Best Practices in Interpreting Developmental Toxicity Data for Classification and Labeling

A satellite workshop to the 45th Annual Meeting of the European Teratology Society

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Boric acid and borates

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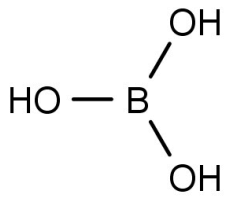


Commission Working Group of Specialised Experts (2004)

Conclusion: Boric acid and Borates

- The evidence from different animal species 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.
- The **effects observed across species were very similar**, both in nature and effective doses (mg boron per kg body weight per day).
- The **epidemiological studies** in humans are **insufficient** to demonstrate the absence of an adverse effect on fertility. Lacking of epidemiological studies on development.
- Regarding the relevance of the animal data to humans the Specialised Experts considered **kinetic and dynamic aspects** in relation to exposure levels that **could potentially be experienced by humans**.
- The available data on **kinetics do not indicate major differences between laboratory animals** and **humans**. It is not known whether there are significant differences in the dynamics between humans and laboratory animal models and **in the absence of such knowledge it must be assumed that the effects seen in animals could occur in humans.** On the basis of kinetic and dynamic considerations it is assumed that the animal data are relevant to humans.

Commission Working Group of Specialised Experts (2004)

UNCERTAINTY!!!

√ Potential human exposure levels via inhalation and oral routes could be within one order of magnitude below the NOELs for reproductive toxicity found in animal studies

√ The **threshold level for effects in humans is not known** but it cannot be excluded that **it could be below the level causing vomiting** in humans. Given the clear effects on fertility and development seen in animal models that are considered as relevant to humans the Specialised Experts recommend to classify boric acid and the borates with Repr. Cat. 2: R60-61.

CLP Repr. 1B H360FD

Health hazard

May damage fertility.
May damage the unborn child

1999

Initial proposal from DK in 1999

Clear effects on fertility in three different species (rat, mouse, dog)

Human data should normally not be used to negate animal data

For development: similar malformation seen in rats, mice and rabbits, no severe maternal toxicity

2013

On 2013 PL proposed to revise the current harmonised Repr. 1B classification of boric acid and to remove the classification for fertility effects and to downgrade the classification for developmental effects from category 1B to 2 (Repr. 2, H361d).

According to PL, extensive evaluations of sperm parameters in highly exposed workers demonstrated no effects on male fertility, justifying no classification.

While no developmental effects were seen in highly exposed populations, the epidemiological studies of developmental effects were not considered to be as robust as the fertility studies, and would therefore warrant classification in reproductive toxicity category 2 (H361d).

PL concluded that based on adverse developmental effects of boron in rats and rabbits, boric acid should be classified with Repr. 2, H361d ‘Suspected of damaging the unborn child’ according to CLP.

Studies of reproductive toxicity and repeated dose toxicity studies in mice, rats and dogs clearly indicate that boron (B) impairs fertility through an effect on the testes. The effects observed in the different species are similar in nature. Based on data from the 2 years feeding study with boric acid in rats (Weir, 1996), the overall NOAEL for fertility is therefore 100 mg/kg bw/day, equal to 17.5 mg B/kg bw/day. This conclusion is supported by the study with 4 disodium tetraborate decahydrate (Weir, 1996). **There are no indications that the impaired fertility is secondary to other toxic effects.**

Developmental toxicity (malformations) was clearly observed in studies in rats and rabbits, the rat being the most sensitive species, with an overall NOAEL of 9.6 mg B/kg bw/day. Malformations consisted primarily of anomalies of the eyes, the central nervous system, the cardiovascular system, and the axial skeleton. The most common malformations were enlargement of lateral ventricles in the brain and agenesis or shortening of rib XIII. **There were no indications that the developmental effects were secondary to maternal toxicity.**

RAC indicated that the mechanism of the teratogenicity was possibly an **altered hox gene expression**, caused by inhibition of histone deacetylases, a mechanism that is likely to be **also relevant for humans**.

RAC ECHA
EUROPEAN CHEMICALS AGENCY

There are a number of **cross sectional epidemiological studies** available on cohorts of workers from China, Turkey and the US on the potential effects of boron exposure on parameters mainly related to fertility among workers occupationally exposed to B.

The average daily boron exposure for the high exposure groups in these studies were estimated to be 1.8 mg B/kg/day (n=16), 0.2 mg B/kg/day (n=39) and 0.4 mg B/kg/day (n=109) (Scialli et al., 2010, Duydu et al., 2011, and Whorton et al., 1994, respectively). **Average daily exposure values in these workers were one to two orders of magnitude below the lowest observed adverse effect levels (LOAEL) for fertility in mice** (Fail et al., 1991, 1998), and for developmental toxicity in rats (Price et al., 1994, 1996).

