CLH report on Disodium octaborate Tetrahydrate

EBA's comments submitted to ECHA

EXECUTIVE SUMMARY

The European Borates Association (EBA) accepts that there is a reproductive effect of certain boron compounds in laboratory animals under test conditions and that read across between boric acid and disodium tetraborates and disodium octaborates is applicable. However, the EBA questions the relevancy of these data to consider disodium octaborate tetrahydrate as meeting the classification and labeling criteria of Category 1B as is proposed in this CLH Report. The EBA is of the view that a Repr. Category 2 H361d classification is appropriate.

Although the CLH Report has given some consideration to data not previously reviewed at the time of the original harmonized classification of boric acid in 2008, some key information has been omitted. Secondly, new studies have only just become available or are still ongoing which investigate the protective effect of innately higher background levels of zinc in humans compared to laboratory animals have on the toxicity of boric acid. Finally, the CLP Regulation provides that weight of evidence should be used to determine the category of classification, and this evaluation is missing from the CLH Report.

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

- **Worker exposure studies:** No evidence of developmental effects in humans attributable to boron has been observed in studies of populations in China, Turkey and Chile with high exposures to boron. Furthermore, while boron has been shown to adversely affect male reproduction in laboratory animals, studies of highly exposed boron industry workers consistently show no reproductive effects attributable to boron. Workers in boron mining and processing industries represent the maximum possible human exposure.
    - The highest exposed workers in China were exposed to about 5 mg B/kg/day, which is more than 100 times greater than the average daily exposure of the general population.
    - In the Turkish studies, the mean calculated daily boron exposure of the highly exposed group was 14.45 ± 6.57 (3.32–35.62) mg B/day. As with the Chinese study, there were no negative effects observed for boron exposure on the reproductive toxicity indicators (concentration, motility, morphology of the sperm cells and blood levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone), and prostate specific antigen (PSA) levels.
    - The Chinese and Turkish semen studies in highly exposed workers are a major source of information as to human reproductive toxicity. These are the most exposed workers with exposures measured directly from food, drink and inhalation. In addition, as semen analysis was performed (a very sensitive detection method for

testicular damage) the Chinese and Turkish workers studies are the most sensitive boron studies that have been carried out to date.
    - These studies show that humans are not more sensitive to fertility toxic effects than laboratory animals.

- **Protective effect of zinc in humans:** A key difference between humans and laboratory animals relative to boric acid toxicity is the large zinc stores in humans compared to laboratory animals. Zinc has been shown to protect against testicular toxicity of chromium, cobalt and cadmium and developmental toxicity of cadmium. Zinc has also been shown to protect against developmental and fertility effects of boric acid in animal and *in vitro* studies including: low acute toxicity of zinc borate, increased fertility NOAEL in 28-day toxicity studies of zinc borate, increased NOAEL for developmental effects (reduced fetal body weights) in a zinc borate developmental dose range finder study, a dose dependent reduction in the boric acid inhibition of differentiation of embryonic stem cells in an embryonic stem cell test, and absence of effects on spermatogenesis in the presence of zinc in boric acid treated cultures of seminiferous tubules. 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.

- **Effect of boric acid on HDACi and Hox genes:** 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 bw 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 on 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.

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

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