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Comments on Strategi for risikohåndtering af visse borstoffer

Comments on the use of certain references used in the Danish survey report on boric acid and sodium borates (part of the LOUS review) used as the basis of this risk management strategy document.

- *ECHA/transitional annex XV reports (2009a & b) for boric acid and disodium tetraborate anhydrous and the HERA report (2005)*
  The transitional dossiers do not provide the latest information submitted by industry. The transitional dossiers have been updated as a result of registration under REACH in 2010 and have been spontaneously updated in 2012 and 2014 in respect of new hazard data for both human health and the environment that were not available in 2009. These additional data include epidemiological data from Chinese and Turkish workers and data demonstrating that it is improbable that boric acid will cause reproductive or developmental effects in humans.

- *RPA (2008)*
  The RPA report (2008) does not portray a correct overview of the market size and uses of borates today.
  - The volume summary given in the RPA 2008 report includes sodium perborate which is not a substance included in the review by LOUS. This leads to a misrepresentation of the volumes of boric acid, sodium tetraborates and boric oxide that are supplied specifically into the detergents market. EBA 2012 data indicates that only 1.5% is supplied for enzyme stabilisation in detergents. Even that volume of sodium tetraborate which is sold as a precursor for sodium perborate manufacture has sharply declined since 2008. Further, the majority of the sodium perborate manufactured in Europe is for export.
  - Although it is not possible to comment on the specific imports and uses in Denmark, we can comment that the overall borate volumes in the EU market have shown a significant and continuing decline since 2008, stabilising since 2012 at around 300,000 metric tonnes.
  - The REACH registration dossiers should be used to identify the current uses and exposures to these borates as this represents the current situation given that REACH registration has been required for these substances since 2010 and that those dossiers have been updated twice since.

***3.3.2. Sundhedsvurdering* (Health Assessment)**

Irritation – Respiratory tract

Strategy Document Statement
In humans, the critical effects after inhalation of dust containing boric acid/borax nose and eye irritation, throat irritation, coughing and shortness of breath. Human data and data from animal experimental studies indicate that boric acid/borax works in the

airways by annoying levels above 0.8 mg B/m3, which is considered to be non-impact-level.

RTM Comment

Acute irritant effects are extensively documented in human workers exposed to sodium borates (Wegman et al. 1991; Garabrant 1984, 1985; Woskie et al., 1994, 1998; Cain et al., 2004, 2008). Symptoms include nasal and eye irritation, throat irritations, cough, and breathlessness. However, boric acid exposure was only studied by Garabrant 1984 and Cain et al. 2008. The Garabrant 1984 study did not distinguish which of the two exposures (boron oxide or boric acid) was associated with reported symptoms. Boron oxide reacts exothermically with water to form boric acid suggesting a possible mechanism for boron oxide irritancy. It is believed that these irritant effects are caused by the exothermic hydration of boron oxide to boric acid. Cain et al. (2008) reported a NOAEL for irritation among human volunteers inhaling 10 mg/m^3 boric acid, the highest exposure evaluated for boric acid. The exposures of 10 mg/m^3 evaluated in Cain et al. did not reach a level defined by the investigators as being irritating. Furthermore, for any given point in exposure time the dose-response curve had a very low slope, not characteristic of an irritant.

Cain et al. (2008) clearly state the levels of exposure did not reach the level considered irritating by subjects "…the highest levels studied here lay at the edge of where people would agree that feel in the nose becomes irritating, about 17-18 % carbon dioxide. None of the functions actually reached that concentration, though those for 2.5 mg/m^3 calcium oxide and 10 mg/m^3 sodium borate came close. "

In addition, a GLP airway sensory irritation respiratory depression (RD50) study of boric acid and sodium tetraborate pentahydrate (SB) was conducted in male Swiss-Webster mice based on the ASTM E981-04 (2004) standard test method of estimating sensory irritancy of airborne chemicals (Kirkpatrick 2010, Maier et al. 2014). The ASTM E981-04 sensory irritancy test (Alarie assay) has been demonstrated to be a reliable test for estimating sensory irritancy of airborne irritants and RD50s are a basis, at least partially, for OELs by ACGIH (Kuwabara et al. 2007). ECHA guidelines acknowledge the use of the Alarie assay in assessing respiratory irritation.

It was not possible to achieve an aerosol concentration high enough to result in a 50% respiratory depression (RD50) in mice for boric acid or sodium tetraborate pentahydrate based on the results in the mouse sensory irritation model. The highest concentration of boric acid that was achievable with acceptable control of the aerosol concentration was 1096 mg/m3 with a %RD of 19%. Based on these results, the RD50 is > 1096 mg/m3 for boric acid. The ASTM standard uses the value of 0.03 x RD50 for estimation of threshold limit values (TLV). Alarie et al. (2001) has established that a value of 0.01 x RD50 as the concentration where no sensory irritation would be seen in humans. Therefore, although the highest achievable concentration was below the RD50 value for boric acid, based on the high aerosol concentrations achieved with %RD values below 50%, it is clear that boric acid is not a respiratory irritant or at worst has an extremely low potency as a sensory irritant. Exposure to a mean boric acid concentration of 1096 mg/m3 resulted in a decrease in a 19% reduction in respiratory rate, graded as slight irritation. A 9% reduction in respiratory rate was recorded at an exposure concentration of 221 mg/m3. This response was graded as no irritation (ASTM, 2004).

