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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

Table 2
Uncertainty factors (UFs) used in developing occupational exposure limits (OELs) for developmental and sensory irritant effects[a].

Uncertainty factor	Default uncertainty factor from U.S. EPA (1994)	Rationale for applied uncertainty factor (see separate reference list)		Data-supported uncertainty factor	
		Developmental effects	Sensory irritant effects	Developmental effects	Sensory irritant effects
Database	10	The likely sensitive effect was used as the basis of the OEL, so it is unlikely that additional studies would identify a more sensitive effect	The likely sensitive effect was used as the basis of the OEL	1	1
Interspecies – Toxicokinetics	10	Chemical-specific kinetic data were used to modify the UF (US EPA, 2004)	Human effects data were used, so no interspecies extrapolation was needed	3.3	1
Interspecies – Toxicodynamics				2.5	
Intraspecies – Toxicokinetics	3	Chemical-specific kinetic data were used to modify the UF (US EPA, 2004)	The subjects in the critical study were representative of a sensitive population	1.5	1
Intraspecies – Toxicodynamics				3.2	
LOAEL to NOAEL[d] adjustment	10	For both endpoints: BMC[b] modeling was used. The resulting $BMCL_{10}$[c] values serve as a sensitive point of departure (i.e., a surrogate for the NOAEL)		1	1
Subchronic to chronic adjustment	10	The window for toxicity was included in the critical study	Cain et al. (2008) show directly that the irritant response peaks shortly after exposure, and the epidemiology data suggest that longer-term effects on pulmonary function are not evident in workers at typical occupational exposure levels (Garabrant et al., 1985)	1	1
Composite factor				40	1

[a] The IPCS (2005) approach for chemical specific adjustment factors (CSAFs) was used.
[b] Benchmark concentration.
[c] Benchmark concentration lower limit associated with an excess risk of 10%.
[d] Lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL).

to be the least protective basis for OEL development due to a significantly higher POD and, therefore, were not further considered in the OEL derivations.

2.3. Dose–response modeling

Dose–response modeling was employed to identify POD estimates for the alternative critical effects (i.e., systemic toxicity and sensory irritant endpoints). For systemic toxicity the benchmark-dose modeling results from the United States Environmental Protection Agency (US EPA, 2004) assessment for developmental effects following oral dosing in rats were used. This technique is commonly applied for estimating the POD for risk assessment (U.S. EPA, 2012; Haber et al., 2001). This endpoint is directly relevant to occupational exposures and could serve as the basis for an OEL. Since inorganic borates are soluble, the systemic dose was converted to an inhalation equivalent based on the health-protective assumptions of 100% systemic bioavailability and default physiological parameters commonly used by organizations that derive exposure guidance (U.S. EPA, 1994).

For the sensory irritation endpoint, the CO_2 equivalent sensory response data from volunteers exposed to sodium tetraborate pentahydrate (sodium borate) in studies by Cain et al. (2004) were modeled. Among the endpoints measured by Cain et al. (2004), the CO_2 equivalent response was chosen for modeling since it was calibrated against a level of CO_2 response corresponding to an irritating sensation – the primary adverse endpoint of concern for portal of entry effects for occupational exposure to inorganic borates. Other possible response metrics (e.g., the amount of nasal secretion or nasal airway resistance) were also considered; these non-adverse effects were not judged as the most appropriate basis for assessing sensory irritation for OEL purposes since they are surrogate measures for the adverse sensory response of interest, for which we had a direct outcome measure. However, the concurrent presence of these objective findings with the subjective responses most relevant to the occupational risk endpoint of concern (i.e., human irritation) strengthens the reliability of the overall assessment (Arts et al., 2006). Pair-wise comparisons (reported by Cain et al., 2004) indicate the chemosensory response of sodium borate in the eye was ~2- to 4- fold less intense than for the throat and nose, respectively (Cain et al., 2008). Therefore, this analysis evaluated only the concentration–response data for nose and throat irritation from Cain et al. (2004).

