo implantation sites (Lanoue et al, 1998).
There is also wide database of references relating to the nutritional importance of boron. In January 2001, the U.S. Food and Nutrition Board (FNB) accepted the nutritional importance for boron and determined a safe Tolerable Upper Intake Level, of 20 mg boron /day. This implies that the average person can safely ingest 20 mg boron/day in food (U.S. Food and Nutrition Board 2001).

Federchimica Position
Federchimica, in agreement with EBA (European Borates Association , see position attached), supports the Polish proposal for re-classification of boric acid as a Category 2 reproductive toxicant under the EU's classification. As described in the Boric Acid CLH Report, contrary to the laboratory animal data, studies in humans have not demonstrated adverse effects of high boron exposures in boron workers in the U.S., China and Turkey. Furthermore, since these studies are considered reliable, they should take precedence over animal studies as outlined in CLP Regulation (1272/2008/EC) section 1.1.1.4.
Moreover, new studies have recently been completed since the publication of the Boric Acid CLH Report for public consultation that investigates the protective effect of zinc against boric acid related developmental and fertility toxicity. Humans have intrinsically higher levels of zinc than laboratory animals that in part explain the absence of boric acid related reproductive toxicity effects in humans. These new studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans.
Furthermore, there are also available data coming from poison control centers. In fact from the mid-1800s to around 1940 boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhea, malaria, epilepsy, urinary tract infection and exudative pleuritis (Kliegel, 1980). In all these cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. Besides, there are also data related to the result of accidental use of boric acid. Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g (Litovitz et al, 1988).
Moreover, since the human response to ingestion of boric acid indicates vomiting at fraction of concentrations that are the animal NOAEL values, chronic exposures of humans are likely to be self-limiting unlike rodents that are unable to vomit. These acute effects demonstrate that it is not possible for humans to be exposed to the high doses that could give rise to reproductive effects. Furthermore nausea, vomiting and diarrhoea would prevent repeated exposure through accidental misuse.

Data to support the fact that the developmental or fertility effects have never been demonstrated among human with high exposure to borates arise also from legislation on safety and health at work. In Italy the Decree n.81/2008, related to health and safety at work, establishes that the company, using some dangerous substances, has to perform a health monitoring system. The feedback from Federchimica members, performing this system, demonstrates that no adverse effect has ever been arisen to the workers exposed to boric acid.

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Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment

				number
28.06.2013	Germany	Josef Opavsky und Sohn Inh. Dipl.-Ing. (FH) Heinz Kropp GmbH	Company-Manufacturer	61
Comment received				
The company Josef Opavsky und Sohn Inh. Dipl.-Ing. (FH) Heinz Kropp GmbH is a downstream user of boric acid or related sodium borates. 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 company Josef Opavsky und Sohn Inh. Dipl.-Ing. (FH) Heinz Kropp GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Belgium	Agoria	BehalfOfAnOrganisation	62
Comment received				
Agoria represents downstream users in different sectors using boric acid or related sodium borates within their production process. In the past, Agoria was active in this dossier in liaison with the European Borates Association (EBA) given the importance of these substances for our member companies. EBA has provided a consolidated response on behalf of the European borate manufacturers and importers and on behalf of the REACH consortium for borates on the proposal of reclassification of these substances. As a consequence, Agoria would like to refer to these comments submitted by EBA and we would like to ask to take EBA's evaluation and conclusion into account.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Germany		Company-Downstream user	63
Comment received				
Support of the Polish proposal to downgrade the classification of boric acid With the EC-Regulation No. 790/2009 of August 2009, amending the CLP-Regulation for the classification and labelling of substances and mixtures for the purpose of its adaptation to technical and scientific progress, inorganic boron compounds like boric acid and disodium tetraborate have been reclassified as toxic to reproduction Category 1B and have been labelled with the GHS pictogram GHS088, the signal word "Danger" as well as the hazard				

statement H360FD "May damage fertility, may damage the unborn child".

This classification is from our point of view disproportional.

The current classification is based on adverse developmental and fertility effects of borates observed in rats and rabbits in laboratory studies.
Contrary to the laboratory studies, no adverse effects have been observed at high boron exposures in several worker exposure studies.

Boric acid and disodium tetraborate are used in a lot of applications since hundred of years and there has never been casted doubt on their safety for humans when used under the intended conditions.

Boric acid and disodium tetraborates are used in wood preservation area over decades to protect non resistant wood species against wood destroying organisms. The intrinsic properties of the substances enable to protect wood against a wide range of destroying organisms (not only fungi but also insects) both in the preventive and the curative domain. As inorganic compounds with really negligible vapour pressure they have particularly been recommended by health and safety bodies for indoor uses where they have been used safely over years.

The experience gained over the years from worker and environmental exposure should be considered instead of laboratory worst-case animal studies.

We therefore support the Polish proposal to downgrade the classification of boric acid.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Spain		Company-Downstream user	64

Comment received

Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment

				number
27.06.2013	Spain		Company-Downstream user	65
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	France		Company-Manufacturer	66
Comment received				
Boric Acid is a naturally occurring chemical used widely such as in detergents, cleaners, personal care products, agriculture. It is even available as a food supplement and used in a range of health products including medical devices, such as contact lens buffered solutions, contact lens care products and eye drops. Boric acid provides benefits that alternative products cannot currently provide. Boric acid has been classified as Repr 1B, H360FD for equal or higher concentration than 5.5% because of adverse effects observed in animal studies. No human studies showed any adverse effects but recently, new and more precised studies show how workers, exposed to significant doses of boric acid, by oral route with water consumption but also by air and food, did not develop any adverse effect. The European Chemical Agency (ECHA) has proposed a public consultation in order to re-classify boric acid as a Category 2 reproductive toxicant under the EU's Classification, Labelling and Packaging Regulation (CLP). We approve this first step of de-classification and re-classification of boric acid as a less reproductive toxicant in Category 2. Two recent clinical studies in two different countries have been performed. Previous clinical studies had shown no effect but these new studies bring evidence based on semen quality analysis, level of hormones and doses in urine and blood. A clinical study (Scialli et al, 2010), performed on boron (B) exposure of Chinese male workers, has shown no effect on fertility of men and even their wives compared to controls. The workers were exposed to high daily concentration of boron via water contamination (75 workers with a mean daily boron intake of 31.3mg B/day, and a subset of 16 of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125mg B/day). The no-adverse-effect level for reproductive effects in male rats is 17.5mg B/kg bw/day. The clinical results obtained in the Chinese study do not correlate with observations in the animal, even for higher doses of exposure to boron. The other clinical study (Dudu et al, 2011) was performed in Turkey. The reproductive				

effects of exposure to Boron was investigated on workers in a boric acid plant based on air, food and water sources. In the highly exposed group, the mean daily dose of B was 14.45 ± 6.57 mg B/day in the conditions of work, daily handling and use. No adverse effect on semen, urine and blood was observed. Even if the dose in this plant is lower than the animal study for determination of NOAEL, the study shows how the workers are really exposed when producing boric acid in some plant.

Scialli AR, Bonde JP, Hohlfeld IB, Culver BD, Li Y, Sullivan FM. An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reproductive Toxicology 29 (2010) 10-24

Dudu Y, Basaran N, Ustundag A, Aydin S, Undeger U, Ataman OY, Aydos K, Duker Y, Katja Ickstadt, Waltrup BS, Golka K, Bolt HM. Reproductive toxicity parameters and biological monitoring in occupationally and environmentally boron-exposed persons in Bandirma. Arch Toxicol 85 (2011) 589-600

(ECHA's comment: This comment replaces 2 previously submitted comments as requested by the commenter)

(ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: Public attachment; and 1 confidential attachment submitted, see the list of Confidential attachments received: Confidential attachment)

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany	Calderys Refractory Solutions	BehalfOfAnOrganisation	67

Comment received

Calderys Refractory Solutions is a downstream user of boric acid or related sodium borates. 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, Calderys Refractory Solutions fully supports and endorses the comments submitted to this consultation by the EBA.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany	Bundesverband Glasindustrie e.V.	BehalfOfAnOrganisation	68

Comment received
Some of the members of Bundesverband Glasindustrie e.V., the federal association of the glass industry in Germany, are downstream users 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, BV Glas fully supports and endorses the comments submitted to this consultation by the EBA. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: BV GLAS COMMENTS ON THE CONSULTATION ON THE RECLASSIFICATION OF BORIC ACID AS CATEGORY 2 TOXIC FOR REPRODUCTION)
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany		Company-Downstream user	69
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	France		Company-Downstream user	70
Comment received				
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 downstream user of boric acid or related sodium borates, we fully support and endorse the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the				

submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany	Johns Manville Europe GmbH	BehalfOfAnOrganisation	71
Comment received				
Johns Manville is a downstream user of boric acid or related sodium borates. 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, Johns Manville fully supports and endorses the comments submitted to this consultation by the EBA. (ECHA's comment: 1 non-confidential attachment submitted, see the list of Attachments received: Detailed Comments on Boric Acid CLH Report, 20 June 2013)				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Poland		Company-Manufacturer	72
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Spain	ENDEKA CERAMICS, SA	BehalfOfAnOrganisation	73
Comment received				
Endeka Ceramics SA is a downstream user of boric acid or related sodium borates. 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, Endeka Ceramics SA fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				

Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Finland	Oy HomePro Ab	BehalfOfAnOrganisation	74
Comment received				
Oy HomePro Ab is a downstream user of boric acid or related sodium borates. 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, Oy HomePro Ab fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Finland	Oy Sabado Group Ltd	BehalfOfAnOrganisation	75
Comment received				
Oy Sabado Group Ltd is a downstream user of boric acid or related sodium borates. 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, Oy Sabado Group Ltd fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany	German Refractory Association	BehalfOfAnOrganisation	76
Comment received				
Member companies of our association are downstream users of boric acid or related sodium borates. 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, German Refractory Association fully supports				

and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	United Kingdom		Company-Downstream user	77
Comment received				
My company and other associated companies within the EEA are downstream users of boric acid, boric oxide and related sodium borates and in one case an importer of sodium tetraborate. 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. Having reviewed the contents of this response, we fully support and endorse the comments submitted to this consultation by the EBA with regard to the reclassification of boric acid (CAS 10043-35-3) to Category 2, H361d.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany		Company-Downstream user	78
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Germany		Individual	79

Comment received
CWA Cellulosewerk Angelbachtal GmbH is a downstream user of boric acid or related sodium borates. 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, CWA fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Poland	Polish Society of Toxicology	BehalfOfAnOrganisation	80
Comment received				
The Polish Society of Toxicology has carefully reviewed the proposed reclassification of boric acid as a Category 2 reproductive toxicant. The Polish Society of Toxicology is of the opinion that the new studies and scientific data and insights justify this reclassification and therefore endorses the boric acid CLH report. The Polish Society of Toxicology was created in March, 1978. It is an interdisciplinary scientific association, which comprises 11 regional sections gathering over 300 members. It organises scientific congresses, conferences, symposia, trainings, methodological seminars as well as courses, both at the national and international level. The Society has been publishing periodically the "Guide to the Polish Society of Toxicology" and its own scientific journal "Acta Poloniae Toxicologica" since 1987 and 1993, respectively. The Polish Society of Toxicology is a member of two international scientific associations, namely the European Toxicological Association - EUROTOX and the International Union of Toxicology – IUTOX.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Austria	Wolfinger GmbH	BehalfOfAnOrganisation	81
Comment received				
Wolfinger GmbH is a downstream user of boric acid or related sodium borates. 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, Wolfinger GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Hungary	Michelin	BehalfOfAnOrganisation	82
Comment received				
Michelin is a downstream user of sodium borates derivate from boric acid. 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, Michelin fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany	Henkel AG & Co. KGaA	BehalfOfAnOrganisation	83
Comment received				

Henkel is a downstream user of boric acid or related sodium borates. Based on the following argumentation, we raise doubt that the results observed in animal feeding studies with boric acid are relevant with respect to effects in humans. Henkel therefore fully supports the proposed classification of boric acid as Category 2, H361d.

Route of exposure
The greatest exposure to boron for the general population comes from food intake. Boron is a normal constituent of blood and tissues in humans as a result of ingestion in food and drinking water containing boric acid and borates. Even among population groups with relatively high exposure to boron e.g. as borates, developmental or fertility effects have never been observed.

Consumers may be exposed to boric acid and borates mainly via the skin and to a minor extent by inhalation. Dermal absorption of boric acid and borates across intact skin is insignificant which results in a very low dermal uptake. Furthermore, workplace exposure usually takes place both by dermal contact during direct handling of products and contaminated equipment as well as by inhalation of aerosols (ECETOC Technical Report No. 93 on Targeted Risk Assessment, 2004).

Classification and labelling of boric acid and borates was derived from feeding studies in laboratory animals at high dietary doses. Humans could only reach equivalent doses under conditions of serious abuse by deliberate ingestion. Humans generally would vomit when given orally high doses of borates at levels that caused reproductive toxic effects. Since rodents cannot vomit, high oral doses can be used in rodent studies, but do not properly reflect the realistic exposure situation in humans and are not a satisfactory model for human exposure. Even exaggerated work place exposure conditions will not result in

exposures above the levels tested in the animal feeding studies.

Relevance to humans
In the past it was not known whether there are significant differences in the toxicokinetic and toxicodynamic between humans and laboratory animal models with regards to the toxicity of boric acid. In the absence of such knowledge it was assumed that the animal data are relevant to humans. Recent studies provide mechanisms of boric acid related effects on reproduction in laboratory animals and show major differences between laboratory animals and humans. Large zinc stores in bone and soft tissues in humans compared to laboratory animals have shown to be protective against the reproductive effects of boron.

Consideration of epidemiological studies
According to the REACH Guidance on information requirements and chemical safety assessment, Chapter R. 7a, Section 7.5.3.2: "Human data adequate to serve as the sole basis for the hazard and dose-response assessment are rare. When available, reliable and relevant human data are preferable over animal data and can contribute to the overall Weight of Evidence".

Also CLP Regulation clearly foresees the use of human data. Furthermore, human data should have precedence over other data if reliable (Regulation (EC) No. 1272/2008, Section 1.1.1.4).

Current legislation clearly emphasizes that human data should be considered in a Weight of Evidence approach. The results of epidemiological studies confirm that the effects of boric acid are different in man compared to animals, thus, these studies have to be considered for classification and labelling.

Conclusion:
While exposure of consumers and workers may happen via dermal and inhalation route, the relevance of the animal feeding studies for humans are doubtful because of the doses administered and the route of administration. Furthermore, available data show that the effects seen in laboratory animals are not relevant to humans. As legislation requires that human data should be considered for the purpose of classification and labelling decisions and have precedence over other data the proposed classification as Category 2, H361d is considered to be appropriate.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion. It is the intrinsic hazardous properties that are assessed in the classification and labelling system (CLP), and not the exposure potential.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Netherlands		MemberState	84
Comment received				
Since classification deals with the intrinsic hazardous of a substance only (and not its risks), exposure arguments are in principle not relevant for classification purposes.				
Dossier Submitter's Response				

Since the argument used for disregarding the human data is that the exposure levels are less than doses received by laboratory animals, it is important to put in context the various human exposure levels, including blood, urine and semen levels. Based on the chronic high exposures of boron workers, if the intrinsic hazard was the same in humans as in rats, effects would have been seen in the individual sperm evaluations of these workers.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion. It is the intrinsic hazardous properties that are assessed in the classification and labelling system (CLP), and not the exposure potential.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany		Individual	85
Comment received				
(ECHA's comment: 1 confidential attachment submitted, see the list of Confidential attachments received)				
Dossier Submitter's Response				
See confidential RCOM				
RAC's response				
See confidential RCOM				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Italy		Industry or trade association	86
Comment received				
We support the reclassification of boric acidas a Category 2 reproductive toxicant under the EU's Classification, Labelling and Packaging Regulation (CLP), we can conclude that the human studies made with Chinese and Turkish workers that were exposed to boron at concentrations higher than the recommend, shown that there is no adverse in reproduction, also that human are not more sensitive to any effect or damage than animals. These studies involved biological, epidemiological and hormonal test that support these conclusions. Also the previous studies made not comprise role zinc plays in developmental and fertility effects of boric acid include. Otherwise boron is considerate as an essential nutrient to maintaining optimal human health; this is supported by different American entities, like U.S. Food and Nutrition Board. Boron as well is necessary for correct development on plants, it works in cell wall strength and development, and stimulation or inhibition of specific metabolic pathways. We recognise that 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, we support the proposed Category 2 classification for boric acid.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B				

classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Italy		Company-Downstream user	87
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	France		BehalfOfAnOrganisation	88
Comment received				
Our company is a distributor selling to downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	United Kingdom	Afton Chemical Limited	BehalfOfAnOrganisation	89
Comment received				
Afton Chemical Limited is a downstream user of boric acid. 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, Afton Chemical Limited fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Switzerland	isofloc AG	BehalfOfAnOrganisation	90
Comment received				
isofloc AG is a downstream user of boric acid or related sodium borates. 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, isofloc AG fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany	Chemische Werke Kluthe GmbH	Company-Downstream user	91
Comment received				
Chemische Werke Kluthe is a downstream user of boric acid and related sodium borates. 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, Chemische Werke Kluthe fully supports and endorses the comments submitted to this consultation by the EBA. Sincerely yours, Elmar Biel REACh-coordinator Chemische Werke Kluthe GmbH Mittelgewannweg 4-8 G-69123 Heidelberg				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Finland	Ekocell Oy	BehalfOfAnOrganisation	92
Comment received				
Ekocell Oy is a downstream user of boric acid or related sodium borates. 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, Ekocell Oy fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany	Additiv-Chemie Luers GmbH	Company – downstream user	93
Comment received				
Additiv-Chemie Luers GmbH is a downstream user of boric acid or related sodium borates. 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, Additiv-Chemie Luers GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Norway		MemberState	94
Comment received				
Norway have evaluated the proposal for a new harmonised classification and labelling of Boric acid, cas no. 10043-35-3 from Poland. We cannot support the proposal to change the classification of boric acid from reproductive toxicity with Repr. 1B - H360FD to Repr. 2 - H361d. The current proposal is based on several epidemiological studies, where no effect of exposure to boric acid is shown. However, for boric acid the evidence of a reproductive hazard has been derived from animal studies. The REACH guidance on information requirements and chemical safety assessment, chapter R.7a, R.7.6.4.2 (Human data on reproductive toxicity) describes the limitations which should be considered when using epidemiological data: "When evidence of a reproductive hazard has been derived from animal studies it is unlikely that the absence of evidence of this hazard in an exposed human population will negate the concerns raised by the animal model. This is because there will usually be methodological and statistical limitations to the human data." In our opinion this is applicable for the new studies in the CLH proposal from Poland. We are also of the opinion that there are several shortcomings to the studies mentioned in the CLH proposal from Poland. The study design and the statistical power are limited. Hence, these				

studies are unable to rule out effects on human fertility. Also for developmental toxicity no new data support a reclassification.

Dossier Submitter's Response

MS Comment

When evidence of a reproductive hazard has been derived from animal studies it is unlikely that the absence of evidence of this hazard in an exposed human population will negate the concerns raised by the animal model. This is because there will usually be methodological and statistical limitations to the human data.

Response

Statistical Power

The statistical power of the worker studies in China and Turkey are actually better than the animal studies. The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm. (Mangelsdorg I and Buschmann J (2002) Extrapolation from Results of Animals Studies to Humans for the Endpoint Male Fertility – Research Report. Federal Institute for Occupational Safety and Health, Dortmun/Berlin/Dresden, Germany)

Robbins et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters.

Scialli et al. (2010): "The study size of some 65 men in each exposure group allow, according to our computations, the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. The power is not expected to be substantially increased by analyses of several samples per man and the power to detect differences in total count is lower. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel believes the statistical power of analyses based on these end points was adequate."

Epidemiological studies:

The studies of highly exposed boron industry workers in China and Turkery were well conducted studies of high statistical power conducted by independent experience researchers. Individual level data was obtained on participants and utilized in statistical analyses in all phases of this research; it is not an ecologic study. Exposure is reported as individual level blood or urine boron.

Robbins et al. (2008; 2010) and Duydu et al. (2011) conducted a comprehensive assessment of semen quality indicators that included targeting human correlates of the toxic endpoints previously described in published animal toxicology literature related to boron. The researchers included both light microscope and computer aided measures for sperm motility. No significant association between boron exposure and sperm motility was found for the range of exposures in the study cohorts that were lower than those causing toxic effects in the animal work.

The same sperm evaluations were conducted on the boron workers as conducted on laboratory animals. In both instances, sperm evaluations are the most sensitive measurements of male fertility effects correlated with individual boron measurements in blood, urine and semen. This level of absorbed dose measurements in humans is what distinguishes these worker studies from other epidemiological studies. The workers studies in Turkey and China actually provide better exposure measurements than in animal studies since in the animal toxicity studies comparative blood, urine and semen measurements are not conducted and correlated to effects.

In addition, recent studies submitted by the EBA (in vitro spermatogenesis and embryonic stem cell tests, studies of zinc borate) as part of the public consultation provide additional mechanistic information that raises doubt about the relevance of the effect for humans, and therefore, classification in Category 2 is more appropriate. With the human worker data combined with the studies of boric acid and zinc, raises doubt about the relevance of the effect for humans. Furthermore, the criteria for Category 2 "Suspected Human Reproductive Toxicant", does not require that an absence of effects in humans be proven. In fact, "Substances are classified in Category 2 for reproductive toxicity when there is **some evidence from humans** or experimental animals,…" No evidence of developmental effects in humans has been demonstrated.

MS Comment

The REACH guidance on information requirements and chemical safety assessment, chapter R.7a, R.7.6.4.2 (Human data on reproductive toxicity) describes the limitations which should be considered when using

epidemiological data: "When evidence of a reproductive hazard has been derived from animal studies it is unlikely that the absence of evidence of this hazard in an exposed human population will negate the concerns raised by the animal model.

Hence, these studies are unable to rule out effects on human fertility. Also for developmental toxicity no new data support a reclassification.

Response
Additional *in vitro* and animals studies of boric acid and zinc sponsored by the European Borates Association have demonstrated a dose dependent protective effect of zinc against boric acid related fertility effects. A full discussion of these studies was submitted by the EBA in support of the proposed Category 2, H361d classification. To investigate the effect of zinc on boric acid related toxicity on fertility effects an *in vitro* spermatogenesis study with boric acid in the presence of varying amounts of zinc were recently completed (Martin 2013). An absence of boric acid related effects on spermatogenesis was observed in the presence of zinc at concentrations lower than the level of zinc found in human testes. Based on these new studies and the intrinsic high levels of zinc in target tissues in humans compared to laboratory animals, provides a probable mechanism for absence of fertility effects in humans. As presented earlier, the power of the worker studies in China and Turkey are actually better than animal studies (Mangelsdorf & Buschmann 2002).

Criteria for Category 2 "Suspected Human Reproductive Toxicant", does not require that absence of effects in humans be proven. In fact, "Substances are classified in Category 2 for reproductive toxicity when there is **some evidence from humans** or experimental animals,…" Furthermore, "However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate." The fact that no evidence of reproductive effects has been seen in studies of high statistical power of highly exposed populations and recent studies demonstrating the protective effects of zinc coupled with the intrinsically higher levels in target tissues in humans, raises doubt about the relevance of the effects in humans.