The RD_{50} for SB was >1704 mg/m^3 when male Swiss-Webster mice were exposed to a dust aerosol of the test substance as a single, 30-minute, head-only exposure. A

maximum exposure concentration of 1704 mg/m^3 resulted in a 33% reduction in respiratory rate, graded as moderate irritation. The lowest exposure concentration of 186 mg/m^3 resulted in a respiratory rate reduction of 11%, graded as no irritation.

The practical side of these results is that occupational exposure limit of 10 mg/m^3 total particulate will prevent any sensory irritation in workers.

Acute toxicity

Strategy Document Statement
In humans, acute poisoning can occur after oral and inhalation exposure as well as after dermal exposure via damaged skin. A human oral lethal dose is quoted to be 2-3 g boric acid for infants, 5-6g boric acid for children, and 15-30 g boric acid for adults (ECHA/RAC opinion (2010b). This may be the reason that some of the sodium borates have been classified as Acute Tox4; H302 in the company notifications to ECHA.

RTM Comment

Sodium borates are not classified for acute oral, dermal or inhalation toxicity in the Borate REACH consortium joint registration dossiers.

In the literature, the human oral lethal dose is regularly quoted as 2-3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults based on an old case review by Goldbloom and Goldbloom (1953). However, this data is largely unsubstantiated and considerable confusion surrounds differences between acute and chronic boric acid ingestions. In most cases it is difficult to make a good quantitative judgment particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions (Culver and Hubbard, 1996).

A review of previously reported cases indicates that much higher blood levels are well tolerated (Litovitz et al. 1988). Of 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). Litovitz et al. (1988) conducted a meticulous review of prior reports of boric acid poisoning and found that prior reports of toxic effects following single acute ingestions of boric acid are few in number. Only two cases from the 1920s are the only fatalities following the acute ingestion of boric acid or sodium borate reported in the medical literature. The first case is a 66 year-old man following the accidental ingestion of 1 to 1.5 oz of borax (sodium borate) powder mistaken for a saline cathartic and a second case in 1928 of a fatality in a 53-year-old woman following the ingestion of four pancakes made from flour containing 51 % sodium borate. The authors found that the majority of acute boric acid ingestions produce no toxicity and that boric acid ingestions produce minimal toxicity at serum boric acid levels of 340 µg/mL or less.

3.3.4. Identifikation af miljø- og sundhedsrisici (Identification of Environmental and Health Risks)

Strategy Document Statement
The human exposure from food and drinking water alone can result in an exposure that exceeds Derived No Effect Level (DNEL) of 0.09 mg B/kg body weight/day.

RTM Comment

Based on the identified NOAEL value of 9.6 mg B/kg bw/day for developmental effects established in a prenatal rat study using boric acid (identified as the key study), a DNEL consumer = 0.096 mg B/kg bw/day could be established using the default assessment factor of 100. This value is generally rounded to 0.1 mg B/kg bw/day, not 0.09 mg B/kg bw/day as cited in the strategy document.

Some members of the RAC during the tenth meeting of the RAC pointed out that several elements of the risk assessment of boric acid and borate compounds in photographic applications had been over estimated such as the DNEL value and several elements of the exposure worst case scenarios. Considering the toxicokinetic profile or boron and boron compounds it was considered that the 10x10 assessment factor was an over conservative approach and that there were good scientific justifications to derogate from these default values. In fact, WHO had used a 6 (intraspecies) x10 (interspecies) uncertainty factor in deriving its Guidelines for Drinking Water Quality (2003 & 2009) for boron and, based on the same data, EFSA in 2004 had also utilised a combined assessment factor of 60.

However, because a quantitative estimation of the assessment factor to be used in the opinion would require an in-depth assessment of the toxicokinetic information and due to timeline constrains the RAC decided to utilise the 10x10 assessment factors. But the RAC also noted in the final opinion that there are grounds for derogating from the use of default values, and the use of the conservative default value could contribute to an overestimation of the risk (ECHA RAC 2010).

Based on the more commonly used AF of 60 and NOAEL of 9.6 mg B/kg bw/day, the DNEL value of 0.16 mg B/kg bw/day is derived.

The maximum worst case estimated exposure to boron as reported in the LOUS review Survey of Boric Acid and Sodium Borates (Borax) was 3.94 mg B per person per day, or 0.066 mg B/kg/day for a 60 kg person. However, studies by Rainey et al. estimated intakes around 1.2 mg B/person/day or 0.02 mg B/kg/day.

Therefore, based on a DNEL of 0.16 mg B/kg bw/day, human exposure from food and drinking water alone is well below the DNEL.

Food

Strategy Document Statement

Further, EFSA (2013) concluded that exposure to boron from its natural occurrence in the diet and from other sources (dietary supplements, food contact materials, feed for food-producing animals, cosmetics, oral hygiene products, etc.) already may lead to an exposure that exceeds the ADI.

RTM Comment

The Panel on Food Additives and Nutrient Sources added to Food (ANS) Panel also concluded that it is unlikely that a regular exceedance of the ADI occurs.

For children and adolescents, at the highest 95th percentile, exposure estimates indicate exceedance of this ADI. However, exposure to boron from its use as a food additive in the form of boric acid and sodium tetraborate in caviar is unlikely to occur on a regular basis. Therefore, the Panel noted that even at high consumption and in consumers only, it is unlikely that a regular exceedance of the ADI occurs.

Photographic applications

Strategy Document Statement

An example of this has been recently identified by the risk assessment Committee in ECHA, which found that the extra contribution from a practical application of photo chemicals containing boric acid/borax exposure could lead to a total that exceeded the DNEL value.

RTM Comment

No exceedances of the DNEL would have occurred had the more commonly used AF of 60 been used.

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