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Derivation of an occupational exposure limit for inorganic borates using a weight of evidence approach

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ABSTRACT

Inorganic borates are encountered in many settings worldwide, spurring international efforts to develop exposure guidance (US EPA, 2004; WHO, 2009; ATSDR, 2010) and occupational exposure limits (OEL) (ACGIH, 2005; MAK, 2011). We derived an updated OEL to reflect new data and current international risk assessment frameworks. We assessed toxicity and epidemiology data on inorganic borates to identify relevant adverse effects. International risk assessment frameworks (IPCS, 2005, 2007) were used to evaluate endpoint candidates: reproductive toxicity, developmental toxicity, and sensory irritation. For each endpoint, a preliminary OEL was derived and adjusted based on consideration of toxicokinetics, toxicodynamics, and other uncertainties. Selection of the endpoint point of departures (PODs) is supported by dose–response modeling. Developmental toxicity was the most sensitive systemic effect. An OEL of 1.6 mg B/m^3 was estimated for this effect based on a POD of 63 mg B/m^3 with an uncertainty factor (UF) of 40. Sensory irritation was considered to be the most sensitive effect for the portal of entry. An OEL of 1.4 mg B/m^3 was estimated for this effect based on the identified POD and an UF of 1. An OEL of 1.4 mg B/m^3 as an 8-h time-weighted average (TWA) is recommended.

1. Introduction

The inorganic borates are a commercially important series of related compounds that include boric acid and various tetraborate salts (Woods, 1994; Hubbard, 1998; ATSDR, 2010). Although boron is a naturally-occurring element that is widely found in environmental media, it almost always exists in combination with oxygen (e.g., boric acid and borate salts) (Moore, 1997). Some properties of borates are shown in Table 1. Interest in environmental and occupational exposures to inorganic borates reflects their significant commercial and consumer product uses and is reflected in significant activity in the regulatory and health risk assessment arena. Numerous agencies have developed recommended exposure guidance for a variety of scenarios, including general population exposures via the oral or inhalation route (US EPA, 2004; ATSDR, 2010; WHO, 2009). Boron compounds are encountered in a variety of occupations, such as mining, manufacturing, agriculture, and industrial processing, which has spurred additional efforts to develop inhalation-based limits geared to worker health protection (ACGIH, 2005; MAK, 2011). Absorption of borates via the oral route is nearly 100% and for the inhalation route 100% absorption is also assumed. In contrast to oral and inhalation routes of exposure, dermal absorption through intact skin is very low with a percent dose absorbed of 0.226 ± 0.125 in humans (Wester et al., 1998). Because dermal absorption of borates across intact skin is minimal, the dermal route of exposure was not considered relevant for derivation of an OEL. Moreover, requirements for risk analyses under European regulatory activities include derivation of derived no effect levels (DNELs) for a variety of exposure scenarios as an input to the chemical registration process (ECHA, 2010).

Continuing interest in occupational risk assessment of borates coupled with the availability of new inhalation toxicology data allows for further examination of the most appropriate basis for developing an occupational exposure limit (OEL). An updated analysis is of significant importance in the context of borate risk assessment. In addition, updating the OEL provides an opportunity to demonstrate the use of current international risk assessment frameworks related to chemical specific adjustment factors (IPCS, 2005) and weight of evidence and mode of action assessment (IPCS, 2007) principles as important tools in OEL setting. The current data sets also provide an opportunity for illuminating the

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Table 1
Physical properties of borates, from Bingham and Cohrssen (2012).