Furthermore, a GLP conducted *in vitro* embryonic stem cell test of boric acid with varying concentrations of zinc and developmental dose range finder study of zinc borate studies have demonstrated a dose dependent protective effect of zinc against boric acid related developmental effects (Martin 2013; Hofman-Huther 2013). In the embryonic stem cell test, a reduction in the boric acid inhibition of differentiation of D3 embryonic stem cells was observed with increasing concentrations of zinc, and at levels of zinc below that found in the human fetus. Based on these new studies and the intrinsic high levels of zinc in target tissues in humans compared to laboratory animals, provides a probable mechanism for absence of effects seen in animal studies for humans.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany		BehalfOfAnOrganisation	95

Comment received

Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Germany	Hermann Bantleon GmbH	BehalfOfAnOrganisation	96
Comment received				
Hermann Bantleon GmbH is a downstream user of boric acid or related sodium borates. 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, Hermann Bantleon GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Italy		Company-Downstream user	97
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	United Kingdom		Company-Downstream user	98
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B				

classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Belgium		Company-Downstream user	99
Comment received				
We are a downstream user of boric acid or related sodium borates. In the past we were in contact with the European Borates Association (EBA) and provided EBA with relevant information. The 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, we would like to refer to the comments submitted by EBA and we would like to ask to take EBA's evaluation and conclusion into account.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	United Kingdom	British Adhesives and Sealants Association	BehalfOfAnOrganisation	100
Comment received				
BASA members are downstream users of boric acid or related sodium borates. 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, BASA members fully support and endorse the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Italy		Individual	101
Comment received				
FOUNDRY ECOCER is a downstream user of boric acid or related sodium borates. The European Borates Association (EBA) has provided a consolidated response on behalf of the European borate Manufacturers and Importers and on the behalf of the REACH consortium for borates. As a consequence FOUNDRY ECOCER fully support and endorses the comments submitted to this consultation to the EBA.				
Dossier Submitter's Response				

Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Spain		Company-Downstream user	102
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Belgium	ETHIC (European Thermoplastic Independent Compounders and Masterbatcherst	BehalfOfAnOrganisation	103
Comment received				
ETHIC members are downstream users of boric acid or related sodium borates. 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, name of your organisation fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany		BehalfOfAnOrganisation	104
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA. In our opinion, boron and its different salts could show substantial benefits when performing a comparative assessment to many other active ingredients underlying regulation through Biocidal Products Regulation; most important is that at least with regard to biocidal products' applications not exposed to frequent weathering they are more or less immobile during use phase, resulting in acceptable exposure towards men and environment. But instead boron and its different salts are facing a very near end as actives in biocidal products because of the a-priori exclusion criteria laid down in the new Biocidal Products Regulation. These are only addressing boron's un-proportionate classification without taking into regard exposition and risk assessment anymore.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Peru		Company-Manufacturer	105
Comment received				
Our company is a manufacturer of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany	Chemetall GmbH	BehalfOfAnOrganisation	106
Comment received				
Chemetall GmbH is a downstream user of boric acid or related sodium borates. 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, Chemetall GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B				

classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany	Rockwood Lithium GmbH	BehalfOfAnOrganisation	107
Comment received				
Rockwood Lithium GmbH is a downstream user of boric acid or related sodium borates. 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, Rockwood Lithium GmbH fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Poland		Company-Downstream user	108
Comment received				
WE are a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Finland	Ekovilla Oy	BehalfOfAnOrganisation	109
Comment received				
Ekovilla Oy is a downstream user of boric acid or related sodium borates. 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, Ekovilla Oy fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Italy	NORD COLOR SRL	BehalfOfAnOrganisation	110
Comment received				
NORD COLOR SRL is a downstream user of boric acid . 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, NORD COLOR SRL fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Belgium	Unil Lubricants NV	BehalfOfAnOrganisation	111
Comment received				
Unil Lubricants is a downstream user of boric acid and/or related sodium borates. 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, Unil Lubricants fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany		Company-Downstream user	112
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				

RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	United Kingdom	Ferro (Great Britain) Limited	BehalfOfAnOrganisation	113
Comment received				
Ferro (Great Britain) Limited is an importer of boric acid or related sodium borates. 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, Ferro (Great Britain) Limited fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	United Kingdom	Property Care Association	BehalfOfAnOrganisation	114
Comment received				
Property Care Association (PCA) represents downstream users of boric acid or related sodium borates. 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, PCA fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	United Kingdom	Outokumpu Stainless Ltd.	Company-Downstream user	115
Comment received				
Outokumpu Stainless Ltd. is a downstream user of a related sodium borate. 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, Outokumpu Stainless Ltd. fully supports and endorses the comments				

submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany		MemberState	116
Comment received				
The current classification of boric acid CAS 10043-35-3 is Repr 1B H360FD. The Polish CA proposes a classification as Repr. 2 H361d (Suspected of damaging the unborn child). The Polish CA substantiates the proposal for reclassification based on the following arguments: 1)Epidemiological Data: Further epidemiological studies have become available since classification of boric acid in 2005 (at that time classification was Repr. Cat. 2 R60-61 (corresponding to Repr. 1B H360FD in Annex VI, Table 3.1. in the CLP regulation)). In these epidemiological studies, no impairment of the reproductive parameters investigated in these studies could be observed after human boron exposure (mostly in occupational settings). 2)Consideration of inherent toxicological hazard versus real-life exposure situation in humans: All human epidemiolocigal studies demonstrated that boron exposure levels due to environmental and workplace exposure (e.g. in boric acid production plants) are far lower than dose levels of boron leading to adverse toxic effects on fertility and development in experimental animals. 3)Recent mechanistic studies: New studies providing insight into the mechanistic pathways leading to developmental effects of boric acid in animals are considered as having low likelihood to occur in humans. 4)Beneficial effects of Boron: Boron meets the criteria for essentiality in humans. After critically evaluating these arguments which are discussed in detail in the subsequent specific comments the German CA comes to the conclusion that all arguments given do not justify a reclassification and that the current classification as Repr 1B H360 FD should not be changed. The German CA further recommends to allocate a potency group and to assess the SCL for reproductive toxicity to assure accordance to the revised CLP criteria (2nd ATP).				
Dossier Submitter's Response				
See comment No 132 **MS Comment** The German CA further recommends to allocate a potency group and to assess the SCL for reproductive toxicity to assure accordance to the revised CLP criteria (2nd ATP).				

Response The SCL for boric acid has been determined in 2005 by experts from the ECB Technical Committee on Classification & Labelling (TCC&L). Despite a novel approach introduced in the ECHA Guidance to the CLP regulation to assess the potency of reproductive toxicants based on the ED10 value, we suggest to maintain the current SCL previously agreed by the experts based on the developmental NOAEL..
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion. Using the new guidance for setting SCL, it is acknowledged by the RAC that the GCL applies when the new guidance to derive SCL is used.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany		BehalfOfAnOrganisation	117
Comment received				
Our company is a downstream user of boric acid or related sodium borates. 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, our company fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Finland	TERMEX-ERISTE OY	BehalfOfAnOrganisation	118
Comment received				
TERMEX-ERISTE OY is a downstream user of boric acid or related sodium borates. 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, TERMEX-ERISTE OY fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Spain		Individual	120

Comment received
Quimicer, S.A. is a downstream user of boric acid or related sodium borates. 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, Quimicer, S.A. fully supports and endorses the comments submitted to this consultation by the EBA.
Dossier Submitter's Response
Thank you for your support of PL proposal of boric acid classification.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	France	FERRO France	BehalfOfAnOrganisation	121
Comment received				
FERRO France is a downstream user of boric acid and related sodium borates. 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, FERRO France fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	Germany	Klüber Lubrication München SE & Co. KG	BehalfOfAnOrganisation	122
Comment received				
Klüber Lubrication München SE & Co. KG is a downstream user of boric acid or related sodium borates. 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, Klüber Lubrication München SE & Co. KG fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment

				number
24.06.2013	Sweden	Jerbol System AB	BehalfOfAnOrganisation	123
Comment received				
Jerbol System AB is a downstream user of boric acid or related sodium borates. 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, Jerbol System AB fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	United Kingdom	United Kingdom Lubricants Association UKLA	BehalfOfAnOrganisation	124
Comment received				
Members of the UKLA are downstream user of boric acid or related sodium borates. 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, UKLA metal working product stewardship group fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	United Kingdom	Fuchs Lubricants UK plc.	BehalfOfAnOrganisation	125
Comment received				
Fuchs Lubricants UK plc. is a downstream user of boric acid or related sodium borates. 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, Fuchs Lubricants UK plc. fully supports and endorses the comments submitted to this consultation by the EBA.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the				

submitted information. For more reasoning, please see the RAC opinion.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2013	Italy	IGDT Srl	BehalfOfAnOrganisation	126
Comment received				
Well to know the potential and suspected anti cancer effects of Boric Acid.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Finland		MemberState	127
Comment received				
The Finnish CA is on the opinions that to warrant a lower classification than an existing one, the information should be very conclusive. Epidemiological studies are difficult to control and the presented studies in humans are considered insufficient to demonstrate an absence of adverse effects. Classification is based on the intrinsic properties of the substance. Exposure levels in these epidemiological studies are lower than those that caused reproductive effects in experimental animals. Thus the human data do not contradict with animal data. According to the guidance the negative human data is not sufficient to overrule the more solid animal data.				
Dossier Submitter's Response				
MS Comment Epidemiological studies are difficult to control and the presented studies in humans are considered insufficient to demonstrate an absence of adverse effects. **Response** Individual level data was obtained on participants and utilized in statistical analyses in all phases of this research. Exposure is reported as individual level blood or urine boron. Robbins et al. (2008; 2010) and Duydu et al. (2011) conducted a comprehensive assessment of semen quality indicators that included targeting human correlates of the toxic endpoints previously described in published animal toxicology literature related to boron. The investigators included both light microscope and computer aided measures for sperm motility. No significant association between boron exposure and sperm motility was found for the range of exposures in our human population that were lower than those causing toxic effects in the animal work. The same sperm evaluations were conducted on the boron workers as conducted on laboratory animals. In both instances, sperm evaluations are the most sensitive measurements of male fertility effects correlated with individual boron measurements in blood, urine and semen. This level of absorbed dose measurements in humans is what distinguishes these worker studies from other epidemiological studies. The statistical power of the worker studies in China and Turkey are actually better than the animal studies. Robbins et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters. Scialli et al. (2010) calculated the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. Additionally, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect				

fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm. (Mangelsdorg I and Buschmann J 2002).

Additional *in vitro* and animals studies of boric acid and zinc sponsored by the European Borates Association have been submitted as part of the public consultation that demonstrate that zinc inhibits in a dose dependent manner the adverse developmental and fertility effects of boric acid. These results coupled with the fact that human tissues (fetus, testis) have intrinsically higher levels, over 2 times that of laboratory animals, provides the mechanism by which humans are different than laboratory animals.

Criteria for Category 2 "Suspected Human Reproductive Toxicant", does not require proof of an absence of effects in humans. In fact, "Substances are classified in Category 2 for reproductive toxicity when there is **some evidence from humans** or experimental animals,…" Furthermore, the fact that no evidence of reproductive effects has been seen in highly exposed populations and recent studies demonstrating the protective effects of zinc coupled with the intrinsically higher levels in target tissues in humans, raises doubt about the relevance of the effect seen in animal studies for humans.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	France		Company-manufacturer	128

Comment received

CLP classification of boric acid (page 5 of the report) must be changed based on new available clinical studies.

(ECHA's comment: This comment replaces 2 previously submitted comments as requested by the commenter)

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Austria		MemberState	129

Comment received

Boric acid is clearly toxic for reproduction in different animal species (developmental toxicity: rat, mouse & rabbit, fertility: rat, mouse, deer mouse & dog). Several epidemiological studies of populations exposed to boron compounds at the workplace or via the environment have been available already before the inclusion of boric acid (as well as several other boron compounds) in Annex VI of the CLP regulation, but could not clearly demonstrate the absence or presence of reproductive toxicity in humans.
Overall the whole dataset clearly shows that the CLP criteria for the classification as Repr 1B for development as well as fertility are fulfilled: The effects on fertility are similar in nature across species (testicular atrophy) and the developmental effects observed in different species seem to be caused by a common mechanism of action (altered expression of hox

genes). The effects are therefore also relevant for humans. Toxicodynamics and –kinetics are similar in different animal species as well as in humans, further supporting the relevance of the findings in animals for humans and the effects did not occur secondary to other toxic effects.
Since the inclusion of boric acid in Annex VI of the CLP regulation new epidemiological studies of boron exposed workers in China and Turkey became available, both focusing on the endpoint fertility only. A recent review on the studies carried out on Chinese boron workers (Scialli et al., 2009) was generated by an expert panel initiated by industry. It allows no final conclusion on effects of boron exposure on human fertility (see also section 2.2b of http://echa.europa.eu/
documents/10162/13641/rac_opinion_borates_annex_1_en.pdf).
Although not all publications on the Turkish study cited in the Polish CLH report are publicly available the data presented in the report are not considered sufficiently conclusive to contradict the animal data (e.g. low number of volunteers per group too small to show possible weak effects; smoker status not reported).
It is noted that the boron burden reached in highly exposed boron workers is below the boron levels in animals at the NOAEL (Bolt et al., 2012). This information might be useful for any discussion of risk assessment/management related questions.
To conclude, Austria does not support the Polish proposal to downgrade the classification of boric acid from Repr 1B, H360FD to Repr 2, H361d.

Scialli, AR, Bonde, JP, Brüske-Hohlfeld, I, Culver, BD, Li, Y, Sullivan, FM. An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers Reprod. Toxicol 29 (2010) 10-24.
Bolt H, Basaran N and Duydu Y. (2012) Human environmental and occupational exposures to boric acid: reconciliation with experimental reproductive toxicity data. Journal of Toxicology and Environmental Health, Part A, 75:508–514.

Dossier Submitter's Response

MS Comment

Several epidemiological studies of populations exposed to boron compounds at the workplace or via the environment have been available already before the inclusion of boric acid (as well as several other boron compounds) in Annex VI of the CLP regulation, but could not clearly demonstrate the absence or presence of reproductive toxicity in humans.

The effects on fertility are similar in nature across species (testicular atrophy) and the developmental effects observed in different species seem to be caused by a common mechanism of action (altered expression of hox genes). The effects are therefore also relevant for humans.

Since the inclusion of boric acid in Annex VI of the CLP regulation new epidemiological studies of boron exposed workers in China and Turkey became available, both focusing on the endpoint fertility only. A recent review on the studies carried out on Chinese boron workers (Scialli et al., 2009) was generated by an expert panel initiated by industry. It allows no final conclusion on effects of boron exposure on human fertility.

Response

The statistical power of the worker studies in China and Turkey are sufficiently strong demonstrating an absence of fertility effects in boron industry workers chronically exposed to very high levels of boron. The power of the worker studies in China and Turkey is greater than the statistical power of the animal studies. Robbins et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters. Scialli et al. (2010) calculated the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. Additionally, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm. (Mangelsdorg I and Buschmann J 2002).

Criteria for Category 2 "Suspected Human Reproductive Toxicant", does not require proof of an absence of effects in humans. In fact, "Substances are classified in Category 2 for reproductive toxicity when there is **some evidence from humans** or experimental animals,…" Furthermore, no evidence of developmental or fertility effects have been demonstrated in highly exposed populations and recent studies demonstrating the protective effects of zinc coupled with the intrinsically higher levels in target tissues in humans, raises doubt about the relevance of the effect in humans.

Mechanistic data show that the action of boric acid on HDACi and Hox genes occurs at a high dose (1000 mg boric acid/kg bw) and during a very narrow window of gestation (GD 8,9) in laboratory animals. These effects are not likely to be relevant to humans, since the dose of 1000 mg/kg in humans would be about 60-70 g of boric acid which is more than twice the lethal dose in humans.

As presented in the report, humans have intrinsically higher levels of zinc than laboratory animals in all tissues, including the target tissues of boric acid that differentiate humans from laboratory animals. These higher zinc levels explain in part the absence of boric acid related reproductive toxicity effects in humans. In addition to the studies of zinc borate discussed in the Boric Acid CLH report that show the protective effect of zinc against boric acid related toxicity, new studies have recently been completed since the release of the Boric Acid CLH Report that investigate the protective effect of zinc against boric acid related developmental and fertility toxicity of boric acid. Summaries of these studies were submitted as comments as by the European Borates Association as part of the public consultation.

To investigate the effect of zinc on boric acid related toxicity on fertility and developmental effects an *in vitro* spermatogenesis study and an *in vitro* embryonic stem cell test with boric acid in the presence of varying amounts of zinc were recently completed (Martin 2013; Hofman-Huther 2013). An absence of boric acid related effects on spermatogenesis was observed in the presence of zinc (Martin 2013).

No greater sensitivity of embryonic stem cells compared to fully differentiated cells was observed and no concern for *in vivo* embryotoxicity is triggered for boric acid at various concentrations of zinc. A reduction in the boric acid inhibition of differentiation of D3 embryonic stem cells was observed with increasing concentrations of zinc (Hofman-Huther 2013).

In a 28-day dose range finding study of zinc borate a NOAEL of 37.3 mg B/kg bw and LOAEL of 74.6 mg B/kg bw for male fertility effects determined by minimal histopathologic findings in testes and epididymides was observed. Since hypospermia was not observed at the LOAEL, and the histopathological changes were graded as minimal, the effects observed in the 75 mg B/kg bw group were not considered toxicologically significant (Kirkpatrick 2013).

Compared to boric acid, a 55% increase in the developmental NOAEL based on lower fetal body weights was demonstrated in the GLP developmental dose range finder study of zinc borate (Edwards 2013). The developmental toxicity NOAEL of zinc borate was 14.92 mg B/kg bw compared to 9.6 mg B/kg bw for boric acid and sodium borates in the absence of zinc.

These studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans.
Copies of the draft reports for these studies are attached.

RAC's response

The comment is noted. The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	United Kingdom		Company-Downstream user	130

Comment received

It is recognised that there is a reproductive effect of boron compounds in laboratory animals under experimental test conditions. However, more recent studies and scientific evidence demonstrate that such effects are not found in humans, even when exposed to high levels as presented in the Boric acid CLH report. Additionally, our company has handled boric acid

(and borax) as an additive during metalworking fluid formulation at many sites in- and outside Europe for a number of years. Under the appropriate conditions of use no known human health effects, potentially resulting from the boric acid (or borax) are known during formulation nor were reported to us from our customers, the industrial users.
The European Borates Association (EBA) presented a consolidated response on the case for a Category 2 Toxic to Reproduction reclassification for Borates based on the previously not considered scientific data from the human studies. From the human studies in highly exposed workers evaluations of sperm parameters have demonstrated no effects on male fertility which appears to justify the removal of the fertility classification. No developmental effects have been seen in highly exposed populations. However, as epidemiological studies of developmental effects are not as robust as the fertility studies, a Category 2 H361d: suspected of damaging the unborn child is considered appropriate.
As a downstream user of boric acid (or related sodium borates) we support the EBA consolidated response (provided on behalf of the European Borate Manufacturers and Importers and on behalf of the REACH consortium for borates) which has been submitted to this consultation by the EBA and supports the proposed Category 2, H361d: suspected of damaging the unborn child classification for boric acid. This classification accommodates for both the findings in laboratory animals and the absence of fertility effects in highly exposed humans.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2013	Denmark		MemberState	131

Comment received

Denmark does not support the proposal for a down-classification of boric acid from Repr. 1B, H360FD to Repr. 2, H360d. Multiple animal studies using different species have shown adverse effects of boric acid on fertility (rat, mouse, dog) and development (rat, mouse, rabbit), which has led to the classification of borid acid as well as different borates as Repr. 1B. Furthermore, the observed effects on fertility and development are similar in nature and effect levels across species.

The CLH report suggests that the findings of various epidemiological studies in humans should be given higher priority than the animal studies. It is thus a principal discussion of the weight given to the human data presented versus the well-established and consistent animal data.

The epidemiological studies have not demonstrated effects on either fertility or development at exposure levels observed for workers in various settings. The exposure levels did, however, not reach the levels leading to adverse effects in animal studies. With exception of the highest exposed group of workers in the Chinese study (~5 mg B/kg bw/day), the exposure levels in the studies from USA, Turkey and China are considerably lower than the NOAEL's obtained in animal studies (lowest NOAEL: 17,5 mg B/kg bw/day – fertility and 9,6 mg B/kg bw/day - reproduction). For the highest exposed group of workers in the Chinese study (~5 mg B/kg bw/day) there is no information on how this value was derived, on the number of workers exposed and on whether these data can be considered representative

and reliable. 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.

It is stated that only under extreme conditions will human exposure levels reach the effect levels observed in animal studies. This is a risk based approach which is not in line with a hazard assessment on which a classification should be based. The CLP regulation further states that available, reliable epidemiological data may be given priority over data derived from animal studies when they demonstrate hazards not identified from these (animal) studies. Furthermore, positive results from well conducted animal studies should not necessarily be negated by the lack of positive human experience but require and assessment of the robustness and statistical power of both the human and animal data. In our view the quality of the human data presented does not justify a lower classification category for boric acid.

Dossier Submitter's Response

MS Comment
For the highest exposed group of workers in the Chinese study (~5 mg B/kg bw/day) there is no information on how this value was derived, on the number of workers exposed and on whether these data can be considered representative and reliable.

Response
The information on the 5 mg B/kg bw/day value can be found in Scialli et al. (2010) Table 5, based on 60 kg person. The use of a 60 kg person vs 70 kg is found in Xing et al. 2007) using the upper ranges 1.60-469 mg B/day and 2.83-354 mg B/day. The number of workers exposed to these upper ranges is not reported. The mean exposure level of the highest exposed subgroup of 16 workers is 125 mg B/kg bw/day or 2.08 mg B/kg bw/day based on 60 kg body weight (Scialli et al. 2010; Xing et al 2007).

MS Comment
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.

Response
Additional *in vitro* and animals studies of boric acid and zinc have been submitted by the European Borates Association as part of the public consultation that demonstrate that zinc inhibits in a dose dependent manner the adverse developmental and fertility effects of boric acid. Since humans have intrinsically higher zinc levels in the various target tissues (fetus, testes) than laboratory animals, the data strongly suggests that humans would be less susceptible to boric acid than the animal models.

MS Comment
Furthermore it can be questioned whether the human data are adequate and representative.

Response
The Chinese workers research was conducted in three phases. Recruitment was conducted separately for each phase. In all three phases eligibility was based on age, employment in the same industry for at least the previous year, not currently under treatment for chronic disease, and no history of vasectomy. Boron workers were recruited at five boron industry sites and controls were recruited from a town ~30 miles away with no boron mining or industry and low-environmental boron. Phase three added an additional community control group of non-boron workers who lived in the vicinity of the boron industry sites with high environmental boron.

Phase one was conducted in 2002. This phase aimed to collect information on industry, workers, lifestyles, and health in this part of the world in order to inform subsequent study design. Interviews with environmental and boron industry representatives were conducted. An interview guide was developed in collaboration with local representatives. Interviews were conducted with boron workers (n=936) and control workers (n=251). Important information was learned about the organization of boron work plus worker health and safety. No biological samples were collected.

Phase two was conducted in 2003. Phase two aimed to establish exposure ranges for boron workers and feasibility

of biological sampling SOPs. Recruitment for this phase was targeted to different work stations. Sixty boron workers and nine controls provided biological samples and were monitored in the workplace. Important information was learned about daily boron exposure/dose and health outcomes. Data were used for the design /power calculations for phase three.

Phase three was conducted in 2004. This was a longitudinal, intensive repeated measures sampling design. Workers were monitored for three months to capture boron exposure data for one full cycle of spermatogenesis. Over-enrollment was built in to compensate for expected attrition over repeated sampling. Only men with complete exposure assessment sampling over three months (blood, urine, and workplace inhalable dust) were included in the final analysis. A randomly selected subset per group based on previous sample size calculations was analyzed for Y:X ratio in sperm (n=146).

The authors concluded (Robbins et al. 2010): "Boron workers in our study experienced chronic exposure to boron over one complete cycle of spermatogenesis. When compared to healthy working men living in an area of low environmental boron and healthy working men living near or on the boron ore beds but not employed in the boron industry, we found no adverse association between exposure group and conventional semen parameters (total sperm count, sperm concentration, motility and morphology) or sperm DNA integrity measures (aneuploidy, DNA strand breakage and apoptosis). We specifically looked in our human subjects for toxicological endpoints reported in animal chronic dosing experiments but did not find evidence to suggest human sensitivity at the exposure levels encountered by our study population that averaged 42mg boron per day (standard deviation 58 mg boron per day)."

Robbin et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters.

Scialli et al. (2010): "The study size of some 65 men in each exposure group allow, according to our computations, the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. The power is not expected to be substantially increased by analyses of several samples per man and the power to detect differences in total count is lower. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel believes the statistical power of analyses based on these end points was adequate."