Data were modeled using benchmark concentration (BMC) methods (Crump, 1984; U.S. EPA, 2012) in the US EPA (2005) Benchmark Dose Modeling Software (BMDS). Such modeling is a preferred technique in current risk assessments, compared to the traditional approach of identifying a no observed adverse effect level (NOAEL), and has been recommended as a tool for setting OELs in the international context (EC, 2011). The advantages of the BMC approach have been described extensively (Haber et al., 2001). Both the BMC and the BMCL (the lower 95% confidence bound of the BMC) were determined. The response data are CO_2 port numbers indicated by the test subjects to describe nose and throat sensations due to sodium borate exposure. The 20-min responses in Cain et al. (2004) were adjusted to derive estimated maximum response values. The ratio of the average of the 17- and 22-min responses (approximating the 20-min response) and the average of the 32 and 37 min responses (approximating the maximum response) from Cain et al. (2008) were used to compute the adjustment. The resulting ratios were 1.0 for nose irritation and 1.1 for throat irritation. These differences were considered negligible, indicating that response was near the maximum by the end of the 20-min exposure in the Cain et al. (2004) study. This assumption is supported by data from Cain et al. (2008) that shows little-to-no increase, and even some decline, in response beyond 20 min

of exposure. This consideration supported the use of the 20-min response data from Cain et al. (2004) to represent the maximum likely response for durations of exposures relevant for OEL setting in the context of establishing an OEL as a full-shift time-weighted average (TWA).

A CO_2 level of 15% was considered to be the experimental study threshold for sensory irritation, since subjects from Cain et al. (2004) noted irritation at concentrations between 15% and 20% CO_2; data from Cain et al. (2008) confirmed this range, with a median at 17.7% CO_2. Lower CO_2 levels produced sensation (an awareness of exposure, or chemosensory feel) without irritation (discomfort). Therefore, a benchmark response (BMR) of 15% CO_2, the lowest observation for sensory irritation based on data from Cain et al. (2004, 2008), was used in the BMC modeling. This value is supported by the qualitative statement from Cain et al. (2004) that very few subjects used the term irritation to describe the nasal sensation at 10% CO_2; some subjects reported irritation at 15%, and most at 20%. The use of the 15% value was considered appropriate, given the uncertainty in estimating a precise cut point. However, selection of this BMR is a health protective choice given the sensitivity and marginal toxicological severity of the endpoint and the use of a BMCL estimate, rather than the BMC for estimating the POD. With the BMR set at 15%, the BMCL represents the lower bound estimate for the concentration of sodium borate (mg/m^3) that elicits nasal sensations equivalent to those experienced during exposure to 15% CO_2.

Response data were normalized to reduce the influence of individual differences in sensitivity. Each individual's control response was subtracted from the corresponding response to sodium borate exposure. In this way, the data represent the response above control for each subject. The control group response was not modeled explicitly with the normalized data since the normalization process would transform it into a group with a response of 0% CO_2 and a SD of 0.0; the control group was, instead, implicitly taken into account via the normalization. Since the magnitudes of the responses were reduced by the normalization, the BMR used for the onset of sensory irritation was also reduced accordingly. The average of the raw control responses was subtracted from the 15% CO_2 threshold to obtain an adjusted BMR that was used as the selected cut point.

The Cain et al. (2004) data showed some inconsistency in the dose–response relationship. At all time points for the throat and most time points for the nose, the mean response to 10 mg/m^3 exposure is greater than the mean response to 20 mg/m^3. Additional findings from Cain et al. (2008) reported that subjects exposed to 10 mg/m^3 sodium borate responded at a level that fell between the response of the 5 and 20 mg/m^3 groups in the 2004 study, indicating that the dose–response inconsistency in Cain et al. (2004) likely occurs within the 10 mg/m^3 group. Models including this data point did not provide an adequate statistical fit. Based on these observations, the 10 mg/m^3 group was dropped from the BMC modeling analysis since data were available for both a lower and higher concentration that showed clear concentration–response behavior.

3. Results

The relevant human effects and toxicology data were analyzed to array candidate endpoints that might ultimately serve as the most sensitive basis for OEL derivation. Existing risk assessment documents allowed for a focused evaluation of two potential systemic effects of interest (reproductive or developmental toxicity), and portal of entry effects (sensory irritation of the upper respiratory tract). The potential OELs derived from the most sensitive systemic toxicity endpoint (developmental toxicity) versus portal-of-entry effects (sensory irritation) are shown in Fig. 1.