No effects were observed

In conclusion, based on the adverse developmental and fertility effects of boric acid in different species, **RAC does not support the proposal from PL** to revise the current harmonised classification of boric acid (index number 005-007-00-2 in Annex VI to the CLP Regulation (EC) No 1272/2008). Boric acid should be classified with Repr. 1B, H360FD 'May damage fertility. May damage the unborn child.' according to Regulation (EC) No 1272/2008. T

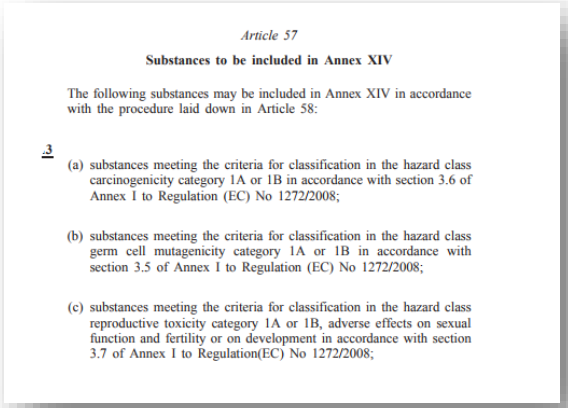
Boric acid has many uses for consumers and professionals. It is known for its antiseptic properties.

Boric acid is used in some nuclear power plants since reduces the probability of thermal fission by absorbing some thermal neutrons.

Boric acid is used as fertiliser

February 2010

SVHC



Article 57

Substances to be included in Annex XIV

The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

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(a) substances meeting the criteria for classification in the hazard class carcinogenicity category 1A or 1B in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008;

(b) substances meeting the criteria for classification in the hazard class germ cell mutagenicity category 1A or 1B in accordance with section 3.5 of Annex I to Regulation (EC) No 1272/2008;

(c) substances meeting the criteria for classification in the hazard class reproductive toxicity category 1A or 1B, adverse effects on sexual function and fertility or on development in accordance with section 3.7 of Annex I to Regulation(EC) No 1272/2008;

Annex XV dossier
PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS SUBSTANCE OF VERY HIGH CONCERN (SVHC)

The classification of the substance in Commission Regulation shows that the substance meets the criteria of Article 57 (c) of REACH.

MSC
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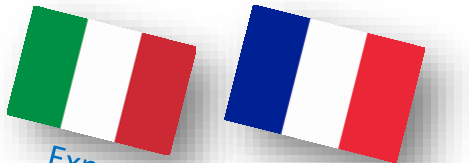
The substance has been included in the Candidate List on 18.06.2010

Recommendation of the European Chemicals Agency of 1 July 2015
for the inclusion of substances in Annex XIV to REACH
(List of Substances subject to Authorisation)

Draft Annex XIV entries									
#	Substance	EC number	CAS Number	SVHC-relevant intrinsic properties*	Latest application date pursuant to REACH Art. 58 (1) (c) (ii) **	Sunset date	Review periods	Exempted uses or categories of uses	Exemptions for PPORD
12	Boric acid	233-139-2, 234-343-4	10043-35-3, 11113-50-1	Toxic for Reproduction (category 1B)	Date of inclusion in Annex XIV plus 27 months [5)]	Latest application date plus 18 months	None	None	None
13	Disodium tetraborate, anhydrous	215-540-4	1330-43-4, 12179-04-3, 1303-96-4	Toxic for Reproduction (category 1B)	Date of inclusion in Annex XIV plus 27 months [5)]	Latest application date plus 18 months	None	None	None
14	Diboron trioxide	215-125-8	1303-86-2	Toxic for Reproduction (category 1B)	Date of inclusion in Annex XIV plus 27 months [5)]	Latest application date plus 18 months	None	None	None
15	Tetraboron disodium heptaoxide, hydrate	235-541-3	12267-73-1	Toxic for Reproduction (category 1B)	Date of inclusion in Annex XIV plus 27 months [5)]	Latest application date plus 18 months	None	None	None

Reasons for prioritising boric acid:

Boric acid is classified as toxic for reproduction, cat. 1B (meeting the criteria of Art. 57 (c) of the REACH Regulation). The amount of the substance used in the scope of authorisation is very high. The substance is used at industrial sites and by professional workers. Furthermore, the substance is used in articles. Boric acid received high priority among the substances on the Candidate List assessed; hence ECHA has recommended it for inclusion in Annex XIV



Expressed concern for the inclusion

The majority of the MSC agreed to the prioritisation of the boron compounds, however, **six MSC members** provided a minority position against the inclusion of boron compounds in the 6th recommendation. They argue that the important use of boric acid in nuclear power plants is covered by EU legislation and that therefore the environmental and health risks are managed efficiently. They further argue that the essential use of boron as micronutrient in fertilisers cannot be replaced.

Borates have not yet been included in the Annex XIV

Conclusions

No evidence from Epidemiological studies with uncertainties

Socio-economic factors

Clear evidence from Animal studies

Socio-economic factors do not influence C&L