The statistical power of the worker studies in China and Turkey are essentially better than animal studies (Mangelsdorf & Buschmann 2002). The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm.
(Mangelsdorf I, Buschmann J (2002) Extrapolation from Results of Animal Studies to Humans for the Endpoint Male Fertility, Project F 1642. Federal Institute for Occupational Safety and Health, Friedrich-Henkel-Weg 1-25, D-44149 Dortmund, Germany. www.baua.de)

Individual level data was obtained on participants and utilized in statistical analyses in all phases of this research. Exposure is reported as individual level blood or urine boron.

Robbins et al. (2008; 2010) and Duydu et al. (2011) conducted a comprehensive assessment of semen quality indicators that included targeting human correlates of the toxic endpoints previously described in published animal toxicology literature related to boron. The investigators included both light microscope and computer aided measures for sperm motility. No significant association between boron exposure and sperm motility was found for the range of exposures in the human population studied.

The same sperm evaluations were conducted on the boron workers as conducted on laboratory animals. In both instances, sperm evaluations are the most sensitive measurements of male fertility effects correlated with individual boron measurements in blood, urine and semen. This level of absorbed dose measurements in humans is what distinguishes these worker studies from other epidemiological studies.

MS Comment
It is stated that only under extreme conditions will human exposure levels reach the effect levels observed in animal studies. This is a risk based approach which is not in line with a hazard assessment on which a classification should be based.

Response
Since the argument used for disregarding the human data is that the exposure levels are less than doses received

by laboratory animals, it is important to put in context the various human exposure levels, including blood, urine and semen levels. A basic comparison of boron blood levels was conducted between laboratory animals and humans that included observed effects at the respective NOAELs (2.08 mg B/kg bw/day in humans) as part of the evaluation of the intrinsic hazard in humans. If the intrinsic hazard in humans was the same as in laboratory animals, effects should have been seen at the exposure levels in these workers chronically exposed to high levels of boron.

MS Comment
The CLP regulation further states that available, reliable epidemiological data may be given priority over data derived from animal studies when they demonstrate hazards not identified from these (animal) studies.

Response
We could not find in the CLP regulations where human data is give priority over animal data **only** "when they demonstrate hazards not identified from these (animal) studies." Scientific evidence cannot be chosen or dismissed to suit an outcome. That is why the CLH report conclusions are based on a total weight of evidence evaluation, which includes consideration of the animal and human studies.

In addition to the passages presented in the Boric Acid CLH Report describing the basis for classification of reproductive toxicity extracted from REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008, the paragraphs 1.1.1.3 – 1.1.1.5 are relevant to the use of the worker exposure and new mechanistic data in determining the appropriate classification of boric acid. In particular paragraph 1.1.1.4 "Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data." "…positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data." An assessment of the robustness, quality and statistical power of the human shows the studies of the Chinese and Turkish boron industry workers are sufficiently robust with high statistical power, and meet the quality criteria established under REACH.

MS Comments
Furthermore, positive results from well conducted animal studies should not necessarily be negated by the lack of positive human experience but require and assessment of the robustness and statistical power of both the human and animal data. In our view the quality of the human data presented does not justify a lower classification category for boric acid.

Response
A Category 2 classification does not negate the concerns raised by the animal data nor does a Cat. 2 require proof of the absence of effects in humans. "Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals,…" Furthermore, the fact that no evidence of reproductive effects have been seen in highly exposed populations and recent studies demonstrated the protective effects of zinc coupled with the intrinsically higher levels of zinc in target tissues in humans (fetus and testes), raises doubt about the relevance of the effect in humans.

Statistical power of these studies has been addressed by the authors. Robbins et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters. Scialli et al. (2010): "The study size of some 65 men in each exposure group allow, according to our computations, the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. The power is not expected to be substantially increased by analyses of several samples per man and the power to detect differences in total count is lower. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel believes the statistical power of analyses based on these end points was adequate." The statistical power of the worker studies can be compared to the statistical power to detect fertility effects in rodent bioassays with a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm (Mangelsdorf & Buschmann 2002).

Robbins et al. (2008; 2010) and Duydu et al. (2011) conducted a comprehensive assessment of semen quality indicators that included targeting human correlates of the toxic endpoints previously described in published animal toxicology literature related to boron. The investigators included both light microscope and computer aided measures for sperm motility. No significant association between boron exposure and sperm motility was found for

the range of exposures in the study population that were lower than those causing toxic effects in the animal work.

The same sperm evaluations were conducted on the boron workers as conducted on laboratory animals. In both instances, sperm evaluations are the most sensitive measurements of male fertility effects correlated with individual boron measurements in blood, urine and semen. This level of absorbed dose measurements in humans is what distinguishes these worker studies from other epidemiological studies. The workers studies in Turkey and China may actually provide better exposure measurements than in animal studies since in the animal toxicity studies comparative blood, urine and semen measurements are not conducted and correlated to effects.

The Chinese and Turkish worker studies meet the quality criteria for assessing the adequacy of human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, as specified in Annex XI, Section 1.1.3. from REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

(1) The proper selection and characterisation of the exposed and control groups;
(2) adequate characterisation of exposure;
(3) sufficient length of follow-up for disease occurrence;
(4) valid method for observing an effect;
(5) proper consideration of bias and confounding factors;
(6) a reasonable statistical reliability to justify the conclusion.

Scialli et al. (2010) determined that the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power and the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel concluded that the statistical power of analyses based on these end points was adequate.

Robbins et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters.

The power of the borate worker studies in China and Turkey are actually better than animal studies (Mangelsdorf & Buschmann 2002). The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm.

The expert panel also evaluated the number of subjects presenting seminal values below or above WHO reference values, considered by some as a more relevant indicator than the analysis of mean values that can mask heterogeneity of values. The expert panel determined that there was no statistically significant difference between high-boron and low-boron groups in the proportion of men failing to meet WHO criteria for normal semen analysis (Scialli et al. 2010).

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
25.06.2013	Germany		MemberState	132

Comment received

Epidemiology
The epidemiological studies used in order to substantiate the reclassification of Boric acid do not adequately and sufficiently address the complex endpoints of fertility and developmental toxicity and their informative value is questionable:
The endpoints addressed in the epidemiological studies described in the CLH Annex XV were mainly sperm parameters (e.g. count, concentration, motility, velocity), hormones in blood

(follicle-stimulating hormone (FSH), testosterone, luteinising hormone (LH)), reproductive success, chromosome X:Y ratio and DNA integrity of cryopreserved sperm cells. Scialli et al. (2010) conclude that data on reproductive success in men are not reliable.
Thus, parameters utilized to investigate a probable association between boron exposure and reproductive outcome in humans were sperm parameters, hormones in blood, chromosome X:Y ratio and DNA integrity (tail % intensity in the COMET assay). These parameters do not sufficiently and consistently address the endpoints reproductive toxicity (fertility) and developmental toxicity in their respective complexity. Thus, it is questionable whether these parameters were the adequate surrogate parameters capable of fully addressing the adverse reprotoxic and developmental effects as observed in experimental animals. Moreover, the studies solely focus on male reproductive toxicity. In animal experiments, on the other hand, it could be clearly demonstrated, that boron/boric acid also adversely affects female fertility: when female animals were treated with doses of boric acid or disodium tetraborate decahydrate equivalent to 58.8 mg B/kg bw/day and mated with untreated males, the animals had no offspring, i.e. they were infertile. Female fertility was not adequately addressed in the studies considered here.

With respect to the informative value of the epidemiological studies it can be generally stated that depending on the studies, the sample sizes are too small to detect small differences of effects.
For example, when looking at the three sperm parameters 'sperm concentration', 'sperm motility' and 'sperm morphology' a difference between 10% and 25%, between 10 % and 36 %, between 20 % and 70 % and between 27 % and 36 % would have been needed to detect an effect in Scialli et al. (2010), Korkmaz et al. (2011), Duydu et al. (2011)*) and Robbins et al. (2010), respectively. However, biologically relevant effect sizes for the different parameters are not clearly defined. The effects / differences as observed in the four studies are far below the numerical differences that could detect statistically significant differences at such small sample sizes. With the present sample sizes only larger effects as detailed above would turn out significant. If smaller effects are biologically important, far more participants should have been recruited to observe statistically significant results at the levels observed in the studies.

In summary, the endpoints reproductive toxicity (fertility) and developmental toxicity are not adequately and sufficiently addressed by the epidemiological studies discussed in the document. Further, the informative value of these studies has to be questioned. The statistical power of the studies is not sufficient.
By no means can these studies be used to overrule positive results from animal studies with respect to reproductive and developmental toxicity.

Consideration of inherent toxicological hazard versus real-life exposure situation in humans:
It is argued in the Polish C&L proposal that boron exposures in the epidemiological studies due to environmental and workplace exposure (e.g. in boric acid production plants) are far lower than dose levels of boron leading to adverse toxic effects on fertility and development in experimental animals. Further, it is argued, that exposure levels leading to reproductive and developmental effects in experimental animals would never be reached in humans. However, the CLH process is hazard driven and based on the inherent toxicological properties of the substance under question. Exposure considerations came into play when risks are described and characterized. In case of boric acid, the court took already a note of a confusion of mixing up assessment of the hazards and assessment of the risks of a substance was addressed in Judgment of the Court (Fourth Chamber) of 21 July 2011 (Case C 15/10; Etimine SA v Secretary of State for Work and Pensions. 62010CJ0015) where it is stated in para 73 and 74:
"73. Second, it must be stated, as the Advocate General has observed in point 79 et seq. of his Opinion, that the criticism advanced by the claimant in the main proceedings rests,

essentially, on confusion between assessment of the hazards and that of the risks presented by a substance.
74. As is apparent, in particular, from Article 4 of Directive 67/548, read in conjunction with Articles 2 to 5 of Directive 93/67, the classification and labelling of substances established by Directive 67/548 are based on the transmission of information on the hazards linked to the substances' intrinsic properties. Hazard assessment constitutes the first stage of the process of risk assessment, which is a more specific concept. This distinction between hazards and risks was moreover maintained in the CLP Regulation and in the REACH Regulation."
Thus, it is not appropriate to argue with exposure and risk in the context of classification and labelling.

Mechanism (pp 102 ff of the classification proposal)

Recently, studies have been performed which provide possible mechanisms of boric acid related developmental effects in laboratory animals. These mechanisms are the inhibition of histone deacetylase by boric acid and effects of boric acid on hox gene expression. It is stated in the Polish C&L proposal that these effects are unlikely to occur in humans. However, sound scientific evidence that these mechanisms are unlikely to occur in humans is not given. It is further argued that human tissue exhibits higher zinc levels than comparative tissues in animals and that zinc stores in the human body could protect against testicular toxicity effects of boric acid (as is the case for e.g. chromium, cobalt and cadmium). However - apart from experimentally determined comparative zinc levels in human and animal tissue - also this is just a hypothetical statement and lacks experimental proof.
Thus, since classification of boric acid in 2005 as Repr. Cat. 2 R60-61 (corresponding to Repr. 1B H360FD in Annex VI, Table 3.1. in the CLP regulation), no data have become available which could give insight into probable differences between laboratory animals and humans with respect to toxicokinetics and toxicodynamics of boron/boric acid.
Thus, it must still be assumed that the effects seen in animals**) could also occur in humans and that the animal data are relevant to humans.

Beneficial effects (pp 104 ff of the classification proposal)

The Polish CA argues in its C&L proposal, that boron plays an important nutritional role and that the essentiality of dietary boron had recently been demonstrated.
This argument however, does not invalidate the adverse reproductive and developmental effects of boric acid. Further, it should be mentioned here, that there are much more chemical elements, which are on one hand essential and on the other hand classified under CLP (e.g. chromium is essential for humans, but most chromium salts are classified as Carc Cat 1 and e.g. molybdenium – molybdenium trioxide is classified as Carc Cat 2).

In the context of essentiality it is also stated that epidemiological studies indicate that boron exposure in drinking water is associated with lower incidences of some types of cancer including prostate, lung, cervical and oesophageal cancer. However, these studies concern the endpoint "carcinogenicity" and not the endpoint reproductive toxicity which is the endpoint considered here for classification and labelling.

*) the publication Basaran et al. 2012 is an extension of the Duydu 2011 publication (i.e. the same study population was investigated). The extension concerns the investigation of

cryopreserved sperm cells by the neutral version of the COMET assay. The study demonstrated that DNA strand breaks expressed as tail % intensity did not increase with increasing blood boron concentration. However it is stated in the same publication that "DNA damage in sperm cells appears as a predictor of infertility". Thus, also this parameter is a surrogate parameter, which is not capable of fully addressing the adverse reprotoxic and developmental effects as observed in experimental animals.

**) From ECBI/43/05 Rev.1: "Studies investigating the effects of exposure to boric acid on fertility in the rat and mouse identified the male as the most sensitive sex. Acute exposure to boric acid results in changes in sperm parameters and histopathological changes in the testes of the male rat. The effects were irreversible at higher doses. Repeated exposure to boric acid can affect the spermatogenesis and sperm quality of the male adult rat, mouse and dog, resulting either in partial reduction in fertility or sterility depending on the dose. Reproductive performance was also affected in female rats during repeated exposure to high doses (caused by decreased ovulation). These effects occur at doses well below 1000 mg/kg bw per day which do not produce marked signs of other toxicity and which are not a secondary consequence of other toxicity. A NOAEL of 100 mg/kg bw per day can be established.
Exposure to boric acid during pregnancy (given either throughout gestation or only during major organogenesis) results in decreased fetal body weight, and fetal cardiovascular and rib malformations in the rat, mouse and rabbit. The rat appears the most sensitive species for developmental toxicity, since the developmental effects were observed at a dose which did not induce any significant maternal toxicity. A NOAEL for pre-natal effects in all 3 species has been established at 55 mg/kg bw per day.
The effects observed across species were very similar, both in nature and effective doses (mg boron per kg bodyweight per day). The evidence from different animal species therefore shows that boric acid and the borates have an adverse effect on fertility (rat, mouse, dog) and development (rat, mouse, rabbit), which is not a consequence of general systemic toxicity."

References mentioned:
Başaran, N., Duydu, Y. and Bort, H.M. (2012): Reproductive toxicity in boron exposed workers in Bandirma, Turkey. Journal of Trace Elements in Medicine and Biology 26, 165 – 167.

Duydu, Y., Başaran, N., Üstündağ, A., Aydın, S., Ündeğer, Ü., Araman, O.Y., Aydos, K., Düker, Y., Ickstadt, K., Schulze Wltrup, B., Golka, K., and Bolt, H.M. (2011): Reproductive toxicity parameters and biological monitoring in occupationally and environmentally boron-exposed persons in Bandirma, Turkey. Arch. Toxicol. 85, 589 – 600.

Korkmaz, M., Yenigün, M., Bakıdere, S., Ataman, O.Y., Keskin, S., Müezzinoğlo, T. And Lekili, M. (2011): Effects of chronic boron exposure on semen profile. Biol. Trace Elem. Res. DOI 10.1007/s12011-010-8928-2

Robbins, W.A., Xun, L., Jia, J., Kennedy, N., Elashoff, D.A., and Ping, L. (2010): Chronic boron exposure and human semen parameters. Reproductive Toxicology 29, 184 – 190.

Scialli, A.R., Bonde, J.P., Brüske-Hohlfeld, I., Culver, B.D., Li, Y. and Sullivan, F.M. (2010): An overview of male prepoductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reproductive Toxicology 29, 10 – 24.

Dossier Submitter's Response

MS Comment

The epidemiological studies used in order to substantiate the reclassification of boric acid do not adequately and

sufficiently address the complex endpoints of fertility and developmental toxicity and their informative value is questionable.

Response
Individual level data was obtained on participants and utilized in statistical analyses in all phases of this research; it is not an ecologic study. Exposure is reported as individual level blood or urine boron. Robbins et al. (2008; 2010) and Duydu et al. (2011) conducted comprehensive assessments of semen quality indicators that included targeting human correlates of the toxic endpoints previously described in published animal toxicology literature related to boron. Both light microscope and computer aided measures were used in the study to evaluate sperm motility. No significant association between boron exposure and sperm motility was found for the range of exposures in our human population that were lower than those causing toxic effects in the animal work.

The same sperm evaluations were conducted on the boron workers as conducted on laboratory animals. In both instances, sperm evaluations are the most sensitive measurements of male fertility effects correlated with individual boron measurements in blood, urine and semen. This level of absorbed dose measurements in humans is what distinguishes these worker studies from other epidemiological studies. The workers studies in Turkey and China actually provide better exposure measurements than in animal studies since in the animal toxicity studies comparative blood, urine and semen measurements for boron are not conducted and correlated to effects.

MS Comment
In animal experiments, on the other hand, it could be clearly demonstrated, that boron/boric acid also adversely affects female fertility: when female animals were treated with doses of boric acid or disodium tetraborate decahydrate equivalent to 58.8 mg B/kg bw/day and mated with untreated males, the animals had no offspring, i.e. they were infertile. Female fertility was not adequately addressed in the studies considered here.

Reproductive performance was also affected in female rats during repeated exposure to high doses (caused by decreased ovulation). These effects occur at doses well below 1000 mg/kg bw per day which do not produce marked signs of other toxicity and which are not a secondary consequence of other toxicity. A NOAEL of 100 mg/kg bw per day can be established.

Response
The evaluation of the effects of boric acid and disodium tetraborate decahydrate on female fertility was presented in the report. In a three generation study in rats groups of 8 males and 16 females were treated with boric acid or disodium tetraborate decahydrate equivalent to 0, 5.9, 17.5 and 58.8 mg B/kg bw/day (Weir 1966c,d). An attempt was made to study the fertility of the P1 females at the top dose level by mating them with untreated males but only one litter of 16 pairs was produced. This highest dose level was clearly clinically toxic to the females after 2-3 weeks of dosing, with rough fur, scaly tails, inflamed eyelids and staining of the fur on the face and abdomen. The mating procedure to test the fertility of the females was not a satisfactory one. To avoid treatment of the males used for pairing, food was withdrawn from the cages of the females for 8 hours per day during the pairing process, and this is known to be very stressful to laboratory rats. There was no evidence on whether mating actually occurred for any of the rats, and no vaginal examinations for the presence of sperm were carried out. The females of the top dose P1 generation were sacrificed after 45 weeks of treatment and histopathological examination of the ovaries and uterus carried out. In the ovaries the presence of corpora lutea was regarded as a major indication of cyclic function, and these were found in 7 of 15 females, with reduced or absent function in the remaining 8 animals. The changes in the ovaries were not clearly different from those of controls. No treatment related changes were found in the uterus. No changes were found that could account for the reduced litter production, and no conclusions could be drawn about fertility in the top dose females. Comparable results were found in the Weir and Fisher multigeneration study on borax, with clear testicular atrophy at the top dose levels in males, and no clear explanation of the reduced number of litters in the top dose females, using the same unsatisfactory mating technique. The authors of the study concluded that testis atrophy was clearly produced in males at the top dose level, but that the evidence of the decreased ovulation in females did not account for the reduced number of litters in the cross mating study in females. Thus the Weir and Fisher studies produced clear evidence of adverse effects on male fertility, but did not produce clear evidence for an adverse effect on female fertility.

MS Comment
**) From ECBI/43/05 Rev.1: Reproductive performance was also affected in female rats during repeated exposure to high doses (caused by decreased ovulation). These effects occur at doses well below 1000 mg/kg bw per day which do not produce marked signs of other toxicity and which are not a secondary consequence of other toxicity. A NOAEL of 100 mg/kg bw per day can be established.

Response
A NOAEL of 17.5 mg B/kg bw/day for effects on female fertility was derived in the Transitional Annex XV dossier (TD 2008) based on Weir (1966c-d) and Fail et al.1991. However, the TD failed to adequately distinguish between

effects on female fertility and effects on development. Fertility is generally defined in males as the ability to produce sperm which are capable of producing fertilisation of an ovum leading to conception. In females, it is defined as the ability to produce and release ova which can be fertilised leading to conception. To test fertility in animals males and females are pretreated to cover the period of development of the sperm and eggs, then mate and treat until the time of implantation, around Day 6 following mating, and then stop treatment in the females. To test for effects on development pregnant females are treated from Day 6 till the end of pregnancy. Neither the Weir and Fisher multigeneration study nor the Fail RACB studies were performed with this division of treatments. They both treated animals continuously before and during pregnancy and also after delivery.

MS Comment
The endpoints addressed in the epidemiological studies described in the CLH Annex XV were mainly sperm parameters (e.g. count, concentration, motility, velocity), hormones in blood (follicle-stimulating hormone (FSH), testosterone, luteinising hormone (LH)), reproductive success, chromosome X:Y ratio and DNA integrity of cryopreserved sperm cells. Scialli et al. (2010) conclude that data on reproductive success in men are not reliable. Thus, parameters utilized to investigate a probable association between boron exposure and reproductive outcome in humans were sperm parameters, hormones in blood, chromosome X:Y ratio and DNA integrity (tail % intensity in the COMET assay). These parameters do not sufficiently and consistently address the endpoints reproductive toxicity (fertility) and developmental toxicity in their respective complexity.

Response
Individual worker sperm parameters (e.g. count, concentration, motility, velocity) addressed in the epidemiological studies are the most sensitive measurements of fertility effects in humans and are the same parameters measured in animal bioassays.

MS Comment
With respect to the informative value of the epidemiological studies it can be generally stated that depending on the studies, the sample sizes are too small to detect small differences of effects.

Response
Robbin et al. (2010) reported a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters.

Scialli et al. (2010): "The study size of some 65 men in each exposure group allow, according to our computations, the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. The power is not expected to be substantially increased by analyses of several samples per man and the power to detect differences in total count is lower. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel believes the statistical power of analyses based on these end points was adequate." The statistical power of the boron industry workers in China and Turkey are comparable, if not greater, than corresponding statistical power in rodent bioassays. The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm.
(Mangelsdorf I, Buschmann J (2002) Extrapolation from Results of Animal Studies to Humans for the Endpoint Male Fertility, Project F 1642. Federal Institute for Occupational Safety and Health, Friedrich-Henkel-Weg 1-25, D-44149 Dortmund, Germany. www.baua.de)

MS Comment
Mechanism (pp 102 ff of the classification proposal)
These mechanisms are the inhibition of histone deacetylase by boric acid and effects of boric acid on hox gene expression. It is stated in the Polish C&L proposal that these effects are unlikely to occur in humans. However, sound scientific evidence that these mechanisms are unlikely to occur in humans is not given. It is further argued that human tissue exhibits higher zinc levels than comparative tissues in animals and that zinc stores in the human body could protect against testicular toxicity effects of boric acid (as is the case for e.g. chromium, cobalt and cadmium). However - apart from experimentally determined comparative zinc levels in human and animal tissue - also this is just a hypothetical statement and lacks experimental proof.

Response
Mechanistic data show that the action of boric acid on HDACi and Hox genes occurs at a high dose (1000 mg boric acid/kg bw) and during a very narrow window of gestation (GD 8,9) in laboratory animals. These effects are not likely to be relevant to humans, since the dose of 1000 mg/kg in humans would be about 60-70 g of boric acid which

is more than twice the lethal dose in humans.

In addition to the studies of zinc borate discussed in the Boric Acid CLH report, new studies have recently been completed and submitted as part of the public consultation by the European Borates Association that investigate the protective effect of zinc against boric acid related developmental and fertility toxicity. Humans have intrinsically higher levels of zinc in bone and soft tissues compared to laboratory animals that explain in part the absence of boric acid related reproductive toxicity effects in humans. These new studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects in humans. Recently completed studies show that zinc is protective against developmental and fertility effects of boric acid in animal and *in vitro* studies including: increased fertility NOAEL in 28-day toxicity study of zinc borate, increased NOAEL for developmental effects (reduced fetal body weights) in developmental dose range finder study on zinc borate, a dose dependent reduction of zinc in the boric acid inhibition of differentiation of embryonic stem cells in an embryonic stem cell test and a dose dependent decrease of boric acid related effects on spermatogenesis in an *in vitro* study of seminiferous tubules from rats in the presence of increase concentrations of zinc. Even when rats are exposed to high levels of zinc, concentrations of zinc in the testes do not reach the concentrations found in normal human tissues (Muzzio 2010). In vitro spermatogensis studies do not require uptake into the testes and clearly show a dose dependent decrease in boric acid related effects with increasing zinc concentrations (Martin et al. 2013).