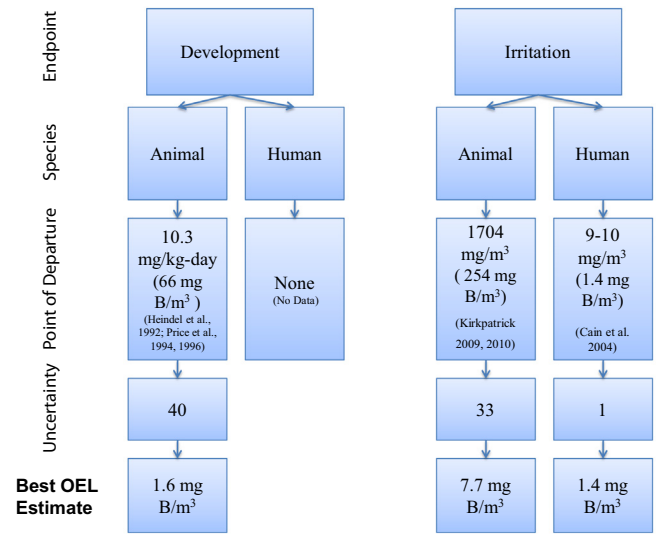

Fig. 1. OELs were derived using the IPCS (2005) framework; for both developmental and irritant effects, a potential point of departure (POD) was identified from both human and animal data when the data allowed. The UF used in the derivation of the potential OEL for developmental effects is summarized in Table 3. The UF for the potential OEL based on irritation in animals uses the ASTM standard (Schaper, 1993). For developmental toxicity endpoints, the POD was derived from oral dosing studies, which was converted to an inhalation equivalent (as described in the text). Qualitative information on developmental effects is available from the epidemiology literature, but the data were not adequate to identify a point of departure. The data for reproductive effects identified higher POD estimates and lower potential uncertainity factors, and would yield a higher OEL for systemic effects than the developmental toxicity endpoint. Thus, developmental toxicty was identified as the most protective systemic toxicity endpoint for inclusion in this figure. For sensory irritation, the human data are based on boron equivalents from modeling of data on irritant responses to sodium tetraborate pentahydrate. For the irritancy data in animals, the results shown are for boric acid, since they yielded a lower potential OEL. The results in the RD50 studies for sodium tetraborate pentahydrate were a POD of 1704 mg/m^3 (254 mg B/m^3) with a resulting OEL estimate of 51 mg/m^3 (7.7 mg B/m^3).

3.1. Reproductive toxicity

Toxicology studies indicate a potential concern for effects on the male reproductive tract. Testicular effects reported in dogs and rats by Weir and Fisher (1972) have been supported by adverse reproductive findings from numerous other studies in laboratory animals (see US EPA, 2004 for a comprehensive review). These effects, however, have not been observed in humans. Multiple modern epidemiological studies on boron-exposed cohorts have examined the relationship between boron exposures, both inhaled and ingested, and changes in reproductive outcomes. These studies did not identify any increased risk of adverse semen parameters or other reproductive effects (Duydu et al., 2011; Liu et al., 2006; Robbins et al., 2010; Sayli, 1998, 2001, 2003; Scialli et al., 2010; Whorton et al., 1994), despite the presence of higher blood boron levels in boron workers, as compared to controls (Duydu et al., 2011; Robbins et al., 2011; Xing et al., 2008).

Other potential reproductive effects have been identified in epidemiology studies of boron exposed populations, but they are not necessarily indicative of or correlated with other adverse or clinically observable reproductive effects and are limited in their application for risk assessment. A decrease in the Y:X sperm ratio was identified in male boron workers (Robbins et al., 2008). However, an earlier study did not identify a significant increase in the percentage of female offspring born to male boron workers

(Whorton et al., 1994). The lack of concordance in these two findings clouds the relevance of this finding for risk assessment. Chang et al. (2006) reported a significant delay in pregnancy, an increase in induced abortion, and a decreased number of live births among the families of Chinese boron workers, but this effect is likely related to lifestyle factors rather than boron exposure; after adjusting their models for the covariates of age, education, soybean, alcohol, and tobacco usage, and race, the authors found no significant relationship between these effects and boron exposure.

Overall, the epidemiology data indicate that there is little risk for adverse reproductive effects at the concentrations to which boron workers are exposed for two reasons: (1) the majority of studies showed no observable effect for reproductive parameters and (2) the few studies that did report effects were not consistent with the body of evidence and/or the effects reported were ascribed to confounding exposures, two important elements of causality analysis in epidemiology studies (Hill, 1965). Additionally, the doses associated with testicular effects in animal toxicology studies are higher than those associated with developmental toxicity. Since the UFs that would be applied to this endpoint do not differ significantly from those for the developmental endpoint, the OEL for reproductive toxicity would not be lower than for developmental toxicity. For this reason, an OEL for this endpoint is not further explored.