Compound	Formula	Formula weight	Weight percent B	Boron equivalent dose	Physical properties	Specific gravity(20 °C)	Melting point (°C)	Boiling point (°C)	Solubility
Boric acid	H_3BO_3	61.83	17.5	0.18	White waxy triclinic solid plates	1.435	170.9 in closed space	No data	In H_2O, 2.52% at 0 °C, 4.72% at 20 °C, 27.5% at 100 °C, soluble in MeOH, EtOH, slightly soluble in acetone, dimethyl ether
Boric oxide	B_2O_3	69.64	31.1	0.31	A White crystalline granules or powder	2.46 (crystals) 1.85 (powder)	450	1500	Slightly soluble in cold H_2O, soluble in hot H_2O; 4.0% at 20 °C H_2O
Disodium tetraborate pentahydrate	$Na_2B_4O_7{\cdot}5H_2O$	291.4	14.8	0.15	White, trigonal, crystalline solid	1.815	<200 closed space	No data	In H_2O, 1.52% at 0 °C, 3.2% at 20 °C, 51.2% at 100 °C; soluble in glycerol, ethylene glycol
Disodium tetraborate decahydrate (borax)	$Na_2B_4O_7{\cdot}10H_2O$	381.4	11.3	0.11	Colorless, monoclinic crystalline solid	1.73	62 in closed space	No data	In H_2O, 1.18% at 0 °C, 2.58% at 20 °C, 9.55% at 50 °C; soluble in EtOH,
Disodium tetraborate anhydrous	$Na_2B_4O_7$	201.27	21.5	0.21	Light gray glass	2.367 glass	741 crystalline	1575 (decomposes)	16.7% in MeOH at 25 °C, 30% in ethylene glycol at 25 °C
Disodium octaborate tetrahydrate	$NaB_8O_3{\cdot}4H_2O$	412.52	21.0	0.026	White crystalline granules	–	815	No data	In H_2O, 2.4% at 0 °C, 9.7% at 20 °C, 45.3% at 94 °C

landscape surrounding the complexities of setting guidance for sensory irritants, an area of occupational risk assessment that has garnered much attention (Gaffney and Paustenbach, 2007; Nielsen et al., 2007; Paustenbach, 2001; Triebig, 2002). We present a systematic analysis of the current data for inorganic borates to derive an update to currently recommended OELs.

2. Methods

2.1. Literature identification and selection

A literature search using online resources was conducted, including the National Library of Medicine's PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and TOXLINE (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE) databases, to identify relevant information for our analysis. The analysis also incorporates recently available unpublished GLP studies that are intended to be provided to regulatory bodies for chemical registration activities. The robustness of the literature search and critical study selection was confirmed by comparing the literature identified for the OEL to that of several comprehensive risk assessment reviews (ATSDR, 2010; ACGIH, 2005; MAK, 2011; WHO, 2009; US EPA, 2004).

2.2. Risk assessment methods and frameworks

Principles of occupational risk assessment were applied as the basis for the overall analysis (Haber et al., 2001; Nelson et al., 2011), including identification of potential adverse endpoints and selection of relevant uncertainty factors (UFs). Use of information to inform key decisions reflected a weight of evidence assessment influenced by data quality considerations. For this analysis we also used the philosophy of the mode of action (MOA) framework developed by the International Programme on Chemical Safety (IPCS, 2007) to inform the use of weight of evidence and MOA principles in support of OEL development. This approach was not applied in a formulaic manner for this assessment because the MOA for borate is already well-researched and is considered to be relevant to humans (US EPA, 2004). Application of the IPCS (2005) framework on chemical specific adjustment factors (CSAF) allowed for refinement of OEL values based on alternative preliminary candidate endpoints. Using an iterative process, an OEL estimate was generated for each candidate endpoint and its point of departure (POD); adjustments were made for each individual POD using chemical-specific data for toxicokinetics and toxicodynamics and accounting for other elements of uncertainty. The selected OEL value reflects the candidate endpoint that was most sensitive after application of uncertainty factors.

Most organizations that establish OELs do not have documented approaches for addressing areas of uncertainty and instead use a professional judgment approach (Haber and Maier, 2002). While not transparent, application of this approach is very evident in reading OEL documentation. In order to evaluate potential OELs, it is useful to structure the discussion around the U.S. EPA's approach (U.S. EPA, 1994) as modified by the IPCS (2005) to consider chemical-specific data, since the same overarching areas of biological variability and data-related uncertainties are often considered among most chemical health risk assessments. We used the U.S. EPA's benchmark dose modeling results to determine the dose–response and POD of systemic effects. The CSAF method (IPCS, 2005) was applied to address variability and uncertainties in extrapolating from the POD. Table 2 shows the breakdown of the chemical-specific adjustment factors and uncertainty factors for the developmental and sensory irritant effects used in our OEL derivation. Reproductive effects were examined, but were determined