MS Comments
Beneficial effects (pp 104 ff of the classification proposal)

The Polish CA argues in its C&L proposal, that boron plays an important nutritional role and that the essentiality of dietary boron had recently been demonstrated. This argument however, does not invalidate the adverse reproductive and developmental effects of boric acid. Further, it should be mentioned here, that there are much more chemical elements, which are on one hand essential and on the other hand classified under CLP (e.g. chromium is essential for humans, but most chromium salts are classified as Carc Cat 1 and e.g. molybdenium – molybdenium trioxide is classified as Carc Cat 2).

Response
We agree that the beneficial role of boric acid does not invalidate the adverse reproductive and developmental effects in laboratory animals. The nutritional role of boric acid should be considered in a weight of evidence regarding the intrinsic properties. Boric acid and simple borates only exists as undissociated boric acid in the body, so a comparison to chromium and molybdenium would be misleading. The toxicity and carcinogenicity are completely different for both chromium (6+) and chromium (3+) compounds. Chromium (3+) is an essential nutrient that plays a role in glucose, fat, and protein metabolism by potentiating insulin action. Hexavalent chromium compounds have a strong oxidative power. Molybdenum exhibits several oxidation states of 0, 1+, 2+, 3+,4+, 5+, and 6+ with differing toxicity.

MS Comment
In the context of essentiality it is also stated that epidemiological studies indicate that boron exposure in drinking water is associated with lower incidences of some types of cancer including prostate, lung, cervical and esophageal cancer. However, these studies concern the endpoint “carcinogenicity” and not the endpoint reproductive toxicity which is the endpoint considered here for classification and labelling.

Response
As noted, the anti-carcinogenic properties were presented in the context of intrinsic biological beneficial properties of boric acid. The anti-carcinogenic properties of boric acid should be considered when evaluating the intrinsic properties of boric acid as part of a weight of evidence evaluation.

MS Comment
A NOAEL for pre-natal effects in all 3 species has been established at 55 mg/kg bw per day.

Response
The NOAELs for rat, rabbit and mice are 9.6, 21.9 and 43 mg B/kg bw/day, respectively; or 55, 125, and 246 mg BA/kg bw/day.

RAC’s response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2013	Belgium	European Borates Association (EBA)	BehalfOfAnOrganisation	133

Comment received

The European Borates Association (EBA) supports the proposed Category 2, H361d classification. The current classification of boric acid as Repr 1B, H360FD is based on adverse developmental and fertility effects of borates in rats and rabbits. However, as presented in the Boric Acid CLH Report, an in depth evaluation of numerous independent epidemiology, worker exposure and mechanistic studies raises doubt about the relevance to humans of the developmental and reproductive effects of boric acid observed in laboratory animals. In addition new studies have been completed since the Boric Acid CLH Report was published that examine the protective effect of zinc against boric acid related toxicity.

As described in the Boric Acid CLH Report, contrary to the laboratory animal data, studies in humans have not demonstrated adverse effects of high boron exposures in boron workers the U.S., China and Turkey. 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 effect than rodents.

The Chinese and Turkish worker studies meet the quality criteria for human exposure data as defined in the REACH Regulation (1907/2006/EC) and therefore should be considered as valid evidence for assessing the hazard to humans as part of the weight of evidence. Furthermore, since these studies are considered reliable, they should take precedence over animal studies as outlined in CLP Regulation (1272/2008/EC) section 1.1.1.4.

In addition to the studies discussed in the Boric Acid CLH report, new studies have recently been completed since the publication of the Boric Acid CLH Report for public consultation that investigate the protective effect of zinc against boric acid related developmental and fertility toxicity. Humans have intrinsically higher levels of zinc than laboratory animals that explain in part the absence of boric acid related reproductive toxicity effects in humans. These new studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans. Recently completed studies show that zinc is protective against developmental and fertility effects of boric acid in animal and in vitro studies including: increased fertility NOAEL in 28-day toxicity study of zinc borate, increased NOAEL for developmental effects (reduced fetal body weights) in developmental dose range finder study on zinc borate, a dose dependent reduction of zinc in the boric acid inhibition of differentiation of embryonic stem cells in an embryonic stem cell test and an absence of boric acid related effects on spermatogenesis in an in vitro study of seminiferous tubules from rats in the presence of zinc.

The mechanism of boric acid is similar to aspirin (action as a histone deacetylase inhibitor HDACi and on Hox genes), a widely used drug known to cause developmental effects in rodents but not shown to cause teratogenic effects in humans in controlled studies. The similarity of action on HDAC and Hox genes of boric acid and aspirin, and the absence of developmental effects in humans ingesting large amounts of aspirin, provides supporting evidence that developmental effects in humans from exposure to high levels of boric acid is improbable.

The CLP Regulation prescribes the weight-of-evidence approach to be used (CLP Regulation sections 1.1.1 and 3.7.2.3). 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. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility justifying the removal of the fertility classification. 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 a Category 2 H361d classification. Therefore Repr. Category 2 H361d: suspected of damaging the unborn child as presented in the Boric Acid CLH Report is considered the appropriate classification by the EBA. This classification accommodates for both the positive findings in laboratory animals and the absence of effects in humans.

A full discussion and reference to the appropriate sections within the CLH Report is attached with this submission.

At the time of the submission of these comments, the final reports for the recently completed studies that investigated the protective effect of zinc against boric acid related developmental and fertility toxicity were not available. The final reports of the 28-day toxicity study of zinc borate (Kirkpatrick 2013), the developmental dose range finder study on zinc borate (Edwards 2013), the in vitro embryonic stem cell test with zinc chloride and boric acid (Hofman-Huther 2013), and the testicular toxicity evaluation of the combined effect of boric acid with zinc chloride using Bio-Alter Technology (Martin 2013) will be made available when the reports are finalized.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Belgium	European Borates Association (EBA)	BehalfOfAnOrganisation	134

Comment received

As announced in the previous EBA comments submitted on 20 June 2013, the following zinc borate studies (final reports) referenced in our previous EBA comments are made available along with their executive summaries:
• Wragg et al.(1996). Firebrake 415: Twenty-Eight Day Sub-Acute Oral (Gavage) Toxicity Study in The Rat. Safe Pharm Laboratories Ltd. Report No. 801/003. US Borax Inc.
• Muzzio M, Johnson WD (2010). Single-Dose Oral (Gavage) Toxicokinetic Study of Zinc Borate 2335 in Sprague-Dawley Rats. Testing Laboratory: IIT Research Institute. Report No.: 2263-001. Owner Company: US Borax Inc. Report Date: 2010-10-11

(ECHA's comment: 4 confidential attachments submitted, see the list of Confidential attachments received: Firebrake 415: Twenty-Eight Day Sub-Acute Oral (Gavage) Toxicity Study in The Rat (final report);

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B

classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2013	Belgium	European Borates Association (EBA)	BehalfOfAnOrganisation	135
Comment received				
As announced in the previous EBA comments submitted on 20 June 2013, the following new draft study reports on zinc borates and the protective effect of zinc on borate toxicity in human are made available along with their executive summaries: • Kirkpatrick, Jb (2013). A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats-Audited Draft Report. WIL Research Study No. Wil-94601. • Edwards, T.L. (2013). An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate 2335 in Rats. WIL Study Number: Wil-946003. • Hofman-Huther, H (2013). In Vitro Embryonic Stem Cell Test With Zinc Chloride And Boric Acid. Draft Report. BSL Bioservice Scientific Laboratories Gmbh. • Martin, G (2013). Testicular Toxicity Evaluation of the Combined Effect Of Boric Acid With Zinc Chloride Using Bio-Alter Technology – Draft Report. Kallistem, Lyon, France The final reports will be submitted to ECHA when available.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2013	Italy	IGDT Srl	BehalfOfAnOrganisation	136
Comment received				
Finally My previous comments on the very silly conclusions of the first study that lead this substance in SVHC list seems now to be proved. There are not at all effects on the reproductive for male while there isn't evidence of effects on unborn child.				
Dossier Submitter's Response				
Thank you for your support of PL proposal of boric acid classification.				
RAC's response				
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
26.06.2013	Netherlands		MemberState	137
Comment received				
1. Fertility: We agree that epidemiological studies in humans do not show impaired fertility. It is however noted that in these human studies the estimated exposure levels are lower				

than the overall NOAEL for testes effects in rat. This is also confirmed by information on the borate concentration in sperm cells which was higher in rats with effects on the sexual function compared to humans with borate exposure. So, exposure levels in the epidemiological studies may have been too low. Effects may well occur when humans are exposed to higher dose levels. This is likely because consistent effects on sexual function have been observed in all animal species with sufficiently high exposures. The human data thus do not contradict the animal data. Therefore, there is no evidence that the effects observed in animals are not relevant to humans.
2. The fact that the mechanism inducing sperm effects is not endocrine related does not mean that it is not relevant for humans. There are also other mechanisms causing reproductive effects that may be relevant for humans.
3. The fact that boron meets the criteria of essentiality and has a physiological importance (at low levels) in humans does not mean that higher levels may not become toxic and warrant classification. In animals, boron also has a physiological importance at low levels, while it is toxic at higher levels. The CLP legislation does not exclude such substances from classification; zinc salts for instance already have a harmonised classification.
4. A reduction in zinc level is suspected as a mechanism for the effects on sexual function and fertility. However, the evidence for that is limited. For example, it is unclear from the provided data whether the reduced toxicity of zinc borate is due to the protective effect of zinc on the zinc level in the testes or due to a reduced bioavailability. The provided information on the bioavailability study does not allow assessment of the bioavailability of zinc borate compared to other borates. The dossier submitter is requested to provide additional information on this study. In any case, should the MoA be related to a reduction in zinc level, then it should be discussed whether this is a non-specific effect secondary to the general toxicity or a specific effect of borates due to the high demand for zinc ions in the testes. The relation and specificity between the primary effect and the reprotoxic effect is comparable to the effects caused via tyrosineamia.
5. In the epidemiological studies regarding developmental effects the exposure assessment was mainly based on male workers. As the in utero exposure is determined by the maternal exposure these results cannot be used to justify the absence of developmental effects in humans.
6. Also for developmental studies, the estimated exposure levels in humans are lower than the overall NOAEL for developmental effects in rats. It cannot be excluded that effects will occur when humans are exposed to higher dose levels. The human data therefore do not contradict the animal data.
7. Page 102/103: we do not agree that because the gestational period in humans is longer, this diminishes the likelihood of effects caused by hyperacetylation of somites and/or altered hox gene expression. To the contrary, this will probably increase the critical period for the developmental effects of boric acid in humans. Further, this mechanism is also suspected for the known human teratogen valproic acid.
8. Since the human data do not contradict the animal data (see comments above) and there is no information that the mechanism for these effects is not relevant for humans, classification as Cat 1B (with a concentration limit) is required, based on the clear effects for both effects on fertility (sperm) and development.

Dossier Submitter's Response

MS Comment
So, exposure levels in the epidemiological studies may have been too low. Effects may well occur when humans are exposed to higher dose levels.

Response
The Chinese boron industry workers are the highest exposed populations to boron, and were selected for study for that reason.

MS Comment
Fertility: The fact that the mechanism inducing sperm effects is not endocrine related does not mean that it is not

relevant for humans and essentiality.

Response
The absence of an endocrine related mechanism and the physiological importance of boron relate to the intrinsic properties and suggest a low intrinsic hazard that should be considered as part of a weight of evidence evaluation.

MS Comment
A reduction in zinc level is suspected as a mechanism for the effects on sexual function and fertility.

Response
To clarify the mechanism of zinc, boric acid does not cause a reduction of zinc in laboratory animals; rather humans have intrinsic higher concentrations of zinc in bone and soft tissues, including the fetus, epididymis and testis, compared to laboratory animals. Zinc has been shown to protect against developmental and fertility effects of boric acid in animal and *in vitro* studies. The protective effect of the large zinc stores in the human body against boric acid associated toxicity explains in part the absence of effects in humans exposed to high levels of boron. The mechanistic studies evaluating the effect of zinc on boric acid toxicity are pertinent to determining the relevance of boric acid related effects in humans. All but one of the studies was conducted in accordance with Good Laboratory Practice (GLP) regulations assuring the robustness and quality of the data and raising doubt about relevance of boric acid related fertility and developmental effects in humans.

Because zinc borate ($2ZnO \cdot 3B_2O_3 \cdot 3.5H_2O$) hydrolyzes under high dilution conditions to zinc hydroxide via zinc oxide and boric acid formation and subsequently absorbed via the gastrointestinal tract as boric acid and zinc, toxicity studies of zinc borate provide valuable information on the protective effects of zinc (Muzzio et al. 2010). To determine if the low toxicity of zinc borate was due to reduced bioavailability of boric acid a toxicokinetic study in rats of zinc borate was conducted. Following a single oral dose (1000 mg/kg) of zinc borate, zinc and boron appeared in rat plasma and tissue samples, indicating the hydrolysis of zinc borate in the gastrointestinal tract, and subsequent systemic absorption of zinc and boron (Muzzio et al. 2010). The gastrointestinal tract was the primary elimination route for zinc, while urinary excretion via the kidneys was the primary elimination route for boron. A negligible amount of intake zinc (< 0.1%) was recovered from urine, and 5% or less of intake boron was recovered from feces, with no measurable quantities after 24 hours.

Also, high dietary levels of zinc do not substantially increase zinc levels in the testes in laboratory animals, remaining well below zinc levels found in normal human testes (Muzzio 2010). Additional *in vitro* and animals studies of boric acid and zinc sponsored by the European Borates Association have been submitted as part of the public consultation that demonstrate a dose dependent protective effect of zinc against boric acid related fertility and developmental effects. Since the *in vitro* spermatogenesis studies do not require uptake of zinc into the testes, these studies are able to demonstrate a dose dependent decrease in boric acid related toxicity with increasing zinc levels, at zinc levels lower than that found in human testes.

A copy of the report has been made available.

MS Comment
In the epidemiological studies regarding developmental effects the exposure assessment was mainly based on male workers. As the in utero exposure is determined by the maternal exposure these results cannot be used to justify the absence of developmental effects in humans.

Response
As noted in the dossier, there is also no evidence of developmental effects in humans attributable to boron in studies of populations with high exposures to boron (Tuccar et al 1998; Col et al. 2000; Chang et al. 2006). However, studies of human developmental effects are not as robust as the studies of male reproduction because of developmental data ascertainment issues using questionnaires. These studies contribute to the weight-of-evidence when all data should be taken together for an overall evaluation.

MS Comment
Also for developmental studies, the estimated exposure levels in humans are lower than the overall NOAEL for developmental effects in rats. It cannot be excluded that effects will occur when humans are exposed to higher dose levels. The human data therefore do not contradict the animal data.

Response
A Category 2 classification does not negate the concerns raised by the animal data nor does a Cat. 2 require proof of the absence of effects in humans. “Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals,…” Furthermore, the fact that no evidence of reproductive effects has been seen in highly exposed populations and recent studies demonstrated the protective effects of zinc

coupled with the intrinsically higher levels of zinc in target tissues in humans (fetus and testes), raises doubt about the relevance of the effect in humans.

MS Comment
Page 102/103: we do not agree that because the gestational period in humans is longer, this diminishes the likelihood of effects caused by hyperacetylation of somites and/or altered hox gene expression. To the contrary, this will probably increase the critical period for the developmental effects of boric acid in humans. Further, this mechanism is also suspected for the known human teratogen valproic acid.

Response
Mechanistic data show that the action of boric acid on HDACi and Hox genes occurs at a high dose (1000 mg boric acid/kg bw) and during a very narrow window of gestation (GD 8,9) in laboratory animals. These effects are not likely to be relevant to humans, since the dose of 1000 mg/kg in humans would be about 60-70 g of boric acid which is more than twice the lethal dose in humans.

Also, as presented in the dossier, valproic acid (VPA) showed a higher immunostaining at the level of somitic dorsal epithelium, while the reaction of somitic mesenchyme was comparable to those observed in boric acid and TSA groups. A distinguishing difference between boric acid and the other HDACi is that in contrast with results observed in studies on TSA and VPA (Menegola et al., 2005), in which hyperacetylation was also observed at the caudal neural tube level, immunostaining for boric acid group was restricted to somites. This could explain the difference between VPA and malformation after boric acid exposure (Di Renzo et al. 2007).

MS Comment
Since the human data do not contradict the animal data (see comments above) and there is no information that the mechanism for these effects is not relevant for humans, classification as Cat 1B (with a concentration limit) is required, based on the clear effects for both effects on fertility (sperm) and development.

Response
No fertility or developmental effects have been seen in workers and populations chronically exposed to boron for far longer exposure durations than laboratory animals. Although the human data do not contradict the animal data, nor does it support the animal data, necessitating a weight of evidence evaluation.

The statistical power of the boron industry worker studies are sufficiently strong to detect differences in sperm parameters with a 90% power to detect a 20% difference between the exposure groups for the majority of motility parameters (Robbins et al. 2010) and the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80% (Scialli et al. 2010). The statistical power of the worker studies can be compared to the statistical power to detect fertility effects in rodent bioassays with a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm (Mangelsdorf & Buschmann 2002).

Criteria for Category 2 “Suspected Human Reproductive Toxicant”, does not require proof of an absence of effects in humans. In fact, “Substances are classified in Category 2 for reproductive toxicity when there is **some evidence from humans** or experimental animals,…” Furthermore, no evidence of reproductive effects have been demonstrated in highly exposed populations and recent studies demonstrating the protective effects of zinc coupled with the intrinsically higher levels in target tissues in humans, raises doubt about the relevance of the effect in humans.

RAC’s response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	France		MemberState	138
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. These animal data provide a clear evidence of an adverse effect on sexual function and fertility.

Recent epidemiological studies investigate the fertility and reproductive function of workers exposed to borates.

Three studies investigate reproductive performance and sperm quality in groups of workers in China (Chang 2006, Robbins 2008, Robbins 2010).
The two most recent studies focused on subgroups of the initial cohort to include newly recruited workers. Therefore, the populations studied in these articles partially overlap.
The initial study by Chang et al. (2006) identified a higher proportion of couples who were unable to conceive within one year of desiring a child among boron workers (n=936), but this association was not significant after adjustment for various confounding factors. There was no observed effect on the number of ectopic pregnancies or stillbirths. The number of spontaneous miscarriages was higher among boron workers (7.71% vs. 4.92%) but the difference was not statistically significant. The boy/girl ratio was lower in boron workers, but not at a statistically significant level. However, it should be noted that the preponderance of boys in China is due to a cultural and parental preference, complicating the interpretation of this result. The role of educational level (slightly lower in boron workers) may have specifically interfered with this parameter. The number of induced abortions was also higher in the comparison group but the cause of these abortions was not known. It is not clear whether spontaneous miscarriages affected one gender disproportionately. Finally, the total number of live births was statistically lower in boron workers but no information was given on the statistical significance of this association after adjustment.
These results should be considered with caution in view of gaps in the study relating to imprecise or absent definitions of fertility indicators, differences observed in socioeconomic variables among the groups and the lack of consideration of potential co-exposures, which may have an impact on the subjects' fertility, whether or not they were exposed.

The study by Robbins et al. (2008) explored the potential effect on gender ratio in a subgroup and included a more accurate characterisation of exposure to borates through biological measurements in blood, urine and semen. No statistical difference was observed in the number of miscarriages, stillbirths or birth defects between the group of workers exposed through the environment and in the workplace (n=63), the group of subjects from the same community exposed through the environment only (n=39), and the control group considered to be unexposed (n=44). Statistical differences were observed in the number of subjects having more male than female children but with no apparent dose-response relationship (57.7% in exposed workers, 42.3% in the same community, and 76.7% among the controls). Educational levels were similar in the three groups. However, the rate of induced abortions for selective purposes was lower in the community group (28.2%) while it was high and comparable in the groups of exposed workers (49.2%) and controls (50.0%). Between these two groups, the smaller percentage of subjects having more male children among exposed workers (57.7% vs. 76.7%) was thus not explained. Analysis of the Y:X ratio in the semen found a statistically significant difference between the three groups. The ratio was lowest in the exposed workers (0.93), and then in the same community (0.96) compared to the controls (0.99). This ratio was also significantly correlated with boron levels measured in blood, urine and semen.

The study by Robbins et al. (2010) measured sperm quality in the three groups described above and further extended. No statistical difference was observed among the groups on infertility within one year of trying to have a child, number of miscarriages, stillbirths or birth defects. No effect was detected on sperm count, concentration, motility or morphology, or on the level of DNA breakage or apoptosis in sperm cells.

Both subgroup studies were limited by their small size but offered the advantage of properly characterising exposure and taking into account possible confounding factors. They did not indicate any effect on the objective parameters of sperm quality or quantity (Robbins 2010). Analysis of the number of subjects with seminal values below or above the reference values (e.g., WHO reference values) would be a more relevant indicator. However, an analysis of mean values can mask heterogeneous values. Moreover, the size of the population studied could only highlight wide differences, for example in the range of a 30 to 40% reduction in sperm concentration. However, Robbins et al. (2008) confirmed observing a lower percentage of boys being born, although with the same interpretation restrictions as for Chang et al. 2006, and a statistically significant lowering of the Y:X sperm ratio being observed. These studies also show that boric acid was found in humans at higher concentrations in the seminal compartment than in blood or urine, indicating possible accumulation here that had not been identified in animals.

Five references explore fertility and sperm quality in groups of workers in Turkey (Sayli 2003, Sayli 2004, Duydu 2011a; Duydu 2011b, Duydu 2011c).

Both studies by Sayli et al. (2003 and 2004) assessed "primary infertility" (defined in these studies as the failure to conceive after two years of marriage) in a cohort of workers from a borate plant in Bandirma (Sayli 2003), then expanded to several borate production centres in four regions of Turkey (Sayli 2004). These two studies showed no effect on the primary infertility rate among the workers. They did, however, have significant methodological weaknesses: infertility was only approximately assessed by interviewing the workers or through computer data without considering factors such as contraception, frequency of coitus, the age of the worker and spouse and their possible co-exposures. Sociodemographic and lifestyle characteristics (smoking, alcohol consumption, etc.) of the cohorts and comparison groups were minimally or not defined and no adjustment was considered for these parameters. Subject selection criteria were not defined. The subjects' exposure to borates was poorly characterised or left uncharacterised (inclusion of unexposed subjects in cohorts in Sayli 2003, no biological exposure indicators). The results also focused on the fertility of the worker and that of his/her family and the spouse's family for which the exposures and reliability of information collected were uncertain. These analyses do not seem appropriate for assessing the direct potential effect of exposure to borates.
These two studies are therefore considered to be of insufficient quality for drawing valid conclusions.

The articles by Duydu et al. (2011) redefined a cohort of workers from a plant in Bandirma exposed (n=102) and unexposed (n=102) to borate and studied their sperm quality parameters. The subjects were categorised according to exposure level based on biological measurements of boron concentrations in blood, urine and semen. In general, no effect on sperm quality was observed (concentration, motility, morphology) or on hormonal concentrations (FSH, LH, testosterone and PSA). Furthermore, no significant correlation was identified between boron concentrations and DNA integrity in sperm cells (comet assay). However, these studies had numerous methodological weaknesses despite properly characterising exposure, i.e., they lacked an explanation of subject selection criteria and failed to take into account potential co-exposures or primary confounding factors in their analyses. Here again, due to the small numbers studied they only have the power to detect

great differences in sperm parameters, such as a 50 to 60% reduction in sperm cell concentration. Nonetheless, these studies confirm that higher boron concentrations are found in semen compared with blood or urine levels, suggesting a possible accumulation in sperm, irrespective of exposure level.
These studies identified no effect of boric acid on sperm quality or hormone concentrations. Methodological shortcomings and especially the small number of subjects studied, however, limited the validity of these studies. In addition, a potential accumulation of boron in human sperm was identified.

Overall, these epidemiological studies led to the following conclusions:

- An increase in time to conception was observed (Chang 2006) but was not significant. Moreover, this and other studies exploring fertility had methodological weaknesses, particularly an imprecise definition of the parameters measured (all the studies) and a lack of knowledge of and failure to consider the characteristics of the exposed population (Sayli 2003 and 2004). Thus, no conclusions could be drawn from the observations reported.