3.2. Developmental toxicity

U.S. EPA derived its reference dose (RfD) (2004) based on the 5% lower bound on the benchmark dose estimate ($BMDL_{05}$) of 10.3 mg B/kg-day for decreased fetal weight in rats (Allen et al., 1996), using data from several developmental toxicity studies (Heindel et al., 1992; Price et al., 1994, 1996). Other recent risk assessments (ATSDR, 2010; WHO, 2009) identified the same POD, and no new epidemiology or toxicology studies were identified for the current analysis that support lower POD estimates. The critical effect level of 10.3 mg B/kg-day was determined to be an appropriate POD for OEL development after adjustment to an inhalable concentration equivalent.

The US EPA (2004) divided the POD (10.3 mg B/kg-day) by a composite UF of 66 for deriving their Reference Dose (RfD). This composite factor was calculated by multiplying the subfactors of 3.3 for interspecies differences in toxicokinetics (based on data for boron clearance rates in rats versus humans), a default value of 3.2 for interspecies differences in toxicodynamics, a value of 2.0 for variability in human toxicokinetics (based on data on human variability in glomerular filtration rate), and the default factor of 3.2 to account for variability in human toxicodynamics. Application of the composite UF of 66 resulted in a RfD of 0.16 mg B/kg-day. The World Health Organization (WHO, 2009) chose the same POD as was used in the U.S. EPA assessment, but derived a different composite UF. Using international defaults in the CSAF methodology (which vary slightly from the U.S. EPA methods), WHO (2009) calculated a composite UF of 60.

For the current assessment, a composite UF of 40 was derived based on the IPCS (2005) approach for CSAFs and additional considerations appropriate for risk assessment in an occupational setting (see Table 2). The composite UF of 40 resulting from our analysis reflects the same CSAF considerations as applied in the US EPA (2004) and WHO (2009) assessments, but with further refinement of the toxicokinetic subfactor for human variability in sensitivity. The toxicokinetic adjustment factor for human variability was calculated in the US EPA (2004) assessment from data on the variability in glomerular filtration rate (GFR) during pregnancy; GFR was identified as the primary determinant of boron clearance rates. The US EPA (2004) modified the sigma method (Dourson et al., 1998) to calculate the lower bound of risk at 3 standard deviations (SD) instead of 2 with the goal of ensuring adequate coverage of preeclamptic women (the sensitive subpopulation), resulting in a recommended intraspecies (i.e., human variability) toxicokinetic adjustment factor of 2. The estimated lower bounds for acceptable risk at both 2 and 3 SDs, using the Sigma Method, are shown in Table 3. The intraspecies factor for toxicokinetic variability can be further reduced to a data-derived value of 1.5 for occupational assessment based on variability in GFR in populations after excluding preeclamptic women (Dunlop, 1981; Krutzén et al., 1992; Sturgiss et al., 1996). The results from these three studies were averaged to increase the sample size and therefore better reflect the overall population distribution, including median response and variability. The decision to average the results from these three studies also reflects that none of the available studies were significantly more robust than the others. Because the OEL is intended to protect working populations, it is not appropriate to include preeclamptic women, since they would not likely be represented in the work place. Of the total workforce, pregnant women represent a relatively small percentage of total workers. Women with preeclampsia represent an even smaller subset of this population; overall incidence of preeclampsia is estimated at roughly 3%, or less, of total pregnancies (Thornton et al., 2013; WHO, 2005). Women diagnosed with mild preeclampsia are given outpatient, and sometimes inpatient, treatment including blood pressure measurements, laboratory monitoring, physician visits twice weekly and, generally, bed rest, although this is no longer recommended as routine management of hypertension in pregnancy by the American College of Obstetricians and Gynecologists (ACOG, 2013). Women with preeclampsia are, therefore, unlikely to be working during this period of sensitivity. Although it is possible that a pregnant woman with preeclampsia could be found in an occupational setting, specifically if the woman had not been receiving prenatal care, the percentage of the working population, under such circumstances, would be very small. Additionally, working populations are more homogenous than general populations, so increasing the lower bound to 3 SDs instead of 2 is unnecessary for an occupational assessment, especially when preeclamptic women are excluded. Moreover, the GFR values for preeclamptic women are approximately 2 SD below those of healthy women (Krutzén et al., 1992), indicating that using the sigma-method with 2 SD, at most, is adequate.

Application of the principles of the IPCS MOA framework showed that the evidence is not sufficient to reasonably exclude the human relevance of the observed developmental effects in animals. Thus, developmental toxicity is considered the most appropriate potential systemic endpoint as the basis for the OEL. The best POD, based on currently available data, would be 10.3 mg of boron/kg-day (66 mg B/m^3) with a UF of 40, resulting in a best OEL estimate of 1.6 mg B/m^3 for developmental effects.

3.3. Sensory irritation

At extremely high aerosol concentrations in animal lethality studies, some respiratory effects do occur (e.g., nasal inflammation). However, none of the inorganic borates are highly toxic in acute lethality studies, with LC_{50} values for several different inorganic borates reported above 2000 mg/m^3, the highest concentration tested (reviewed in Hubbard (1998)). No effects on organ pathology (including of the respiratory tract) were noted and no signs of pneumoconiosis were evident at any concentration. The absence of both significant respiratory tract histopathology and acute lethality in animal studies is consistent with the epidemiology literature on the respiratory tract effects of inorganic borates (Garabrant et al., 1985; Wegman et al., 1994) and supports sensory irritation as the only significant respiratory tract response of interest for OEL development.

Table 3
Calculation of lower bound estimates for acceptable risk using the Sigma Method from Dourson et al. (1998) and information on glomerular filtration rates (GFR). Estimates indicate that a toxicokinetic (TK) uncertainty factor (UF) of 1.5 is appropriate based on the traditional sigma method approach based on 2 SD.

Study	Mean GFR (SD) (mL/min)	GFR at 2 SD below mean	GFR at 3 SD below mean	TK UF estimate based on Sigma-Method Value for 2 SD	TK UF estimate based on Sigma-Method Value for 3 SD
Dunlop (1981)	150.5 (17.6)	115.3	97.7	1.31	1.54
Sturgiss et al. (1996)	138.9 (26.1)	86.7	60.6	1.60	2.29
Krutzén et al. (1992)	195 (32)	131	99	1.49	1.97
Krutzén et al. (1992) (preeclamptic population)	128 (33.9)	60.2	26.3	2.13	4.87
Average (excluding preeclamptic population)	161.5	111.0	85.8	1.47	1.93

A generalized weight of evidence approach was used to integrate the results of several lines of evidence from the toxicology and human studies with the aim of characterizing the intensity of the sensory irritant response induced by exposure to inorganic borates and the concentration–response characteristics of this response. The lines of evidence considered, in order from most to least weight, were: (1) controlled human exposure studies; (2) occupational epidemiology studies; (3) inhalation-based sensory irritation studies in rodents; (4) standard hazard-based irritation assays by non-inhalation routes. The analysis of each of these lines of evidence and the resulting contributions of these data to developing a potency range for borate-induced sensory irritation for setting an OEL is provided below.

The results of the BMC modeling for nasal sensation response are summarized in Table 4. With the exception of the linear model, the resulting BMCLs are very similar. The quadratic model is the preferred model since it has the highest goodness of fit *p*-value and the lowest AIC value (both parameters indicating the best fit), while the absolute value of the chi-square residuals (i.e., a measure of local model performance in the range of the BMR) are similar across the models. The concentration–response data and quadratic model fit are shown in Fig. 2. The resulting BMCL of 9 mg/m^3 (1.4 mg B/m^3) is consistent with the observations made by Cain et al. (2004) that the perceived magnitude of response was significantly above background at 10 mg/m^3 sodium borate and higher. The maximum likelihood estimate (MLE) of the BMC is 13 mg/m^3 (2.0 mg B/m^3).

The results of the BMC modeling for the throat sensory response are summarized in Table 5. The linear model has the highest goodness of fit *P*-value, although the quadratic and Hill models perform nearly as well. For the power model, the power parameter is restricted to be greater than or equal to 1 to prevent an infinite slope in the concentration–response curve at the control dose, causing this model to be reduced to a linear model; resulting the same fit statistics. The absolute values of the residuals do not strongly favor one model over another because at 20 mg/m^3, they appear to be smaller (i.e., better) for the linear model, but if one considers the residuals at 5 mg/m^3, the Hill and quadratic models most closely match the data (i.e., have the smallest residuals). The AIC for the linear model is significantly better than the other models – reflecting superior overall fit and a smaller number of equation parameters. Thus, all of the models give roughly the same quality of fit to the experimental data, with the linear model somewhat better. The best estimates for the BMC are similar across the models; however, the BMCLs are nearly fivefold different from the lowest to highest estimate. There is sufficient model uncertainty to avoid picking a single model; therefore the results were averaged across the models. If the three results (excluding the power model result, since that reduced to the same mathematical formulation as the linear model) are averaged, a BMCL of ~8 mg/m^3 is obtained (or 1.2 mg B/m^3). This value is very close to the BMCL for nasal responses. Selecting the model averaging approach reflects that none of the BMC models used in this assessment are biologically based and to be preferred a priori, rather they are statistical in nature only and are not intended to infer a biological basis for selecting one curve form over another (U.S. EPA, 2012).