- A non-significant decrease in the proportion of male births was observed in Chinese workers in the main cohort (Chang 2006), ranging from 52.45% in boron workers to 54.35% in the comparison group (respective ratios of 1.10 and 1.19). This proportion in both cases was higher when compared to the relatively stable gender ratio of 51.3% observed in Western countries (Graffelman 1999) but consistent in the comparison group with the ratio of 1.17 reported in China in 2000 (Hemminki 2005). In China, a strong cultural and parental preference for boys associated with a strict population control policy makes interpreting this effect difficult. It was however verified in the subgroup studied by Robbins et al. (2008) by a statistical decrease in the number of workers having more boys compared to the controls, while the number of selective abortions and education level were comparable in both groups. The percentage of boys was also examined in a group of Turkish workers (Sayli 2003) and a 1.0 ratio was reported, but no control group data were available for comparison.
The percentage of male births may have been influenced by various factors such as the proportion of X and Y sperm cells, their ability to fertilise the ovum and/or specific voluntary or involuntary excess foetal mortality. The effect of spontaneous abortions on the gender ratio is not known but the study of exposed subjects' sperm showed a significant correlation between the boron concentration in biological media and the Y:X ratio in sperm cells. This ratio was 0.93 in boron workers and 0.99 in the control group. Values of 1.01 have been reported in the literature among Western subjects, however (Graffelman 1999). Factors that may impact this ratio are also currently poorly understood.
In animals, the first signs of toxicity consist of a delayed release of sperm in seminiferous tubules. According to Robbins et al. (2008) this observation may be consistent with a disruption in the segregation processes of sex chromosomes that would confer a selective advantage on X sperm cells. However, there is no experimental evidence for a link between these various elements. Furthermore, an effect on the gender ratio at birth was not reported in animals (Scialli 2010) although few studies have considered this parameter (a three-generation study in rats by Weir et al., 1972 and a study in mice by Fail et al., 1991).
Overall, the observed effect on the proportion of male births in China is difficult to interpret due to methodological weaknesses and cultural specificities whose impact is not fully understood. The Robbins 2008 study points to an effect of boron on the Y:X ratio in sperm cells that needs to be confirmed by other studies.

- No effect was reported on the quality and quantity of sperm in exposed workers in China and Turkey (Robbins 2010, Duydu 2011). It should be noted that an effect on sperm count was one of the effects occurring at the lowest dose in animals. This dose (26 mg B/kg/d) was still higher by factors of 45 and 130 than the estimated mean exposure in Chinese

(0.58 mg B/kg/d) and Turkish (0.2 mg B/kg/d) workers (See Tables 1 and 2 below). Furthermore, the small size of the population examined only enabled the detection of larger effects whereas less obvious effects might still impact human fertility by increasing the percentage of subfertile couples.

Table 1 - Exposure levels in the main human studies
Estimated mean exposure Estimated range of exposure Median blood concentration Range of blood concentration Reference
Chinese workers
41 ± 37 mg B/d
(0.58 mg B/kg/d)* -
515 ± 806 ng B/g 20 - 3568 ng B/g Robbins 2008, Robbins 2010
Turkish workers
14 ± 7 mg B/d
(0.2 mg B/kg/d)* 3-36 mg B/d 224 ± 69 ng B/g 1876 - 2255 ng B/g Duydu 2011
*Calculated on the basis of a body weight of 70 kg

Table 2 - NOAEL and LOAEL observed in animal studies according to EU RAR (2007)
NOAEL LOAEL
Fertility
17.5 mg B/kg/d 26 mg B/kg/d
Development
9.6 mg B/kg/d 13.3 mg B/kg/d

In conclusion, the data available on humans are insufficiently robust to establish a clear association between exposure to boric acid and fertility effects, but nor do they prove the absence of such effects in humans or challenge the effects identified in animals.
We therefore consider that the current classification Repr 1B for fertility is appropriate for boric acid.

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. These animal data provide a clear evidence of an adverse effect on development.

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 for development.
We therefore consider that the current classification Repr 1B for development is appropriate for boric acid.

Specific concentration limits

It is noted that boric acid has specific concentration limits (SCL). Setting of SCL is also discussed in the context of the classification proposals on two octaborates. The proposed SCL refers to the SCL of boric acid and harmonisation between the three dossiers should be ensured.

Dossier Submitter's Response

MS Comment

Fertility: Three studies investigate reproductive performance and sperm quality in groups of workers in China (Chang 2006, Robbins 2008, Robbins 2010).

Finally, the total number of live births was statistically lower in boron workers but no information was given on the statistical significance of this association after adjustment.

These results should be considered with caution in view of gaps in the study relating to imprecise or absent definitions of fertility indicators, differences observed in socioeconomic variables among the groups and the lack of consideration of potential co-exposures, which may have an impact on the subjects' fertility, whether or not they were exposed.

Response

The study of Chinese workers was a multi-year, multi-investigator study with support from the China National Monitoring Center and the US Centers for Disease Control and Prevention. The total number of publications of this study is at least 30; however, many are published in the Chinese language, some with an English language abstract. The principal investigators were Dr Wendie Robbins, University of California – Los Angeles, and Dr Wei Fu-sheng, National Environmental Monitoring Center, Beijing. Data were obtained over a 3-year period from interviews, measurements of diets and drinking water, dust monitoring, and samples of blood, urine and semen. The unit of study for most parameters was the individual, as exposure and biological parameters (effects) were measured for the same individuals that allows for a more sensitive evaluation of any dose-response patterns. This is in contrast to an ecological epidemiology study, where only group data are obtained.

The expert panel (Scialli et al. 2010) concluded the following: "The delayed pregnancy end point showed a statistically significant difference between groups that disappeared on multivariate analysis, suggesting that confounding could explain the apparent difference. The report of fewer live births in boron workers than controls was based on univariate analysis; adjustment for potential confounders was not reported. The small difference between the groups (0.09 live births per subject) and the lack of adjustment for potential confounders or for multiple comparisons detract from the reliability of the reported difference. The authors' conclusions that boron workers have an increase in miscarriage and a deficit in boy children are not supported by the data presented in these papers. In addition, the reliability of sex ratio data may be severely compromised in societies such as China where selective abortion of female fetuses is practiced, although we do not have information on the prevalence of this practice in Liaoning province at the time of this study. The review panel found that these reports do not add reliable data on male reproductive success associated with boron exposure in humans."

Chang et al. (2006) reported only on interview results with 936 boron workers and 251 men from the remote community, along with their food and liquid intake values. Biological samples from these individuals were not reported by Chang et al. Nine variables regarding reproductive health were reported by Chang et al. (Table 6). Six of these were reported as not significantly different between the groups: multiple births, spontaneous miscarriages, stillbirths, tubal or ectopic pregnancy, "more boys than girls", and mean number of pregnancies fathered altogether. The variable with the most significant observed difference ($p = 0.018$) was not significant ($p=0.11$) after adjusting for age, educational level, race, smoking, alcohol use and soybean intake. The total number of live births was reported to be slightly reduced in the boron worker group (1.26 ± 0.61 vs. 1.35 ± 0.65, $p=0.28$). Chang et al. did not report any attempt to adjust for age or other factors (the boron worker group mean age was younger than the remote community group). The rate of induced abortion was significantly higher among the remote community group ($p=0.030$).

Liu et al. reported no significant difference in sex ratios, although the boron worker group ratio was 109.44 (males:females) vs. the background community value of 118.79. However, the gender ratio in most countries is about 105 to 106, so the boron worker value is not abnormally low by global standards. It may be lower than Chinese ratios, which have been trending upward. Based on statistics from the National Census Office of China, sex ratios at birth (SBR) were 108.5 in 1981, 111.3 in 1989 and 116.9 in 2000. Liu et al. did report an increased ($p<0.05$) rate of spontaneous abortion among wives of boron workers, although this was reduced when adjusted for age and exposure to toxic chemicals. Chang et al. reported no significant difference in spontaneous miscarriage rates ($p=0.134$).

As noted elsewhere, Robbins et al. (2008) reported no significant differences for these variables of reproductive

health. No significant differences in the number of miscarriages, stillbirths or birth defects were reported when comparing the three groups (boron workers, local community and remote/background community). Robbins et al. (2010) found no statistical difference between the groups for infertility after one year of attempts or for the number of miscarriages, stillbirths or birth defects.

Taken together, this portion of the China boron workers investigation indicate that there were no significant adverse effects on reproductive health or outcomes associated with occupational boron exposures.

Semen analysis of borate workers was performed and is considered a very sensitive detection system for testicular damage and measure of male fertility effects. Exposure to boron in these workers was well characterized. The exposure studies conducted in highly exposed workers in China and Turkey provided both external exposure and absorbed dose that included blood and semen boron concentrations with direct individual comparison to corresponding semen parameters.

It is incorrect to state that there was a lack of consideration for potential co-exposures. In the studies of Chinese workers, data were analyzed using stepwise logistic regression evaluating smoking, ethanol use, pesticide exposure, diseases, X-ray exposure, age, nationality, education level, religion, and wearing a mask at work. Univariate linear regression models were constructed to test the predictive value for Y:X ratio of semen concentration, total motile cells, sperm morphology, days of abstinence, boron concentration in biological fluids, total daily boron exposure, diet, years of marriage, medications, chronic diseases, exposure to known reproductive toxicants, and history of reproductive problems. Multiple linear regression was used to evaluate the effect of potential confounders on the Y:X ratio. The final model included age, smoking, alcohol, education, and pesticide exposure.

Robbins et al. (2008)

The issue of sex ratio is a central focus of Robbins et al. (2008) publication, with the hypothesis that high exposure to boron shifts the sex ratio at birth (SBR) toward females. The MS noted that Robbins et al. (2008) reported statistically significant differences in the variable “more boys than girls”, but that this was not consistent with the exposure levels. However, this variable is not the same as SBR – Robbins et al. exclude all men with equal numbers of male and female offspring at birth.

Robbins et al. (2010)

Analysis of seminal values relative to WHO reference values were discussed and presented in Table 7 of Scialli et al. 2010.

Scialli et al. 2010 addressed the issue of study size. “The study size of some 65 men in each exposure group allow, according to our computations, the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power. The power is not expected to be substantially increased by analyses of several samples per man and the power to detect differences in total count is lower. Moreover, the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel believes the statistical power of analyses based on these end points was adequate.”

The power of the borate worker studies in China and Turkey are actually better than animal studies (Mangelsdorf & Buschmann 2002). The German Federal Institute for Occupational Safety and Health calculated the statistical power to detect fertility effects in rodent bioassays. The authors reported a 90% power to detect approximately 32% difference in sperm count in rats, approximately 20% difference in sperm motility (%), and 86% detectable difference in abnormal sperm (%). In B6C3F1 mice, detectable differences for sperm count, sperm motility and abnormal sperm were 50%, 31% and 47% respectively. In CD-1 mice, detectable differences of 30%, 21-30%, and 66-106% for sperm concentration, motility and abnormal sperm.

Even with accumulation of boron in the seminal compartment, no fertility effects were observed in either Turkish or Chinese boron industry workers. Of note, the potential for external contamination of the semen samples collected from the workers was high; even when precautions were take due to the manual collection method of the semen. Whereas sperm samples are obtained surgically at necropsy from rodents. These cohorts are considered to be the highest exposures possible. It is because of the highest known exposures to boric acid and borates that these worker populations were studied by the U.S. and Chinese governments.

MS Comment
Five references explore fertility and sperm quality in groups of workers in Turkey (Sayli 2003, Sayli 2004, Duydu 2011a; Duydu 2011b, Duydu 2011c).

Response
These studies contribute to the total weight-of-evidence showing an absence of effects in exposed populations. Although these studies have methodological deficiencies, collectively with other epidemiologic studies conducted, these studies consistently show an absence of effects in highly exposed populations.

Both Chinese and Turkish studies are in full agreement with each other. There was no indication of an impairment of male reproduction in both studies. Both studies had good exposure characterization (both external and exposed dose measurements), consideration of potential confounders and semen analysis, a very sensitive detection system for testicular damage.

MS Comment
This dose (26 mg B/kg/d) was still higher by factors of 45 and 130 than the estimated mean exposure in Chinese (0.58 mg B/kg/d) and Turkish (0.2 mg B/kg/d) workers (See Tables 1 and 2 below).

Table 1 - Exposure levels in the main human studies *Calculated on the basis of a body weight of 70 kg

Response
For the Chinese cohorts, a standard body weight of 60 kg should be used (Xing et al. 2007). The exposure as reported by Robbins et al. (2010) was 42 mg B/day or 0.7 mg B/kg bw/day.

Workers at the Pengxiang plant (n=16) where drinking water was heavily contaminated with boron, the mean exposure was 125 ± 89.1 mg B/day or 2.08 mg B/kg bw/day (Scialli et al. 2010).

When comparing the NOAEL for fertility effects in the rat of 17.5 mg B/kg/day and the human NOAEL (highest occupational exposures in the Chinese workers study) 2.08 mg B/kgday (based on 125 mg B/day and 60 kg person; Scialli et al. 2010), a factor of only 8.75, less than a 10 fold difference.

MS Comment
Development: These animal data provide a clear evidence of an adverse effect on development.

Response
We agree the animal data provide clear evidence of adverse effects on development in laboratory animals, but no evidence of effects in humans.

MS Comment
In conclusion, the data available on humans are insufficiently robust to establish a clear association between exposure to boric acid and fertility effects, but nor do they prove the absence of such effects in humans or challenge the effects identified in animals. We therefore consider that the current classification Repr 1B for fertility is appropriate for boric acid.

Response
As noted previously, the boron industry worker studies in China and Turkey are sufficiently robust as determined by statistical power calculations that show the statistical power of the Chinese and Turkish boron industry workers are equivalent to or greater than corresponding statistical power for sperm evaluations in animal bioassays.

A Category 2 classification does not negate the concerns raised by the animal data nor does a Cat. 2 require proof of the absence of effects in humans. “Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals,…” Furthermore, the fact that no evidence of reproductive effects have been seen in highly exposed populations and recent studies demonstrated the protective effects of zinc coupled with the intrinsically higher levels of zinc in target tissues in humans (fetus and testes), raises doubt about the relevance of the effect in animals for humans.

MS Comment
Specific concentration limits
It is noted that boric acid has specific concentration limits (SCL). Setting of SCL is also discussed in the context of the classification proposals on two octaborates. The proposed SCL refers to the SCL of boric acid and harmonisation between the three dossiers should be ensured.

Response
The SCL for boric acid has been determined in 2005 by experts from the ECB Technical Committee on Classification & Labelling (TCC&L). Despite a novel approach introduced in the ECHA Guidance to the CLP regulation to assess the potency of reproductive toxicants based on the ED10 value, we suggest to maintain the

current SCL previously agreed by the experts based on the developmental NOAEL.
RAC's response
The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2013	United Kingdom		Company-Downstream user	139
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

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
24.06.2013	United Kingdom	Lubrizol Deutschland GmbH	BehalfOfAnOrganisation	140

Comment received

Lubrizol fully supports the conclusion of the Polish Competent Authority that boric acid should be classified Category 2 toxic for reproduction. The latest epidemiological studies and scientific evidence demonstrate that the reproductive effects of boron compounds seen in some laboratory animals at high concentrations under specific test conditions are not found in humans, even when workers were exposed to high levels. Therefore considering all available information, Lubrizol supports the proposed Category 2 toxic for reproduction classification for boric acid. Lubrizol also agrees that the classification of boric acid as Category 2 toxic for reproduction should apply to the other inorganic borates listed on CLP Annex VI and supports EBA's comment that these new data should be taken into account when the proposed classification of disodium octaborate and disodium octaborate tetrahydrate (DOT) is discussed.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion. DOT and DOA have been classified based on the same information that has been provided for boric acid.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2013	Italy	Lamberti S.p.A.	BehalfOfAnOrganisation	141

Comment received

In agreement with EBA (European Borates Association , see position attached), we supports the Polish proposal for re-classification of boric acid as a Category 2 reproductive toxicant under the EU's classification. As described in the Boric Acid CLH Report, contrary to the laboratory animal data, studies in humans have not demonstrated adverse effects of high boron exposures in boron workers in the U.S., China and Turkey. Furthermore, since these studies are considered reliable, they should take precedence over animal studies as outlined in CLP Regulation (1272/2008/EC) section 1.1.1.4.
Moreover, new studies have recently been completed since the publication of the Boric Acid CLH Report for public consultation that investigates the protective effect of zinc against boric acid related developmental and fertility toxicity. Humans have intrinsically higher levels of zinc than laboratory animals that explain in part the absence of boric acid related reproductive toxicity effects in humans. These new studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans.
Furthermore, there are also available data coming from poison control centers. In fact from the mid-1800s to around 1940 boric acid and disodium tetraborate decahydrate were used systematically for a variety of medical conditions including amenorrhea, malaria, epilepsy, urinary tract infection and exudative pleuritis (Kliegel, 1980). In all these cases where withdrawal of treatment was reported, recovery occurred with no lasting effects. Besides, there are also data related to the result of accidental use of boric acid. Of 784 more recent reports of accidental ingestion, none were reported as fatal and 88.3% were asymptomatic. The estimated dose range was 10 mg to 88.8 g (Litovitz et al, 1988).
Moreover, since the human response to ingestion of boric acid indicates vomiting at fraction of concentrations that are the animal NOAEL values, chronic exposures of humans are likely to be self-limiting unlike rodents that are unable to vomit. These acute effects demonstrate that it is not possible for humans to be exposed to the high doses that could give rise to reproductive effects. Furthermore nausea, vomiting and diarrhoea would prevent repeated exposure through accidental misuse.

Data to support the fact that the developmental or fertility effects have never been demonstrated among human with high exposure to borates arise also from legislation on safety and health at work. In Italy the Decree n.81/2008, related to health and safety at work, establishes that the company, using some dangerous substances, has to perform an health monitoring system. Our personal experiences in the use of boric acid demonstrate that no adverse effect has ever been arisen to the workers exposed to boric acid.

Dossier Submitter's Response

Thank you for your support of PL proposal of boric acid classification.

RAC's response

The RAC has carefully assessed the information in the CLH dossier, and additional information from EBA, but came to the conclusion that a revision of the current Repr. 1B classification (for both development and fertility effects) is not warranted based on the submitted information. For more reasoning, please see the RAC opinion.

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[1] 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].

NON-CONFIDENTIAL ATTACHMENTS RECEIVED:

2. **Public consultation – boric acid (CAS 10043-35-3)** – submitted on 12.06.2013 by a company-downstream user from Germany (copied under comment No 43)

3. **Final report Boric acid and Exposure Inspection at Factory 1 Location –** submitted on 14.06.2013 by a company-manufacturer from the Netherlands

4. **Report for cytotoxicity and biocompatibility testing of boric acid solution in eye care products** – submitted on 20.06.2013 by a company-downstream user from Germany

TITLE: REPORT FOR THE BIOCOMPATIBILITY TESTING OF HYDROPHILIC CONTACT LENSES (GROUPS I AND IV) USING MULTI-PURPOSE SOLUTION (FORMULATION X) FOR JAPAN	DOCUMENT NO.: QDXXX-RPT REV.: 01

1.0 SUMMARY

This report summarizes the biocompatibility studies completed on , Formulation X, a contact lens care multi-purpose solution (MPS). The ISO Standard "10993-1:2003 Biological Evaluation of Medical Devices" and the US FDA 510(k) Guidance document "Guidance for Industry: Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products" dated May 1, 1997 were used to define the toxicity testing scheme for evaluation of formulation X. Table 1 below summarizes the tests performed.

Table 1. Toxicity Summary for Formulation X, contact lens care MPS

Lens Type	Endpoint	Specific Tests	Standard	Study Number	Test Status
Acuvue®2	Cytotoxicity	Agar Overlay Test *in vitro*	USP <87> ISO-10993-5 FDA 510(k)	P109	Pass
	Ocular Irritation	22-day Ocular Irritation in Rabbits	ISO 9394 FDA 510(k)	11T3_02	Pass
Acuvue® Advance®	Cytotoxicity	Agar Overlay Test *in vitro*	USP <87> ISO-10993-5 FDA 510(k)	1138	Pass
	Ocular Irritation	22-day Ocular Irritation in Rabbits	ISO 9394 FDA 510(k)	11T_9_01	Pass

*See Results / Discussion section

Based upon the passing results from the toxicity tests, formulation X is considered compatible with biological tissues.

2.0 BACKGROUND

Cytotoxicity tests were conducted at the Biological Test Center (BTC in Irvine, CA). The 22-Day Ocular Irritation study was conducted at NAMSA (Northwood, Ohio). All test labs performed the testing under Good Laboratory Practice regulations 21 CFR Part 58. All labs are part of the AMO supplier management program.

Acuvue® 2 (A2) and Acuvue® Advance® (AA) soft contact lenses were treated following a specified lens care regimen (QD9-PRO) with MPS, formulation X, in the Corneal R&D lab. Lenses were also treated in conjunction with ISO Saline to serve as control. Formulation X (Lot # 00) is shown below in Table 2. Contact Lens Lot#s used for tests is shown in Table 3 and 4.

TITLE:	REPORT FOR THE BIOCOMPATIBILITY TESTING OF HYDROPHILIC CONTACT LENSES (GROUPS I AND IV) USING MULTI-PURPOSE SOLUTION (FORMULATION X) FOR JAPAN	DOCUMENT NO.: QDXXX-RPT REV.: 01

Table 2. Formulation X used in the toxicity and biocompatibility evaluation.

Components (Lot# RDZJ003)	X % w/w	Function
PHMB[1]	**0.0001**	**Disinfectants**
Boric Acid	0.60	Buffer
Sodium Borate Decahydrate	0.17	Buffer
S		Tonicity agent
0		Chelator
T		Buffer
P		Surfactant
S		Anti-adsorption
P		QS adjust

Table 3. Contact Lenses used in biocompatibility evaluation (Agar Overlay Assay).

Acuvue® Advance® Lenses
(Group I, silicone hydrogel, Vistakon)

Study ID	Lot #	Exp Date	Info
AA #1 AA #2 AA #3 AA #4 AA #5 AA #6 AA #7 AA #8	B0TQ	03017	D -3.00 BC 8.7 Dia 14.0
AA #9 AA #10 AA #11 AA #12 AA #13 AA #14 AA #15 AA #16 AA #17 AA #18 AA #19	BLB9	02017	D -12.00 BC 8.7 Dia 14.0
AA #20 AA #21 AA #22	BGTQ	0017	D -3.00 BC 8.7 Dia 14.0

Acuvue® 2 Lenses
(Group IV, Etafilcon A, Vistakon)

Study ID	Lot #	Exp Date	Info
A2 # 1 A2 # 2 A2 # 3 A2 # 4 A2 # 5 A2 # 6 A2 # 7 A2 # 8	354617	07-16	D -3.00 BC 8.7 Dia 14.0
A2 # 9 A2 # 10 A2 # 11 A2 # 12 A2 # 13 A2 # 14 A2 # 15 A2 # 16 A2 # 17 A2 # 18 A2 # 19	LN6W	05-16	D -12.00 BC 8.7 Dia 14.0
A2 # 20 A2 # 21 A2 # 22	3540910617	07-16	D -3.00 BC 8.7 Dia 14.0

TITLE:	REPORT FOR THE BIOCOMPATIBILITY TESTING OF HYDROPHILIC CONTACT LENSES (GROUPS I AND IV) USING MULTI-PURPOSE SOLUTION (FORMULATION X) FOR JAPAN	DOCUMENT NO.: QDXXX-RPT REV.: 01

Table 4. Contact Lenses used in toxicity evaluation (Ocular Irritation Study).

Acuvue® Advance® Lenses (Group I, silicone hydrogel, Vistakon)	
Lot #	**Exp Date**
B003GN B003GH B003G2 B003GC B033GN	Jul-16

Acuvue® 2 Lenses (Group IV, Etafilcon A, Vistakon)	
Lot #	**Exp Date**
L004VJ L8V4C3 L8V4CD L8V4CR L0V4CN	Mar-13

3.0 RESULTS AND DISCUSSION

3.1 Cytotoxicity – Agar Overlay

Both test lenses AA and A2 were treated with formulation X (lot # RD003) in a 30 day regimen (QDXXX-PRO), and extracted in 1X Minimum Essential Medium (MEM). Their extracts were applied to sterile paper discs ($1cm^2$) and then placed on top of an agar surface of the test plates containing a confluent monolayer of mouse fibroblasts. USP reference standards for positive and negative controls were also tested. The cytotoxicity testing was contracted to Nelson Laboratories in Salt Lake City, Utah and was completed on December 02, 2011. The results of the cytotoxicity study showed the average scores for the AA and A2 test solution and negative control was 0, corresponding to no detectable reactivity.