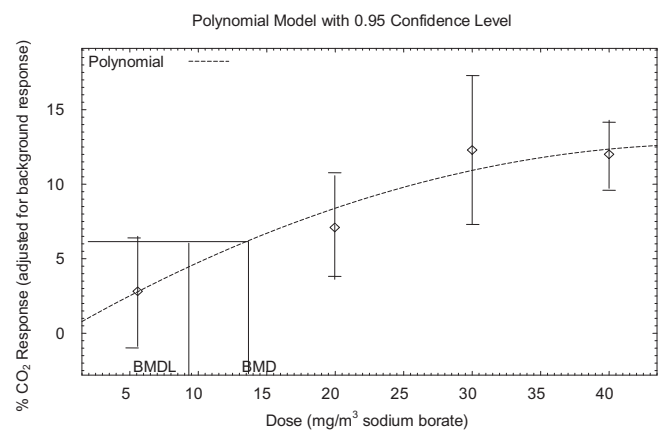

Fig. 2. Benchmark concentration analysis of nasal irritation data (measured CO_2 port equivalents) following 20-min exposures to sodium borate (Cain et al., 2004) estimates a BMCL of 9 mg/m^3 (1.4 mg B/m^3); this estimate is based on a BMR at the equivalent of 15% CO_2. The quadratic model best fits the data and is shown above.

Occupational epidemiology studies report that dust from inorganic borates can cause symptoms associated with ocular and respiratory tract sensory irritation. Several key studies are summarized in Table 6. The most commonly reported symptoms among exposed workers include dryness of the mouth, nose or throat, eye irritation, dry and/or productive coughs, and sore throat (Eisen et al., 1991; Garabrant et al., 1984, 1985; Wegman et al., 1994). Garabrant et al. (1984, 1985) also reported nose bleed, but this symptom was not identified in any other study. It is noteworthy that the workers in these studies were employed in a facility located in a desert environment, and such symptoms observed at higher rates than controls (including office workers) may reflect in part the general environmental conditions at this location. A

Table 4
Summary of benchmark concentration (BMC) modeling for nose irritation.

Model	Chi-square residual (at 5 mg/m^3)	Chi-square residual (at 20 mg/m^3)	AIC	*P*-value	BMC (mg/m^3)	BMCL (mg/m^3)
Linear	0.592	0.258	221	0.37	18	15
Quadratic	0.118	−0.67	221	0.54	13	9.3
Power	−0.182	−0.383	222	0.42	14	7.1
Hill	0.167	−0.613	223	0.23	13	7.4

Table 5
Summary of Benchmark Concentration (BMC) Modeling for Throat Irritation.

Model	Chi-square residual (at 5 mg/m^3)	Chi-square residual (at 20 mg/m^3)	AIC	*P*-value	BMC (mg/m^3)	BMCL (mg/m^3)
Linear	0.809	−0.121	234	0.81	17	14
Quadratic	0.628	−0.475	236	0.71	14	7.9
Power	0.809	−0.121	234	0.81	17	14
Hill	0.538	−0.532	236	0.72	13	3.0

lowest observed adverse effect level (LOAEL) for effects more severe than eye irritation was reported at an average boron oxide and boric acid particulate total level of 4.1 mg/m^3 measured as total dust using a 37 mm filter method cassette (Garabrant et al., 1984, 1985). The equivalent inhalable mass would be approximately 10 mg/m^3 based on demonstration that the 37-mm total dust sampler equipment under-samples suspended particles by factors ranging from 1.2 to 4.0 compared to the IOM sampler (Shen et al., 1991; Culver et al., 1994; Tsai et al., 1995; Werner et al., 1996; Katchen et al., 1998; Teikari et al., 2003; Vincent, 2007). The adjustment for inhalable mass is applicable to these reported upper respiratory tract effects since the IOM sampler would predict deposition of inorganic borate particles in the nose and throat (U.S. EPA, 1994). The dust particles associated with borate mining and processing typically have mass median aerodynamic diameters of 10–15 μm and in this environment the IOM sampler collects between 2 and 3 times more mass per unit volume of air than the total dust sampler (Culver et al., 1994; Katchen et al., 1998). A conversion factor of 2.5 has been suggested for converting "total" personal exposure measures from industries similar to the borate mining and processing facility to equivalent inhalable aerosol exposures (Werner et al., 1996; Vincent, 2007). This is further supported by paired 37 mm closed face cassette and 25 mm IOM sampling at a borate processing facility in France (Shen et al., 1991).

Symptoms related to pulmonary function or respiration were also reported, but were less common, with 5% of subjects reporting shortness of breath and chest tightness, and fewer than 2% reporting chest pain and hemoptysis (indicative of potential hemorrhage) (Garabrant et al., 1985). Pulmonary function measurements (e.g., forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC, peak flow rate (Vmax) and forced expiratory flow at 75% (FEF75) were unchanged (Garabrant et al., 1985; Hu et al., 1992). Hu et al. (1992) provided additional analysis on the concentration–response relationship of nasal irritation symptoms (Table 7) in the same cohort. These data indicate that, at concentrations approximating 10 mg/m^3 of inspirable borate, the probability of a worker experiencing an irritation event during a 6-h exposure period (TWA-6) is low (i.e., ~1%); a finding that supports the results of the BMC modeling (see Table 4) and the observation by Cain et al. (2004) that perceived response of sensory irritation will occur at approximately 10 mg/m^3 sodium borate and higher. A risk of 1:1000 is often used as a benchmark for acceptable risk probability for OEL setting purposes, stemming from risk assessments supporting OSHA permissible exposure limits (PELs), which are often for irreversible and severe effects. There is no published consensus on the acceptable percentage of the population affected at an OEL for minimal sensory irritation (Paustenbach, 2001; Gaffney and Paustenbach, 2007).

The sensory irritation potential of inorganic borates has also been investigated in a recent airway sensory irritation respiratory depression (RD50) study of boric acid and sodium borate conducted in male Swiss-Webster mice based on the ASTM E981-04 (2004) standard test method (Ball et al., 2012). For boric acid, a single 30-min exposure to boric acid dust aerosol at high concentrations produced a maximum decrease in respiratory rate of 24%. Clinical observations included opacity and partial closure of the eye at exposures greater than 513 mg/m^3, which were attributed to the high level of dust loading. These results were replicated in a second study that tested concentrations at the limits of the aerosol generation system employed (Ball et al., 2012) a 21% decrease in respiratory rate was seen at the highest boric acid concentrations tested of 1018 mg/m^3. Similarly to the results for boric acid, it was not possible to achieve an aerosol concentration high enough to result in 50% respiratory depression in mice for sodium borate based on the results in the mouse sensory irritation model. The highest concentration of sodium borate that was achievable with acceptable control of the aerosol concentration was 1704 mg/m^3 with a resulting decrease in respiratory rate of 33%. Based on these results, the RD50 is greater than 1704 mg/m^3 for sodium borate.

Although the highest achievable concentration was below the RD50 value for sodium borate, based on the high aerosol concentrations achieved with respiratory rate depression values below 50%, it is clear that boric acid and sodium borate have low potency as sensory irritants (see Fig. 3). The ASTM standard uses a value of 0.03 × RD50 for estimation of an occupational exposure limit (supported by the analysis of Schaper, 1993). Alarie et al. (1980) has established that a value of 0.01 × RD50 as the concentration where no sensory irritation would be seen in humans. The maximum achievable concentration of 1704 mg/m^3 sodium borate was below the RD50. Thus, based on the conclusions of Alarie et al. (1980), the product of 0.01 × 1704 mg/m^3 (the maximum achievable concentration) is 17 mg/m^3 disodium tetraborate pentahydrate (2.5 mg B/m^3), a concentration at which human sensory irritation would not be expected. Based on the ASTM method the OEL would be expected to be greater than 0.03 × 1704 mg/m^3 or 51 m^3 (7.6 mg B/m^3).

That absence of significant irritant potency in the RD50 assay (Ball et al., 2012) is consistent with observations from standard irritancy assays, which show that inorganic borates are not skin irritants. Inorganic borates range from negligible to mild as eye irritants. The lack of boric acid irritancy to mucosal surfaces is not surprising in view of the use of saturated boric acid solutions in eye wash applications (ATSDR, 2010). Overall, the results from the standard irritancy tests further highlight the likely sensitivity of the subjective responses from the human volunteer studies, suggesting that derivation of an OEL from such data is likely to be health protective.