3.2 22-day Ocular Biocompatibility

The 22-day ocular irritation of both test lenses AA and A2, treated with formulation X using a rub rinse daily lens regimen (QDXXXPRO), was assessed in rabbits following 22-days of daily contact lens wear under GLP guidelines at NAMSA (Northwood, Ohio). Six New Zealand white rabbits were fitted with lenses treated with either X or Complete ® Easy Rub (control) solution. In the first study (11T_45003_02), rabbits were fitted with FDA Group 4 Acuvue® 2 contact lenses (Vistakon) in both right and left eyes. In the second study (11T_46399_01), rabbits were fitted with FDA Group 1 Acuvue® Advance® contact lenses (Vistakon) in both right and left eyes. Right-eye lenses were treated with the test product while left-eye lenses were treated with the control product.

Prior to first wear, lenses were soaked in the respective solutions overnight. In the subsequent 22 consecutive days, the lenses were worn for a minimum of seven hours, then removed and soaked overnight in the respective test and control products. On lens wear day 23, the lenses were worn for at least four hours. All lenses were cared for using a "no-rub" method (to emulate the worst-case scenario) prior to application and following removal. After 22 days of lens wear, results of the study indicate that the ocular toxicity of X is comparable to that of the control solution. Both 22-day ocular irritation studies were completed on September 22, 2011,

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4.0 CONCLUSION

All acceptance criteria have been met for the biocompatibility evaluations with Formulation X.

- The results of the agar overlay cytotoxicity study showed the average score for the test solution resulted in no detectable reactivity.
- After 22 days of contact lens wear in rabbits using contact lenses (Acuvue® 2 and Acuvue® Advance®) the studies indicate that the ocular irritation of X is comparable to that of the marketed control solution, Complete® Easy Rub.

Based upon the passing results from the toxicity tests, formulation X is considered compatible with biological tissues.

5.0 ATTACHMENTS

5.1 **Attachment 1:** Protocol/Report Number P1011139 from BTC (Irvine, CA). Cell Culture Agar Overlay Assay of Acuvue®2 Lenses After a Regimen of 30 Cycles in MPS per AMO Protocol QDXXX-PRO, per USP <87>, ISO-10993-5:2009 and FDA 510(k).

5.2 **Attachment 2:** Protocol/Report Number P1011138 from BTC (Irvine, CA). Cell Culture Agar Overlay Assay of Acuvue® Advance® Lenses After a Regimen of 30 Cycles in MPS per AMO Protocol QDXXX-PRO, per USP <87>, ISO-10993-5:2009 and FDA 510(k).

5.3 **Attachment 3:** Report Number 11T_45003_02: ISO Contact Lens/Solution Ocular Irritation Study with Acuvue®2 contact lenses

5.4 **Attachment 4:** Report Number 11T_46399_01: ISO Contact Lens/Solution Ocular Irritation Study with Acuvue® Advance® contact lenses

6.0 REFERENCES

6.1 Guidance for Industry. Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products. FDA CDRH. May 1, 1997.

6.2 ISO 10993-10:2002 Biological evaluation of medical devices -- Part 10: Tests for irritation and delayed-type hypersensitivity.

6.3 ISO 10993:1999 Biological evaluation of medical devices -- Part 5: Tests for in vitro Cytotoxicity

6.4 United States Pharmacopoeia (USP) <87> Biological reactivity tests, *in vitro*

6.5 QD3169-PRO Rev.02 : Protocol for the Biocompatibility Testing of Hydrophilic Contact Lenses (Groups I and IV) using Multi-Purpose Solution (Formulation X) for Japan

5. **Public attachment** – submitted on 27.06.2013 by a company-manufacturer from France

We are making this submission because boric acid has important properties for development of health products including medical devices. Boric acid provides benefits that alternative products cannot currently provide.

Reprotoxic tests have been performed and effects were found only at high doses of boron in animals by oral route (the no-adverse-effect level for reproductive effects in male rats is 17.5mg B/kg bw/day) where many chemical products would also present strong toxic effects. The results obtained in animals are not transposable to humans, where there is no evidence of harm.

The biological activity of the final product deeply depends on the chemical effect of the mixture, not on the individual ingredients. Boron and boric acid are able to combine with other substances/ingredients which then have different hazardous properties. The objective of REACH is to prove how chemical substances can be used safely, on their own and in mixtures. Eye/skin washing solutions and contact lens buffered solutions which are medical devices can contain boric acid or borates, well below the accepted threshold safety level. Boric acid can exhibit antifungal and bacteriostatic properties and healing properties.

We propose to pay attention to the use of boric acid in medical devices and include the previously published concentration limits (C < 5.5%) as an exemption for labeling.

Specific comments on the justification

Exposure/risks

Boric acid contains boron, which is a natural element. Boric acid has been used for many years with very weak buffer properties which are very similar to amino acids. The main advantage of boron and its derivates are their tendency of hybridization which allows them to create weak links with numerous constituents. So, when used in mixtures, they should not be assessed on their own but in association with other chemical compound(s).The use in the form of neutral salts allows antiseptic effects and biological properties to be obtained, in particular concerning healing, therefore contributing to the success of certain therapies.

Boric acid has been used safely by our company for a long time. Boric acid can be used for the manufacturing of health products such as medical devices. That is the reason why we feel concerned by the proposal of de-classification and re-classification of boric acid as a Category 2 reproductive toxicant under the EU's Classification, Labeling and Packaging Regulation (CLP). Our products are used in an acute manner.

Our products are nonirritant, non-sensitizing non-cytotoxic, non-toxic by oral or dermal routes and non-mutagenic. Our products (medical device, class IIa) can also be used on damaged skin (a study on rabbits showed that no dermal lesion or toxic effect was observed when applied on either scarified or non-scarified skin).

Classification and labeling

The objective of REACH is for producers and importers of substances to prove how their substances can be produced and used safely. The exposure scenarii are a key communication tool. Considering any solutions containing some boric acid without taking into account the other constituents makes no sense as the mixture properties are different

than that of the individual constituents in particular for mixtures used for antisepsis and healing.

The studies which indicate reprotoxic effects of boric acid, indicate effects only at very high doses to animals (1), are not transposable to new studies with human exposure (2a, 2b) nor can be extrapolated to solutions (preparations) containing boric acid. It seems unreasonable to maintain such substance as a Repr 1B, H360FD based on reprotoxic effect observed at high doses in animals only and only by oral route when data on humans have never correlated with such results.

We would like to emphasize that under reasonable foreseeable circumstances, boric acid is not dangerous by different routes of exposure, especially not by the dermal route (4, 5, 6), the route where many cosmetics and drugs are applied. The absorption through the skin is very weak, an indicator that the toxicity cannot not be high. This confirms that boric acid is not the substance of greatest concern and that attention should be focused on other, more potentially dangerous chemicals than this one.

We ask that the level required (C < 5.5%), as an exemption for labeling, for Category 2 reproductive toxicant at least maintained.

Alternatives

Appropriate substitute products for boric acids and borates having the same properties are not known. Chemically speaking, phosphates can be substitutes but they appreciably modify the local free calcium equilibrium and can induce, during eye uses, important calcifications, even after a single use.
In Europe during the 1980s, borates in ocular solutions were replaced by phosphates, under the pressure of some scientific papers. Phosphates could have a lower profile in terms of harmfulness but there are other aspects that should be added: the producers of eye lens solutions added phosphates until they noticed that these solutions containing phosphates could induce calcification on the cornea (7). This subsequently led to the withdrawal from the market of these solutions with phosphates.

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BORIC ACID

6. **Consultation on the reclassification of boric acid as Category 2 Toxic for Reproduction** – submitted on 13.06.2013 by Glass Alliance Europe (copied under comment No 40)

7. **Detailed Comments on Boric Acid, CLH Report, 20 June 2013** – submitted by the European Borates Association A.I.S.B.L. on 21.06.2013

European Borates Association A.I.S.B.L.

Detailed Comments on Boric Acid CLH Report

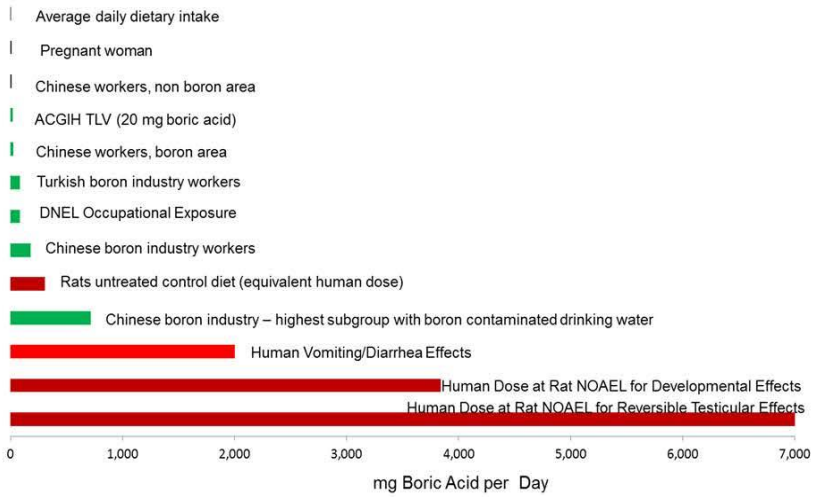
20 June 2013

Reproductive Toxicity

p94 Part B 4.11.3 Toxic for Reproduction, Other relevant information

In addition to the data presented in the Boric Acid CLH Report comparing rodent and human blood, semen and tissue boron levels, a comparison of external exposures is relevant for the potential of adverse effects in humans. Figure 1 below presents a comparison of boric acid exposures in laboratory rat and humans. Basal animal diets are significantly higher in boron than human diets, so total boron exposure is higher than suggested by traditional NOAEL/LOAEL endpoints. Blood plasma levels reflect differences in boron content of diets, so typical human diet contains fraction of untreated control animal diets. Studies of borate workers in the USA, China, and Turkey consistently show no adverse effects on reproductive endpoints at even the highest exposures. Human exposures studied in workers at borate mines and processing operations are likely more exposed than workers in other industries, and several times more exposed than non-worker populations. Background boron levels in rat chow (10-11 ppm) are not always taken into account in considering the dosing levels in animal studies. Indeed control rats received approximately 0.9 mg B/kg/day or 45-times higher dose than background exposure in humans. Humans do not reach the exposure level of the untreated control rats fed rat chow except in extreme exposure conditions (borate workers eating on site and drinking boron contaminated water at the mine site). Furthermore, since the human response to ingestion of boric acid indicates vomiting at fraction of concentrations that are the animal NOAEL values, chronic exposures of humans are likely to be self-limiting unlike rodents that are unable to vomit.

Figure 1. Rat and Human Exposure to Boric Acid



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Protective Effects of Zinc against Boric Acid Reproductive and Developmental Toxicity

As presented in the Boric Acid CLH Report, an important difference between laboratory animals and humans is the intrinsically higher zinc concentration in humans compared to laboratory animals. Normal levels of zinc in soft tissues in humans are over two times greater than in comparative tissues in laboratory animals (Figure 2) (King et al. 2000; Ranjan et al. 2011; Yamaguchi et al. 1996; Florianczyk 2000). The high zinc concentrations in humans compared to laboratory animals is also found in the target organs of boric acid, including fetal tissue, epididymis, and testes (Figure 2) (Ahokas et al. 1980; Dorea et al. 1987; Suescun et al. 1981). The protective effect of the intrinsically large zinc stores in the human body against boric acid associated toxicity explains in part the absence of effects in humans exposed to high levels of boron.

Because zinc homeostasis in humans is highly regulated, the high zinc level relative to laboratory animals is maintained during times of zinc deficiency. The body maintains constant tissue levels of zinc with varying intakes by adjusting gastrointestinal zinc absorption and intestinal endogenous zinc excretion. During times of extremely low intakes or with prolonged marginal intakes, secondary homeostatic processes are functioning. These secondary measures include a reduction in urinary zinc excretion, an increase in plasma fractional turnover rates and retention of zinc released from selected tissues, such as bone, in other tissues to maintain their zinc status. Studies in rats demonstrate a capacity to maintain a relatively constant content of zinc in the whole body while dietary zinc intakes vary by as much as 10-fold (King et al. 2000)

Zinc is found in all body tissues, with 85% of the whole body zinc in muscle and bone, 11% in the skin and liver and the remaining 2–3% in other tissues (Jackson 1989). When the dietary zinc supply is very low or if a marginal intake is consumed for a long period of time, homeostatic adjustments may not be sufficient to replace zinc losses and a negative zinc balance occurs. The bone, about one third of the whole body zinc, is a significant source of endogenous zinc when the dietary supply is low (Jackson et al. 1982; King et al. 2000). A drop in plasma zinc after initiation of a severely low zinc diet signals certain tissues to increase the release of zinc and other tissues to retain zinc. Studies show a marked reduction in dietary zinc is invariably followed quickly by a reduction in food intake and growth failure. Zinc released from tissues during the catabolic phase is taken up and retained very efficiently by other tissues (King et al. 2000).

Plasma provides a metabolically active transport compartment for zinc. Zinc is most often complexed to organic ligands (existing in loosely or firmly bound fractions) rather than free in solution as metallic ion. Zinc is found in diffusible or non-diffusible forms in the blood. In the diffusible form, approximately two-thirds of plasma zinc is freely exchangeable and loosely bound to albumin. The diffusible form of zinc also includes zinc bound to amino acids (primarily histidine and cysteine). The zinc-albumin complex is in equilibrium with the zinc-amino acid complex. The zinc-amino acid complex can be transported passively across tissue membranes. The diffusible form of zinc is likely the form available to interact with boric acid. The liver, pancreas, bone, kidney, and muscle are the major tissue storage sites (ATSDR 2005).

Boron industry worker studies show that boron appears to concentrate in the semen, however without corresponding adverse effects on the semen. This is likely due to the fact that zinc concentrations are higher in semen in humans (112 µg zinc/ml), protective against the adverse effects of boric acid (Sorensen et al. 1999).

Comparative zinc concentrations in humans and rat indicate that the protective effects of zinc are present early in the developing human fetus. Significantly higher concentrations (3x) of zinc in the human fetus compared to laboratory animals have been reported (Figure 2). It is well established that fetuses and neonates have higher concentrations of zinc than adults. The zinc reserves of the human neonate are deposited during fetal development. At the time of birth, a quarter of the body Zn is in the liver. Liver zinc concentration is higher in fetuses and neonates than in

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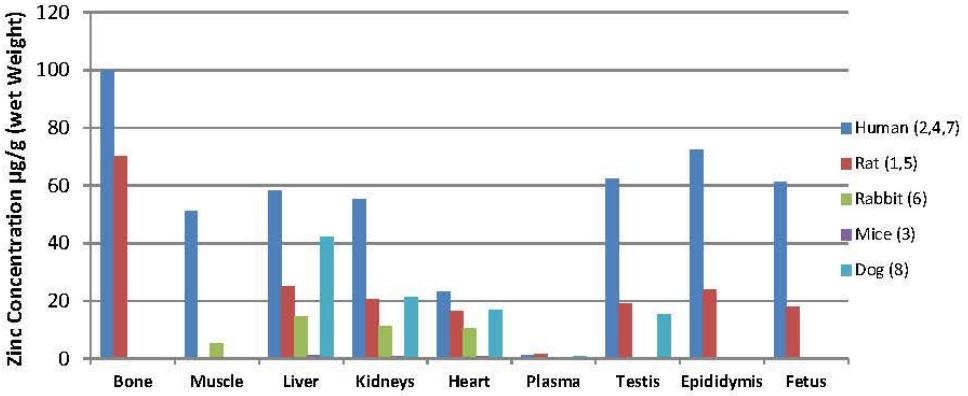
adults. There was a comparable range of zinc values of 10 to 300 µg/g fresh tissue for both pre-term and term babies. The value of 10 µg/g was found only in one 4-month-old infant (Dorea et al. 1987).

The transport of essential trace elements such as zinc from mother to fetus varies throughout gestation with a vigorous mother-to-fetus uphill zinc transfer. Conversely, cord blood zinc is higher than in maternal blood plasma and decreases with gestational age (GA). In addition, the concentration ratio between circulating zinc in the mother and the infant tended to decrease as GA increased. Maternal and cord plasma zinc according to gestational age ranged from 24– 28 weeks a maternal/cord zinc ratio 0.51 (± 0.14) increasing to 0.72 (± 0.21) 38– 42 weeks (Perveen et al. 2002).

Figure 2: Tissue Levels of Zinc in Humans and Laboratory Animals



(1) Ahokas et al. 1980; (2) Dorea et al. 1980; (3) Florianczyk 2000; (4) King et al. 2000; (5) Muzzio 2010; (6) Ranjan et al. 2011; (7) Suescun et al. 1981; (8) Yamaguchi et al. 1996

Studies Evaluating Effect of Zinc on Boric Acid Related Fertility and Developmental Toxicity

As presented in the boric acid CLH Report, the protective effect of zinc against boric acid related toxicity has been shown by the low acute toxicity of zinc borate compared to disodium tetraborate pentahydrate, both with equivalent boron concentrations. No mortality occurred in an acute toxicity study of zinc borate in rats administered 10 g/kg-bw, equivalent to 1492 mg B/kg bw (Daniels 1969) compared to disodium tetraborate pentahydrate with a LD50 value of 3.3 g/kg-bw, equivalent to 488 mg B/kg bw. In addition, an increased male fertility NOAEL of 50 mg Boron/kg bw was observed in a 28-day toxicity study of a similar zinc borate compound (Wragg et al. 1996). The LOAEL for testicular effects for boric acid in the absence of zinc is 26 mg Boron/kg body weight.

In addition to the studies discussed in the Boric Acid CLH report, new studies have recently been completed since the release of the Boric Acid CLH Report that investigate the protective effect of zinc against boric acid related developmental and fertility toxicity of boric acid. Humans have intrinsically higher levels of zinc than laboratory animals that explain in part the absence of boric acid related reproductive toxicity effects in humans. These studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans. These data provide further justification that classification of Repr. Category 2 H361d is more appropriate for boric acid than Repr. Category 1B H360FD.

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To investigate the effect of zinc on boric acid related toxicity on fertility and developmental effects an *in vitro* spermatogenesis study and an *in vitro* embryonic stem cell test with boric acid in the presence of varying amounts of zinc were recently completed (Martin 2013; Hofman-Huther 2013). A summary of these studies is presented below:

Spermatogenesis Study

An *in vitro* study of the effect of zinc on boric acid related toxicity of spermatogenesis was conducted using primary cultures of seminiferous tubules from rats. Seminiferous tubules were cultured in the presence of 32 µg/ml boric acid and varying concentrations of zinc chloride equivalent to 0.48, 1.2, 2.4 and 4.8 µg Zn/ml to determine the effects on the number of somatic cells (sertoli and myoid cells) and germ cells (pre-meiotic cells (spermatogonia), meiotic cells (young spermatocytes, middle to late pachytene spermatocytes and secondary spermatocytes), and post-meiotic cells (round spermatids)) after 1 and 2 weeks of culture. An absence of boric acid related effects on spermatogenesis was observed in the presence of zinc (See Figures 3-10) (Martin 2013).

A dose dependent increase of somatic cells was observed at day 14 in the presence of zinc (Figures 3- 4). In the presence of boric acid, a decrease in the number of total germ cells was seen. A dose dependent increase in the number of germ cells was observed at day 7 and 14 in the presence of zinc (Figure 5). Boric acid decreased the number of spermatogonia (Figure 6) possibly from a direct effect on spermatogonia, which are located before the Sertoli cell barrier (tight junctions between the Sertoli cells: the main component of the blood-testis barrier). In that location the chemical can reach directly spermatogonia without the necessity to cross the Sertoli cell barrier. At D7, the addition of zinc maintained the number of spermatogonia to the number observed in the control (without boric acid) and at D14, the number of spermatogonia in the presence of zinc was always higher than in the control. The number of young spermatocytes was decreased on D7 with boric acid; however, zinc induced a dose dependent increase in the number of young spermatocytes (Figure 7). The number of middle to late pachytene spermatocytes was decreased on D7 with boric acid. Boric acid in the presence of zinc induced a dose dependent increase of the number of middle to late pachytene spermatocytes, both at D7 and D14 (Figure 8). Boric acid decreased the number of secondary spermatocytes at D7 and D14 showing that the meiotic phase is impaired by boric acid (Figure 9). At D14, zinc increased the number of secondary spermatocytes in a dose dependent manner. Moreover, the lower concentrations of zinc were sufficient to raise the number of secondary spermatocytes to the number observed in the control.

Boric acid decreased the number of round spermatids at day 7 and 14 (Figure 10). When zinc is added to the cultures, an increase in the number of round spermatids as compared to the effect of boric acid alone was observed on day 7, and increased the number of round spermatids in a dose dependent manner on day 14. The number of round spermatids is a useful parameter since these cells have completed the two meiotic divisions and the differentiation of round spermatids in elongated spermatids and spermatozoa involves only cytological differentiation, without DNA synthesis (this is an "end-product").

These results suggest that zinc interacts with boric acid reducing its toxicity on the meiotic divisions.

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Figure 3

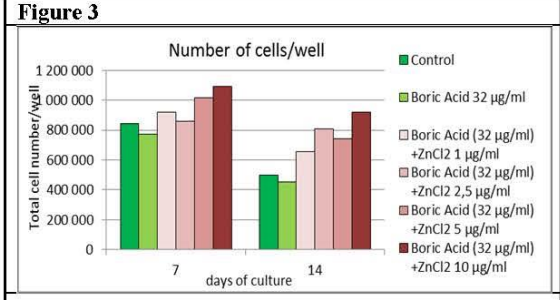

Figure 4

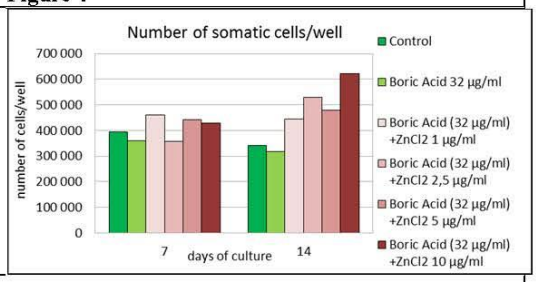

Figure 5

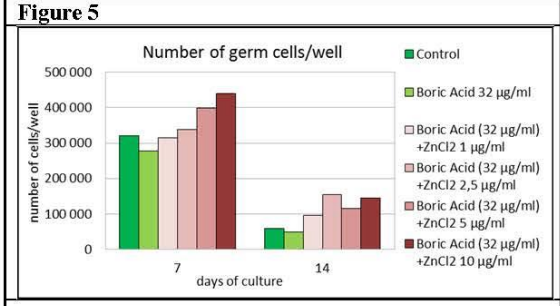

Figure 6

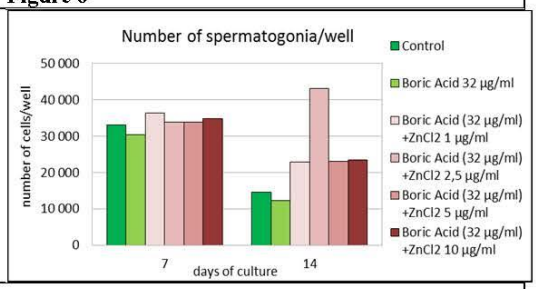

Figure 7

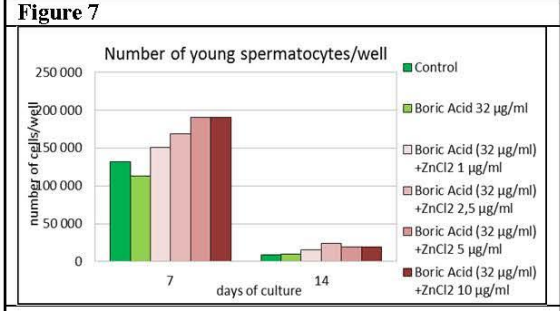

Figure 8

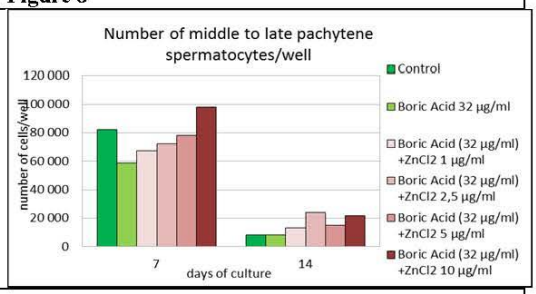

Figure 9

Figure 10

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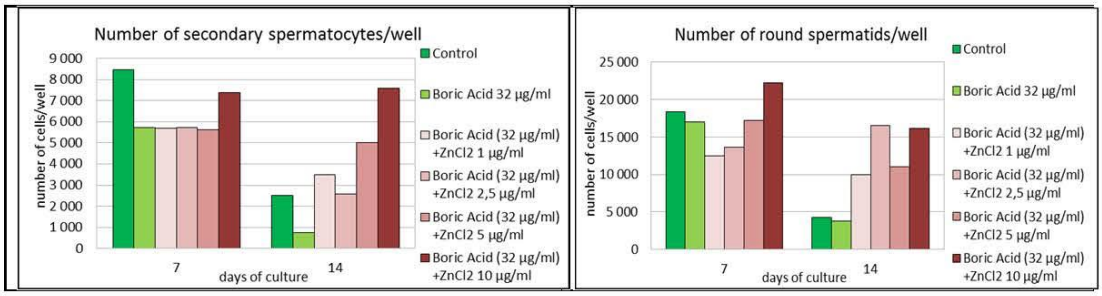

Embryonic Stem Cell Test with Zinc Chloride and Boric Acid

A GLP-compliant embryonic stem cell test (EST) conducted according to INVITTOX Protocol No. 113 was performed to investigate the embryotoxic potential of boric acid in the presence of varying concentrations of zinc *in vitro*. The concentration of boric acid used in this study has been shown in previous EST tests to cause a 50% inhibition of differentiation of D3 cells into contracting myocardial cells (Genschow et al. 2004). The set concentration of boric acid tested was 150 µg/ml with concentrations of zinc chloride of 0, 1.04, 2.08, 10.42, 20.83, 41.67, 83.33 and 125 µg ZnCl/ml, equivalent to 0, 0.5, 1, 5, 10, 20, 40 and 60 µg Zn/ml. The ZnCl was dissolved in culture medium without supplements (DMEM) to the final concentration of 125 µg/ml and dilutions made to the appropriate test concentrations. The highest zinc chloride concentrations of 41.67, 83.33 and 125 µg ZnCl/ml were cytotoxic in this study.

Conclusion
No greater sensitivity of embryonic stem cells compared to fully differentiated cells was observed and no concern for *in vivo* embryotoxicity is triggered for boric acid at various concentrations of zinc. A reduction in the boric acid inhibition of differentiation of D3 embryonic stem cells was observed with increasing concentrations of zinc (See Figure 11) (Hofman-Huther 2013).

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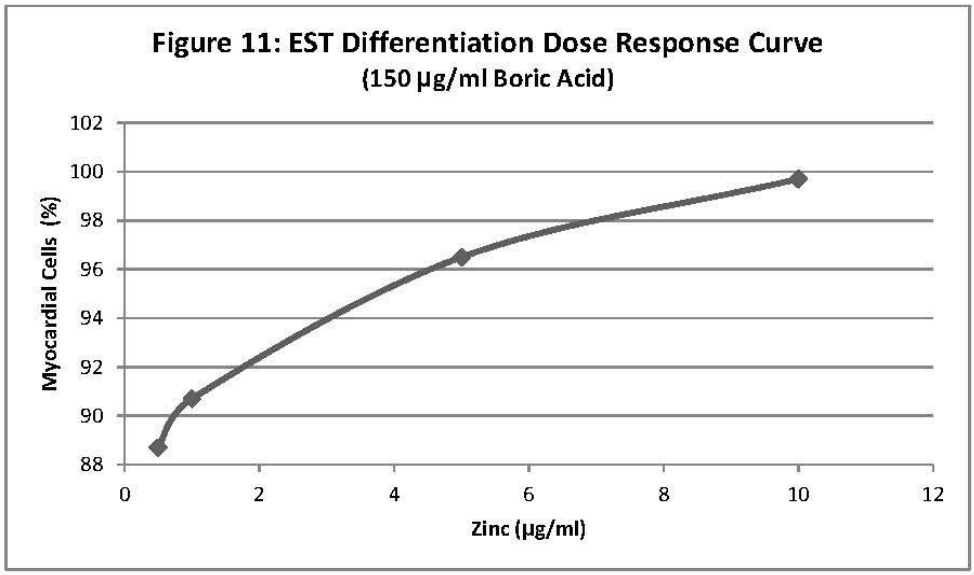

Zinc Borate Toxicity Studies

In addition to the *in vitro* studies, a 28-day oral (gavage) dose range finding toxicity study of zinc borate and a dose range-finding prenatal developmental toxicity study of zinc borate in Sprague-Dawley Rats were also recently completed (Kirkpatrick 2013; Edwards 2013). These studies are presented below.

Because zinc borate ($2ZnO \cdot 3B_2O_3 \cdot 3.5H_2O$) hydrolyzes under high dilution conditions to zinc hydroxide via zinc oxide and boric acid formation and subsequently absorbed via the gastrointestinal tract as boric acid and zinc (Muzzio et al. 2010), these studies provide important data on the effects of zinc on boric acid related fertility and developmental toxicity. Because of the distinctly different toxicological profile of zinc borate compared to boric acid, read across to boric acid has been shown to be inappropriate for zinc borate (Wragg et al. 1996; Kirkpatrick 2013).

Zinc borate breaks down as follows:

$$2ZnO \cdot 3B_2O_3 \cdot 3.5H_2O + 3.5\ H_2O + 4\ H^+ \rightleftharpoons 6\ H_3BO_3 + 2\ Zn^{2+}$$

$$2\ Zn^{2+} + 4\ OH^- \rightleftharpoons 2\ Zn(OH)_2$$

Overall equation:

$$2ZnO \cdot 3B_2O_3 \cdot 3.5H_2O + 7.5\ H_2O \rightleftharpoons 2\ Zn(OH)_2 + 6\ H_3BO_3$$

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A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate in Sprague Dawley Rats

A sub-chronic oral study was conducted to evaluate the potential toxicity of zinc borate (ZB) when administered daily by oral gavage to Sprague Dawley rats for a minimum of 28 consecutive days to aid in selection of dose levels for a 90-day oral gavage toxicity study. Dosage levels tested were 125, 250, 500, 1000 mg ZB/kg bw equivalent to 18.65, 37.3, 74.6 and 149.2 mg Boron/kg bw. Fertility parameters evaluated included weights and microscopic examination of ovaries, testes and epididymides. Statistically significant lower epididymis weights were noted in the 500 and 1000 mg ZB/kg/day groups, while testes and ovaries were lower only in the 1000 mg ZB/kg/day group. Treatment related microscopic findings were noted in the testes and epididymides in the 500 and 1000 mg ZB/kg/day groups; and in the seminal vesicles, in the 1000 mg ZB/kg/day group. Mild to moderate decreased secretion of the seminal vesicle was noted in the 1000 mg ZB/kg/day group.

Severe bilateral seminiferous tubular degeneration was noted in the testes of the 1000 mg ZB/kg/day group males. Severe seminiferous tubular degeneration was characterized by diffuse loss of spermatogonia, spermatocytes, and spermatids, scattered multinucleated cells, and vacuolation of Sertoli cells. These changes were concurrent with severe hypospermia and moderate cellular luminal debris in the epididymides.

In the 500 mg ZB/kg bw/day group males, degeneration of seminiferous tubules was limited to minimal degree and was characterized by scattered multinucleated cells with occasional vacuolation of Sertoli cells. Hypospermia of the epididymides was not observed in the 500 mg ZB/kg bw/day group males. The microscopic findings in the 500 mg ZB/kg bw dose group were considered histologic changes that barely exceeds that which is considered to be within normal limits, and unlikely to produce any functional impairment.

No microscopic findings were noted in the ovaries.

Conclusion
In a 28-day dose range finding study of zinc borate a NOAEL of 37.3 mg B/kg bw and LOAEL of 74.6 mg B/kg bw for male fertility effects determined by minimal histopathologic findings in testes and epididymides was observed. Since hypospermia was not observed at the LOAEL, and the histopathological changes were graded as minimal, the effects observed in the 75 mg B/kg bw group were not considered toxicologically significant (Kirkpatrick 2013). The male fertility NOAEL for boric acid is 17.5 mg B/kg bw.

An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate in Rats

An oral gavage dose range-finding prenatal developmental toxicity study of zinc borate was conducted to determine dose levels of zinc borate to be evaluated in a definitive developmental toxicity study in rats. Eight time mated rats per group were administered via oral gavage 0 (vehicle control), 100, 200, 300, 400 and 500 mg zinc borate/kg bw equivalent to 14.92, 29.84, 44.76, 59.68 and 74.6 mg boron/kg bw. The zinc borate and control substances were administered as a single daily dose from gestation day 6 through 20, inclusively. No maternal toxicity was observed in any of the dose groups. Significantly reduced body weight gain was observed in the high dose group, likely due to the reduced fetal body weights. Statistically significant lower fetal body weights were observed in the 200, 300, 400 and 500 mg zinc borate/kg bw dose groups compared to the vehicle control group. The NOAEL based on fetal body weights is 100 mg zinc borate/kg bw equivalent to 14.92 mg Boron/kg bw.

Conclusion
Compared to boric acid, a 55% increase in the developmental NOAEL based on lower fetal body weights was demonstrated in the GLP developmental dose range finder study of zinc borate (Edwards 2013). The developmental

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toxicity NOAEL of zinc borate was 14.92 mg B/kg bw compared to 9.6 mg B/kg bw for boric acid and sodium borates in the absence of zinc.

These data show that humans are likely less sensitive to the reproductive and developmental effects of boric acid than laboratory animals due to the comparative high zinc stores in target tissues in humans compared to laboratory animals.

90-Day Oral Toxicity Study of Zinc Borate

A 90-day oral toxicity study of zinc borate is currently underway. Endpoints of the 90-day study include complete spermatogenesis evaluation and microscopic examination of the testes and epididymis which will provide more information on the impact of zinc on boric acid related fertility effects in males.

Studies that are currently ongoing or planned that will provide more information on the role zinc plays in developmental and fertility effects of boric acid include:

- 90-day oral toxicity study of zinc borate (to be completed October 2013),
- Developmental toxicity study of zinc borate (to be completed in 2014).

Similarity of aspirin and boric acid developmental effects in laboratory animals

Inhibition of histone deacetylases (HDACi) by sodium salicylate (SAL), the natural deacetylated form of aspirin, has also been shown as a mechanism of teratogenesis (axial skeletal malformations) in laboratory animals (Di Renzo et al. 2007, 2008). Similarly to boric acid, SAL is reported to induce axial abnormalities when administered to pregnant rodents. In particular, supernumerary ribs (lumbar ribs) have been associated with the oral administration of 300 mg/kg SAL to pregnant mice (gestation day 8). The anti-inflammatory properties of salicylates have been known for decades, and they are among the oldest and most widely used drugs in the world. SAL is responsible for the anti-inflammatory action of aspirin, introduced into clinical practice more than 100 years ago and one of the most widely used medicines. Their low toxicity in adults is well known. Although known to cause developmental effects in laboratory animals, there is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings. Controlled human studies of SAL and aspirin have not demonstrated teratogenicity (HSDB 2012). Salicylates have been recently evaluated for new multiple therapeutic activities, including range of antineoplastic properties of both synthetic salicylates and a vegetable-rich diet (Di Renzo et al. 2008).

When aspirin is administered during the third trimester there is an increase in perinatal mortality, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and complicated deliveries; thus, the recommendation against its use during this period (Hardman et al. 2006). During the last weeks of gestation, long-term high-dose salicylate therapy may cause prolonged gestation, increased risk of postmaturity and fetal neonatal hemorrhage. The effects from exposure during the third trimester when organ development is complete are unrelated to the teratogenic effects seen in laboratory animals that occur earlier in the gestation during organogenesis (gestation day 8). Aspirin is classified as FDA pregnancy category C. Chronic maternal ingestion is associated with an increased incidence of stillbirths, antepartum/postpartum bleeding, prolonged pregnancy/labor, and lower birth weight (HSDB 2012).

The mechanism of developmental effects of aspirin in laboratory animals is relevant to boric acid since both SAL and boric acid act via a similar mechanism in causing developmental effects in mice. Although no large scale studies of boric acid have been conducted in humans, large populations routinely use aspirin for extended periods of time and are the most widely used drug worldwide. While developmental effects have been observed in laboratory

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animals, similar effects have not been seen in humans. This provides supporting evidence that developmental effect in humans from exposure to high levels of boric acid is improbable.

p108 Part B 4.11.5 Toxic for Reproduction, Comparison with criteria

In addition to the passages presented in the Boric Acid CLH Report describing the basis for classification of reproductive toxicity extracted from REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008, the following passages are also particularly relevant to the use of the worker exposure and new mechanistic data in determining the appropriate classification of boric acid (emphasis added):

> **"1.1.1. The role and application of expert judgment and weight of evidence determination**
>
> 1.1.1.4. For the purpose of classification for health hazards (Part 3) established hazardous effects seen in appropriate animal studies or from human experience that are consistent with the criteria for classification shall normally justify classification. Where evidence is available from both humans and animals and there is a conflict between the findings, the quality and reliability of the evidence from both sources shall be evaluated in order to resolve the question of classification. **Generally, adequate, reliable and representative data on humans (including epidemiological studies, scientifically valid case studies as specified in this Annex or statistically backed experience) shall have precedence over other data.** However, even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare but still significant effects, to assess potentially confounding factors. Therefore, positive results from well-conducted animal studies are not necessarily negated by the lack of positive human experience but require an assessment of the robustness, quality and statistical power of both the human and animal data.
>
> 1.1.1.5. For the purpose of classification for health hazards (Part 3) route of exposure, mechanistic information and metabolism studies are pertinent to determining the relevance of an effect in humans. **When such information, as far as there is reassurance about the robustness and quality of the data, raises doubt about relevance in humans, a lower classification may be warranted.** When there is scientific evidence that the mechanism or mode of action is not relevant to humans, the substance or mixture should not be classified."

The CLP regulation is clear that human data is to have primacy over animal data for the purpose of classification of health hazards provided the human data are reliable. This is particularly relevant when the same toxicity endpoints are measured in both humans and animals, in this case sensitive sperm analysis. A main principle that underlies all animal toxicity testing is that exposure of experimental animals to chemicals in high doses is a necessary method of discovering possible hazards in humans. But practical considerations in the design of experimental model systems require that the number of animals used in toxicology experiments always be small compared with the size of human populations at risk. Obtaining statistically valid results from such small groups of animals requires the use of relatively large doses so that the effect will occur frequently enough to be detected. However, the use of high doses can create problems in interpretation if the response(s) obtained at high doses in animals does not occur at low doses experienced in humans (Eaton and Gilbert 2008). Since the human exposure studies on boron workers are considered reliable according to the criteria specified in the REACH Regulation (see below), these data should have precedence over studies in animals.

Adequacy of the Human Data

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Criteria for assessing the adequacy of human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, are specified in Annex XI, Section 1.1.3. from REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
"*The strength of the data for a specific human health effect depends, among other things, on the type of analysis and on the parameters covered and on the magnitude and specificity of the response and consequently the predictability of the effect.*"

"*Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, shall be considered.*"

"*Criteria for assessing the adequacy of the data include:*"

(1) "The proper selection and characterisation of the exposed and control groups;"

- Groups were selected based on level of borate exposures. The Chinese worker study involved male workers at one boron mine and four boron processing plants. The five workplaces were selected based on the location, number of employees, and the presence and cooperation of an industrial hygienist at the site. A comparison group of men were recruited from an area 30 miles away from mine and processing plants with low background boron exposure levels. The men were screened with the same questionnaire and physical examination used for the boron workers. Another comparison group was added consisting of workers without occupational exposure to boron but drawn from the same community as the boron workers. The Turkish workers exposure groups were occupationally exposed workers consisted from boric acid and borax production workers. Control group consisted of workers (male) working in the same zone, but outside of the production area of boron products and not occupationally exposed to boron (sulfuric acid workers, steam power plant workers, energy suppliers, mechanical workshop, garage and steelyard workers, demineralized water production workers, construction workers, laboratory technicians, and office workers).

(2) "adequate characterisation of exposure;"

- Exposures were well characterized that included individual worker external exposures measurements (inhalation, diet, drinking water), and the internal (absorbed) dose including blood, semen and urine boron concentrations.

(3) "sufficient length of follow-up for disease occurrence;"

- The Chinese workers were followed for at least a complete spermatogenesis cycle to capture any possible effects of borate exposure on semen parameters. A criterion for enrolment for the study was employment at the same worksite for at least the previous year. The mean employment duration of the Turkish workers was approximately 14 years.

(4) "valid method for observing an effect;"

- In the Chinese worker study, semen analysis included; sperm count, sperm concentration, motility, morphology, percentage of DNA strand breakage and sperm aneuploidy and diploidy. In the Turkish worker studies, in addition to the semen analysis, prostate specific antigen (PSA) levels were measured and sensitive reproductive toxicity indicators that included blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone. These semen and blood analyses are very sensitive measurements of fertility and testicular damage in humans.

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(5) "proper consideration of bias and confounding factors; and"

- In the studies of Chinese workers, data were analyzed using stepwise logistic regression evaluating smoking, ethanol use, pesticide exposure, diseases, X-ray exposure, age, nationality, education level, religion, and wearing a mask at work.

- Univariate linear regression models were constructed to test the predictive value for Y:X chromosome ratio of semen concentration, total motile cells, sperm morphology, days of abstinence, boron concentration in biological fluids, total daily boron exposure, diet, years of marriage, medications, chronic diseases, exposure to known reproductive toxicants, and history of reproductive problems. Multiple linear regression was used to evaluate the effect of potential confounders on the Y:X chromosome ratio. The final model included age, smoking, alcohol, education, and pesticide exposure.

(6) "a reasonable statistical reliability to justify the conclusion."

- Epidemiology studies often lack sufficient statistical power to detect differences that are meaningful. An expert panel evaluated the exposure studies of boron industry workers in China and addressed the issue of study size. Scialli et al. (2010) determined that the detection of a 25% difference in sperm concentration between groups at the 5% significance level with about 80% statistical power and the study power to detect a doubling of risk of failure to meet WHO criteria for normal semen analysis at the 5% significance level is also about 80%. Altogether, the panel concluded that the statistical power of analyses based on these end points was adequate.

- The expert panel also evaluated the number of subjects presenting seminal values below or above WHO reference values, considered by some as a more relevant indicator than the analysis of mean values that can mask heterogeneity of values. The expert panel determined that there was no statistically significant difference between high-boron and low-boron groups in the proportion of men failing to meet WHO criteria for normal semen analysis (Scialli et al. 2010).

The Chinese and Turkish worker studies clearly meet these quality criteria and therefore should be considered as valid evidence for assessing the hazard to humans, as part of the weight of evidence approach to be used as prescribed in CLP Regulation sections 1.1.1 and 3.7.2.3. Furthermore, since the human exposure studies meet the quality criteria, they should take precedence over animal studies as outlined in CLP Regulation section 1.1.1.4.

Non-occupational Exposures

In addition to the non-occupational exposure data presented in the Boric Acid CLH Report (Page 110), the highest non-occupational exposure found were populations in Northern Chile in which estimated intake of boron was 21 to 27 mg B/day, which correlated to naturally high boron concentrations in local rivers (Barr et al. 1993). In recent studies of populations in Chile, exposure levels of boron in drinking water and urine was measured from volunteers in Arica, an area in the North of Chile with high levels of naturally occurring boron (Cortes et al. 2011). The concentration of boron in urine varied between 0.45 and 17.4 mg/L, with a median of 4.28 mg/L and was found to be correlated with tap water sampled from the homes of the volunteers (r=0.64). Espinoza-Navaro et al.(2010) analyzed sperm for total sperm count, sperm concentration, volume, vitality, pH, morphology, overall motility and grade A motility in a sample of 102 healthy young males aged 18 to 30 years residing in Arica, Chile. The volunteers also completed a questionnaire about fertility, habits and andrologic diseases. Males sampled in Arica had normal sperm values in comparison with international reports (Espinoza-Navarro et al. 2010).

Weight-of-Evidence Considerations

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The CLP Regulation prescribes the weight-of-evidence approach to be used (CLP Regulation sections 1.1.1 and 3.7.2.3). An in depth evaluation of numerous independent 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 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 however a comparison of blood, semen and target organ boron levels in studies of laboratory animals and human studies shows that boron industry worker exposures are lower than untreated control rats.
- The human worker studies meet the quality and reliability criteria for assessing the adequacy of human data as specified in Annex XI, Section 1.1.3. from REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), therefore the worker exposure data should have precedence over other data.
- Mechanistic data show that the action of boric acid on HDACi and Hox genes occurs at a high dose (1000 mg boric acid/kg bw) and during a very narrow window of gestation (GD 8,9) in laboratory animals. These effects are not likely to be relevant to humans, since the dose of 1000 mg/kg in humans would be about 60-70 g of boric acid which is more than twice the lethal dose in humans.
- The mechanism of boric acid is similar to aspirin (action as HDACi and on *Hox* genes), a widely used drug known to cause developmental effects in rodents but not shown to cause teratogenic effects in humans in controlled studies. The similarity of action on HDAC and *Hox* genes of boric acid and aspirin, and the absence of developmental effects in humans ingesting large amounts of aspirin, provides supporting evidence that developmental effect in humans from exposure to high levels of boric acid is improbable.
- A key difference between humans and laboratory animals relative to boric acid toxicity is the intrinsically large zinc stores in humans. Zinc has been shown to protect against developmental and fertility effects of boric acid in animal and *in vitro* studies. The protective effect of the large zinc stores in the human body against boric acid associated toxicity explains in part the absence of effects in humans exposed to high levels of boron. The mechanistic studies evaluating the effect of zinc on boric acid toxicity are pertinent to determining the relevance of boric acid related effects in humans. All but one of the studies was conducted in accordance with Good Laboratory Practice (GLP) regulations assuring the robustness and quality of the data and raising doubt about relevance of boric acid related fertility and developmental effects in humans. Therefore, a lower classification is warranted.

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.

EBA Position Conclusions

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Boric acid shows adverse effects on fertility as well as developmental toxicity in laboratory animals. Therefore a classification as a reproductive toxicant is warranted. Nevertheless for classification in category 1 the available data must allow "*a strong presumption that the substance has the capacity to interfere with reproduction in humans.*" Further it is described that "*when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate*".

Based on mechanistic data and contradicting results from animal and human data, the definition for category 2 is the most appropriate: "*Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1.*"

Based on a total weight of evidence, Repr. Category 2 H361d: suspected of damaging the unborn child is considered the appropriate classification by the EBA. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility justifying the removal of the fertility classification. While no developmental effects have been seen in highly exposed populations, 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.

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8. **CLH report on Boric acid, EBA's comments submitted to ECHA, EXECUTIVE SUMMARY, 20 June 2013** – submitted by the European Federation of Corrugated Board Manufacturers on 21.06.2013

The European Borates Association (EBA) supports the proposed Category 2, H361d classification. The current classification of boric acid as Repr 1B, H360FD is based on adverse developmental and fertility effects of borates in rats and rabbits. However, as presented in the Boric Acid CLH Report, an in depth evaluation of numerous independent epidemiology, worker exposure and mechanistic studies raises doubt about the relevance to humans of the developmental and reproductive effects of boric acid observed in laboratory animals. In addition new studies have been completed since the Boric Acid CLH Report was published that examine the protective effect of zinc against boric acid related toxicity.

As described in the Boric Acid CLH Report, contrary to the laboratory animal data, studies in humans have not demonstrated adverse effects of high boron exposures in boron workers the U.S., China and Turkey. 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 effect than rodents.

The Chinese and Turkish worker studies meet the quality criteria for human exposure data as defined in the REACH Regulation (1907/2006/EC) and therefore should be considered as valid evidence for assessing the hazard to humans as part of the weight of evidence. Furthermore, since these studies are considered reliable, they should take precedence over animal studies as outlined in CLP Regulation (1272/2008/EC) section 1.1.1.4.

In addition to the studies discussed in the Boric Acid CLH report, new studies have recently been completed since the publication of the Boric Acid CLH Report for public consultation that investigate the protective effect of zinc against boric acid related developmental and fertility toxicity. Humans have intrinsically higher levels of zinc than laboratory animals that explain in part the absence of boric acid related reproductive toxicity effects in humans. These new studies provide important mechanistic data on the effects of zinc on boric acid related reproductive toxicity that raises doubt about the relevance of the effects for humans. Recently completed studies show that zinc is protective against developmental and fertility effects of boric acid in animal and in vitro studies including: increased fertility NOAEL in 28-day toxicity study of zinc borate, increased NOAEL for developmental effects (reduced fetal body weights) in developmental dose range finder study on zinc borate, a dose dependent reduction of zinc in the boric acid inhibition of differentiation of embryonic stem cells in an embryonic stem cell test and an absence of boric acid related effects on spermatogenesis in an in vitro study of seminiferous tubules from rats in the presence of zinc.

The mechanism of boric acid is similar to aspirin (action as a histone deacetylase inhibitor HDACi and on Hox genes), a widely used drug known to cause developmental effects in rodents but not shown to cause teratogenic effects in humans in controlled studies. The similarity of action on HDAC and Hox genes of boric acid and aspirin, and the absence of developmental effects in humans ingesting large amounts of aspirin, provides supporting evidence that developmental effects in humans from exposure to high levels of boric acid is improbable.

The CLP Regulation prescribes the weight-of-evidence approach to be used (CLP Regulation sections 1.1.1 and 3.7.2.3). 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. Extensive evaluations of sperm parameters in highly exposed workers have demonstrated no effects on male fertility justifying the removal of the fertility classification. 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 a Category 2 H361d classification. Therefore Repr. Category 2 H361d: suspected of damaging the unborn child as presented in the Boric Acid CLH Report is considered the appropriate classification by the EBA. This classification accommodates for both the positive findings in laboratory animals and the absence of effects in humans.

A full discussion and reference to the appropriate sections within the CLH Report is attached with this submission.

At the time of the submission of these comments, the final reports for the recently completed studies that investigated the protective effect of zinc against boric acid related developmental and fertility toxicity were not available. The final reports of the 28-day toxicity study of zinc borate (Kirkpatrick 2013), the developmental dose range finder study on zinc borate (Edwards 2013), the in vitro embryonic stem cell test with zinc chloride and boric acid (Hofman-Huther 2013), and the testicular toxicity evaluation of the combined effect of boric acid with zinc chloride using Bio-Alter Technology (Martin 2013) will be made available when the reports are finalized.

9. BV GLAS COMMENTS ON THE CONSULTATION ON THE RECLASSIFICATION OF BORIC ACID AS CATEGORY 2 TOXIC FOR REPRODUCTION – submitted by Bundesverband Glasindustrie e.V. on 27.06.2013

Bundesverband Glasindustrie e.V. (BV Glas), which is the Federal Association of the German glass industry, welcomes the opportunity to provide its contribution to the public consultation on the proposed reclassification of boric acid as a Category 2 toxic for reproduction substance under the EU's Classification, Labelling and Packaging Regulation (CLP).

Some of our members produce borosilicate glass. For years, borosilicate glass has been used in consumer products (coffee pots, heat-resistant cookware, microwave trays...), laboratory vessels, pharmaceutical packaging material, high strength lenses, LCD television and computer screens, components for chemical plants, continuous filament glass fibres and glass micro fibres. Borosilicate tubing now finds applications in solar energy applications, either directly or after concentration by reflecting panels in solar power plants, fire protecting glass windows and very resistant windscreens for trains and planes.

Recital (2) of the 30th ATP (Commission Directive 2008/58/EC of 21 August 2008), which added certain borates to the Dangerous Substances Directive as toxic to reproduction category 2 (now 1B) and which was inserted by the European Commission, 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" underlining that uncertainty still existed on the exact classification.

The new proposal by Poland is based on scientific evidence from studies conducted on Chinese and Turkish borate mine workers with the highest known exposure levels. 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) and BV Glas wishs to express its support of the Polish proposal and EBA as well. The latest studies seem to demonstrate clearly that reproductive effects of boron compounds, still evident in laboratory animals under test conditions, are not found in humans even when exposed to high levels. Considering all available information, BV Glas supports the proposed Category 2 classification for boric acid. Moreover BV Glas believes that the classification of boric acid as a Category 2 toxic for reproduction should apply also to the other classified borates and Disodium Borate (DOT).

In Germany, the current occupational exposure level for boric acid and disodium borates is 0.5 mg/m³ (expressed as B) (TRGS 900, update 04.02.2010). According to the German Employer's Liability Insurance Association (Verwaltungs-Berufsgenossenschaft - VBG) the measured values of boron compounds pose no risk to workers as they are far below current limit values. Data for boron and disodium tetraborates were obtained between 1996 and 2008 from eleven German glass production plants, e.g. container glass, flat glass, special glass and glass fibre. The data were measured in different working places, e.g. storage of raw materials, weighing and mixing, batch preparing, batch conveying systems, melting, and processing. All measured values were far below the limit value.

Dust measurement in a German fibre glass plant (batch house) showed that respirable (alveolar) dust was below 0.16 mg/m³ and inhalable (total dust) below 1.05 mg/m³. The respirable limit values are 3 mg/m³ and 10 mg/m³. Since 10% borax pentahydrate is used in the batch, we assume that the boron concentrations are far below the occupational exposure limit of 0.5 mg/m³ (expressed as B).

Finally, BV Glas would like to underline that boron is of great importance for the glass industries and that boron compounds are completely consumed in the glass production process and are no longer present as such in the final article. Therefore exposure of humans or the environment to glass (dust) does not result in exposure to boric acid. The final products are definitely safe. Borosilicate glass articles are considered to be amongst the most inert materials from a chemical point of view.

10. Detailed Comments on Boric Acid CLH Report, 20 June 2013 – submitted by Johns Manville Europe GmbH on 27.06.2013 (ECHA's comment: identical with Detailed Comments on Boric Acid, CLH Report, 20 June 2013 – submitted by the European Borates Association A.I.S.B.L. on 21.06.2013)

11. PUBLIC CONSULTATION, Harmonised Classification & Labelling, Comments on the classification proposal on Boric Acid – submitted by the Belgian Competent Authority on 28.06.2013

CLH proposal from PL

	CLP Regulation	Directive 67/548/EEC
Current entry in Annex VI	Repr. 1B H360FD	Repr. 2 R60-61
Proposed classification	Repr. 2 H361d	Repr. 3 R63

Proposed classification based on CLP criteria

Hazard statements: Cat. 2 H361d : suspected of damaging the unborn child.
Signal word: warning
Pictograms:

Proposed classification based on Directive 67/548/EEC criteria

Repr. Cat 3; R63

Overall conclusion and Comments:

Health effects

We would like to thank Poland for the classification proposal.

We cannot support the new classification proposal based on the rational detailed here below.

Epidemiological studies

Fertility

In the Scialli et al. study (2010) (reported as the key study in the dossier), one preliminary and one main studies have been carried out. It is concluded that no impairment on testicular function following Boron exposure is observed in the main study. However,

- in the preliminary study, the semen sample of 60 boron workers and 10 remote background controls had been analysed. A large proportion of these boron workers presented semen not meeting WHO criteria for normal semen analysis:
  - 4 on 58 boron-exposed workers had < 20 million sperm/ml,
  - 26 on 58 failed to have ≥ 50% forwardly motile sperm,
  - 8 on 58 failed to have ≥ 25% rapidly progressive sperm.

Due to the outcome of this preliminary study, the authors reported that *"there were statistically significant decrements in boron workers in percet sperm with forward motility, rapidly progressive sperm, …, and conclude that boron exposure had adverse effects on sperm viability and sperm motion endpoints."* However, this conclusion is not reported in the dossier.

- in the main study, an interview on the reproductive experience of men and their wives were conducted in 957 boron workers and 251 remote background controls. Findings of this study are higher prevalence of miscarriage, delayed pregnancy and a lower sex ratio in the boron workers. Besides, it is also mentioned that men exposed to boron had a decrease in live births.

In another key study in the dossier, Robbins WA et al. (2010), the p-value of the original sale of normal morphology is 0,04 which means that the difference is statistically significant compared to the control group. After adjustment for age, abstinence interval, smoking, alcohol, pesticide exposure and Mg, the p-value rose 0,06. This value is still quite low and just above the reference value p-0.05.

Development

We cannot consider the Tuccar *et al* (1998) and Col et al (2000) studies as supportive studies to assess the effect of boron on human reproductive parameters due to the lack of data.

In the Tuccar et al (1998), it is not clear which exposure is taken into account as the study mentions "the drinking water" – people environmentally exposed- and the questionnaires were sent to the workers at borate plant - occupationally exposed. Besides, no information on the occupational exposure level neither on the criteria selection of the families in each region are presented.

Another concern is the Boron exposure level in the drinking water in 3 chosen regions. The concentration of boron is not measured in the named "Region III". The estimated level of exposure of this population living in this region is unknown and therefore the comparison between the different region cannot be carried out. We consider that no conclusion on the level of exposure and the potential adverse effects observed in human can be drawn. On page 93 in the dossier, it mentioned that the named "Region II" is the *low boron level*. Does it mean that "Region III" present boron level in between? The DS referred also to another study (Korkmaz et al. 2007) to assess the daily exposures "*in the boron rich region"* but it is not clear if it is referring to the corresponding "Region III" and if the drinking water has been assessed. Besides, the data are presented in different units (ppm in the Tuccar study and kg/day in the korkmaz study). Korkmaz study also mentioned the exposure of the control but no detailed data is provided regarding this control group (which region of Turkey, size of the sample, lifestyle, workers at plant, workers in the office, general population,…)

Regarding the Col et al (2000) study, we also have some concerns about the level of exposure in the 3 different regions. The boron level in drinking water ranges from 1.7 to 9.4 ppm for Region I, from 2.79 to 5.94 in Region II and from 0.36 to 0.62 ppm in Region III. The level of exposure in the Region II is already covered by the level of exposure in the Region I and we cannot distinguish those both regions in term of Boron exposure level. We have the same remark regarding the dust concentrations in production departments where the Boron exposure level in Region I is covered by the level exposure in Region II (it varied from 1.11 to 2.96 mg/m³ in Region I, 0.69 to 9.25 mg/m³ in Region II and 0.39 to 9.47 mg/m³ in Region III). For occupational exposure, we question the possible occupational personal protective method in place at the plant (personal protective equipment, risk management measure,…), so that the real worker exposure is lower than the measured exposure. Any information would be helpful to assess the real exposure.

Regarding the boron exposure level of the wives, we disagree with the following statement: "*No boron exposure measurements were available for the spouses of the workers during the pregnancies , **however their exposure were likely lower than the male workers who were also exposed to boron at the production facilities***". We understand the rationale behind this statement however, without no measured blood sample, no relevant conclusion can be drawn on the difference of exposure level between the spouses and the workers.

Regarding those both studies, we finally have a general remark concerning the protocol of those studies. We have doubt on the reliability of those studies only based on personal interview (standardised birth ratio, no spermogram data, lifestyle,…).
We consider that a study based on a questionnaire cannot be used as supportive evidence due to the social and cultural issues that can bring bias to the study and cannot reflect the real adverse effects. How is it possible to establish the correlation between level of inhaled boron dust/ingested boron, the concentration level in the body and the adverse effects observed?

Animal/In vitro studies

The Lanoue et al. (1998) assessed the effects of low boron diets on embryonic and fetal development in Rodents in four studies.
In the first study, rat dams were fed either a low (0,04µg B/g) or an adequate (2,00µg/g) B diet. No marked effects on fetal growth or development are reported. However, the authors point out that "Low" and "Adequate" do not **imply deficiency or adequacy** : " *0.04µg/g of diet is an amount that certainly represented a very low level of intake. 2µg/g of diet also resulted in a significant reduction in blood B concentration in weanling rats previously fed a commercial rodent diet (these diet typically contain 12.0 – 14.0 µgB/g. So whether 2 µg/g represents an adequate B intake is an issue that* ***needs further research***."
Concerning the reproductive outcome with low B diet, the study reported no differences in fetal BW and length, or in the external morphology and skeletal structures of the foetuses. As stated in the study, " *one interpretation of this study could be that B is not essential for mammalian reproduction.*"
Based on the conclusion of the first study, we cannot therefore agree with the statement on page 91 in the dossier that "*Early embryonic development was impaired in rodents fed boron deficient diet*".

In the third study carried out in the Lanoue et al (1998) article, the effects of Boric Acid exposure on the *in vitro* preimplantation development of mouse embryos have been investigated. Preimplantation development was evaluated by determining the number of embryos reaching the blastocyst stage after 72h of culture and by counting the number of cells in fixed blastocysts. The figure below indicates the frequency of blastocyst formation expressed as percent of baseline T6 medium: addition of low amount of BA to the medium (6-12µM) increased the frequency of blastocyst formation but it was reduced by 25% at 2000µM and by 75% at 4000µM BA (statistically significant).

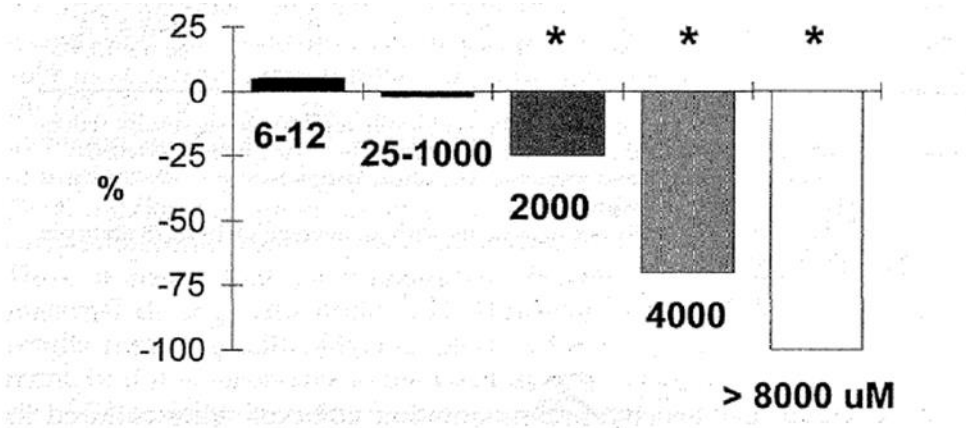

Fig. 7. Effects of varying concentrations of BA on the frequency of blastocyst formation expressed as percent of baseline T6 medium, indicated as 0. *Indicates statistical differences from baseline medium. Note the ameliorative effect of addition of low amounts of BA on early embryonic differentiation in vitro.

The study further reported that "*Blastocyst cell number, an indicator of embryonic cell proliferation, was more susceptible to the effects of BA and may be a better marker for determining toxicity threshold levels. When expressed as percent of control, 50-1000µM boric acid decreased blastocyst cell number by 25% and 2000-4000 µM by 50 %; blastocysts did not form at concentration of BA > 8000 µM"*(see figure below).

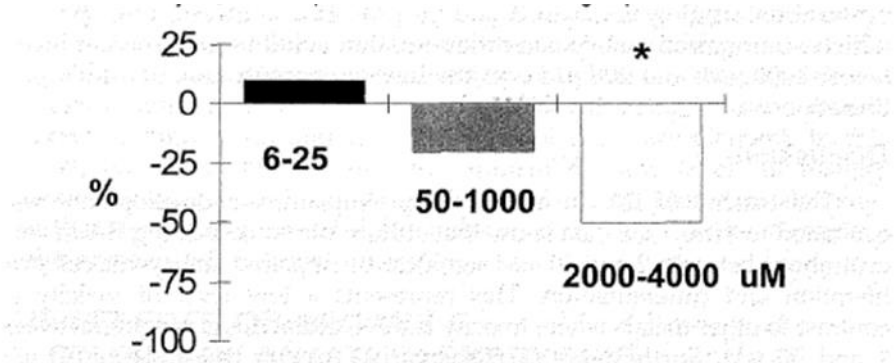

Fig. 8 Effects of varying concentrations of BA on blastocyst cell number expressed as percent of baseline T6 medium, indicated as 0. *Indicates statistical differences from baseline medium.

Although we recognize the limit of the *in vitro* studies, the outcome of the Lanoue et al (1998) study indicates BA-induced embryotoxicity which is not negligible. We would request DS to mention explicitly the findings observed in each study.

Endocrine disrupting properties

The Duydu et al. study (2011) indicates a significant higher mean FSH and LH levels at the high exposure group. The mean FSH level is significantly higher than the control group and the mean LH level is significantly higher than the medium group(see table below).

Table 4 Hormone and total PSA levels in workers

Exposure groups	Control (C)	Low exposure (L)	Medium exposure (M)	High exposure (H)	*P* value
Total PSA ng/mL	1.18 ± 0.62 (0.28–3.04)	1.22 ± 0.70 (0.34–4.34)	1.30 ± 0.94 (0.40–4.07)	1.25 ± 0.65 (0.31–2.76)	>0.05
FSH mIU/mL	5.97 ± 2.71 (2.06–17.40)	5.26 ± 2.39 (1.63–17.40)	4.97 ± 2.29 (1.81–14.10)	7.47 ± 6.36 (1.81–40.20)	<0.05(*)
LH mIU/mL	4.15 ± 1.77 (1.49–8.91)	4.30 ± 2.00 (1.41–11.80)	3.67 ± 1.34 (1.29–7.15)	5.38 ± 3.20 (1.95–20.00)	<0.05 (M-H)
Total testosterone ng/dL	351.78 ± 133.84 (159–907)	337.40 ± 118.64 (127–773)	347.30 ± 110.91 (157–668)	329.56 ± 106.04 (95.9–581)	>0.05

Mean ± SD, range in *brackets*. * The global null hypothesis that all group means are equal is rejected, but the pairwise Mann–Whitney U tests provide no *P* values below 0.05 after adjustment for multiple testing (Bonferroni-Holm). M-H: The global null hypothesis is rejected and the only significant pairwise difference is between medium and high-exposure group

Besides, Acid Boric is listed in the Danish Environmental Protection Agency's list of Undesirable Substances: the substance is classified as Category 1, substance for which evidence of endocrine-disrupting properties has been found in at least one live organism.

We would ask to the DS if the potential Endocrine properties have been assessed and which rationale has been taken into account for not mentioning those properties in the dossier.

Beneficial effects

On page 104 of the dossier, it is stated that "*A recent review of evidence for the essentiality of dietary boron shows that boron meets the criteria for* ***essentiality in humans*** *(Hunt 2007, 2012)…2) it is present in healthy tissues of different animals* ***at comparable concentrations****; 3) toxicity results only* ***at relatively high intakes*** *; 4)* ***tissue concentrations during short term variations*** *in intake are maintained by homeostatic mechanisms…*". We cannot support this statement without any valuable data. More detailed data from the Hunt studies are requested in order to assess the beneficial effects of dietary boron in humans.

Conclusions

We do not consider the new studies presented in the dossier as supportive evidence for the classification proposal. Therefore, we support the previous rationale for the classification Rep.1B H360 FD.

Regarding the testicular toxicity, there are studies in more than one species that demonstrate toxicity after exposure to Boric Acid by oral route. In rat and mouse, many adverse effects like a reversible inhibition of spermiation, testicular atrophy, degeneration of seminiferous tubules, reduced sperm counts and increased morphological aberrations in sperm cells have been observed. A NOAEL of 17.5mg B/kg bw/day for effects on fertility was derived in the Transitional Annex XV dossier based on the study of Weir (1966) and Fail (1991).

Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species being the rat with a NOAEL of 9.6 mg B/kg bw/day. This is based on a reduction in mean foetal body weight/litter, increase in wavy ribs and an increased incidence in short rib XIII at 13.3 mg B/kg bw/day. The reduction in foetal body weight and skeletal malformations had reversed, with the exception of short rib XIII, by 21 days post natal. At maternally toxic doses, visceral malformations observed included enlarged lateral ventricles and cardiovascular effects.

Editorial comments:

- Page 51 : In the study of Korkmaz et al. (2006), the average age of women into the control group is 35.83 ± 83. Then the most elderly women take into account had nearly 120 years largely the age of menopause.
- Page 59 : In the study Yazbeck C & Huel G (2006), it is mentioned that a negative association between blood delta-aminolevulinic acid dehydratase activity and placental boron was discovered and a potential boron threshold for this association was estimated. However, these threshold is not indicated.
- Page 67 : In the study of Duydu Y et al. (2011), the result mentioned for semen boron concentrations in the high exposure group is 1875.68~~.2255.07~~ ± 2255.07.
- Page 121 : Volume and page are lacking in the article of Sayli BS (2003), Low frequency of infertility among workers in a borate processing facility, Biological Trace Element research.

12. **Detailed Comments on Boric Acid, CLH Report, 20 June 2013** – submitted by Federchimica on 28.06.2013 (identical to Detailed Comments on Boric Acid, CLH Report, 20 June 2013 – submitted by the European Borates Association A.I.S.B.L. on 21.06.2013)
13. **CLH report on Boric acid, EBA's comments submitted to ECHA, EXECUTIVE SUMMARY, 20 June 2013** – submitted by Federchimica on 28.06.2013 (identical to CLH report on Boric acid, EBA's comments submitted to ECHA, EXECUTIVE SUMMARY, 20 June 2013 by the European Federation of Corrugated Board Manufacturers on 21.06.2013)

CONFIDENTIAL ATTACHMENTS RECEIVED:

1. **Public consultation – boric acid (CAS 10043-35-3), confidential version** – submitted on 12.06.2013 by a company-downstream user from Germany

2. **Comments on REACh Annex XV considering boric acid (EC# 233-139-2)** – submitted on 14.06.2013 by a company-manufacturer from The Netherlands
3. **Report for cyto toxicity and biocompatibility of boric acid soultution in eye care products - confidential version** – submitted on 20.06.2013 by a company-downstream user from Germany
4. **Confidential attachment** – submitted on 27.06.2013 by a company-manufacturer from France
5. **Expert Scientific Opinion: Comments on the Polish proposal to downgrade boric acid regarding classification and Labeling for reproductive and developmental toxicity –** submitted on 26.06.2013 by an individual from Germany
6. **A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats (draft report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
7. **A 28-Day Oral (Gavage) Dose Range Finding Toxicity Study of Zinc Borate 2335 in Sprague Dawley Rats (executive summary)** - submitted on 27.06.2013 by the European Borates Association (EBA)
8. **An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate 2335 in Rats (draft report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
9. **An Oral (Gavage) Dose Range-Finding Prenatal Developmental Toxicity Study of Zinc Borate 2335 in Rats (executive summary)** – submitted on 27.06.2013 by the European Borates Association (EBA)
10. **In vitro Embryonic Stem Cell Test with Zinc Chloride and Boric Acid (draft report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
11. **In Vitro Embryonic Stem Cell Test With Zinc Chloride And Boric Acid (executive summary)** – submitted on 27.06.2013 by the European Borates Association (EBA)
12. **TESTICULAR TOXICITY EVALUTATION OF THE COMBINED EFFECT OF BORIC ACID WITH ZINC CHLORIDE USING BIO-ALTER TECHNOLOGY (STUDY PHASE 2) (draft report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
13. **Testicular Toxicity Evaluation of the Combined Effect Of Boric Acid With Zinc Chloride Using Bio-Alter Technology (executive summary)** – submitted on 27.06.2013 by the European Borates Association (EBA)
14. **Firebrake 415: Twenty-Eight Day Sub-Acute Oral (Gavage) Toxicity Study in The Rat (final report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
15. **Firebrake 415: Twenty-Eight Day Sub-Acute Oral (Gavage) Toxicity Study in The Rat (executive summary)** – submitted on 27.06.2013 by the European Borates Association (EBA)
16. **Single-Dose Oral (Gavage) Toxicokinetic Study of Zinc Borate 2335 in Sprague-Dawley Rats (final report)** – submitted on 27.06.2013 by the European Borates Association (EBA)
17. **Single-Dose Oral (Gavage) Toxicokinetic Study of Zinc Borate 2335 in Sprague-Dawley Rats (executive summary)** – submitted on 27.06.2013 by the European Borates Association (EBA)