Of the multiple lines of evidence regarding sensory irritation, the result of the human volunteer study by Cain et al. (2004) provides the most scientifically rigorous POD for the sensory irritation endpoint. Cain et al. (2004) concluded that perceived sensory irritation is significantly increased at concentrations approximating 10 mg/m^3 sodium borate and higher. This was selected as the point of departure for the sensory irritation OEL. This result was confirmed in our analysis by additional benchmark dose modeling from the Cain et al. (2004); where a POD of 9 mg/m^3 (or 1.4 mg B/m^3) was estimated. The most sensitive effect as well as the most relevant and reliable result derives from the human volunteers under controlled conditions. Given differences in the relative level of precision inherent in the study designs comparing well-controlled volunteer studies and work-place epidemiology, the results of Cain et al. (2004) are well supported by the occupational epidemiology literature. The most scientifically rigorous POD based on animal sensory irritation data would be 1704 mg/m^3 (254 mg B/m^3) from the RD50 studies; not only is this

Table 6
Summary of occupational epidemiology studies.

Concentration	Exposure measurement	Duration	Population	Responses	Comments	Reference
4.1 mg/m^3 in exposed environment (mean of 8 measurements)	Personal sampler collecting total particulate using 37 mm cassette during work shift	N/A for workers' exposure	Occupational exposure to boron oxide and boric acid	Eye irritation, dryness of mouth, nose or throat, sore throat, and productive cough. The response was reported as percent of group reporting symptoms.	These results cannot be used for deriving occupational exposure limits (OELs) because only exposure concentration of total particles was reported. The paper provided no information on particle size, or the relative exposures to boron oxide versus boric acid. In a later publication, the authors stated that in most of areas of refining plant, the dust was almost entirely borax, and in the mine, other mineral compounds were also present	Garabrant et al. (1984)
4.0 mg/m^3 as the concentration to cause minimal response.Control group exposed to 1.1 mg/m^3	Personal sampler collecting total particulate using 37 mm cassette during work shift	N/A for workers' exposure	Occupational exposure to $Na_2B_4O_7$ in anhydrous or various hydrated forms	At 4 mg/m^3, eye irritation in $\geqslant$ 5% workers; At 14.6 mg/m^3, dryness of the mouth, nose or throat (33%), nose bleeds and dry cough (15%) and sore throats and productive cough (8%). No information on statistical significance was reported for these responses	This study has the same issue as with Garabrant et al. (1984). In addition. There is no information on the statistical significance for each irritant responses reported. Questionnaires were administered weeks after air samples were collected, possibly introducing recall bias	Garabrant et al. (1985)
1 mg/m3, but no information on average exposure level in exposed group	Real-time total particulate exposure was measured with aerosol monitor. The particulate collected on the filter with the aerosol monitor was desiccated, and particle size determined by gravimetric method done by cascade impacter, not on 37 mm	4 days interval	Occupational exposure to sodium borate	Odds Ratio (OR) of 1.31 (CI: 1.08–1.59 from a logistic regression with 1 mg/m^3 increase in boron) for three or more symptom episodes over four days. Five irritation responses: eye, nose, or throat irritation, breathlessness, and chest tightness	Clear dose–response information (see following Table 1). Self controlled OR. There is no detailed information regarding particle composition and size	Eisen et al. (1991)
1.72 mg/m^3 (geometric mean of all exposed workers) Background level was 0.22 mg/m^3.	Exposure measurement was the same as in Eisen et al. (1991)	15 min interval and 6 h time weighted average (TWA) measurement	The same 106 workers reported by Eisen et al. (1991)	Among all five symptoms, the sensitivity is nasal irritation > eye irritation > throat irritation, cough, breathlessness. There was no nose bleeding and very low incidence of sneezing	15 min TWA is a more sensitive exposure index than 6 h TWA. Particle size and composition data might be limited due to the alteration of the borate hydration/ dehydration status in the desiccation process.	Hu et al. (1992)
5.72 mg/m3 total dust in exposed group (arithmetic mean of daily exposure with 0.44 mg B/m^3) 0.45 mg/m^3 total dust in the control group with 0.02 mg/ m^3 boron	Exposure measurement was the same as in Eisen et al. (1991)	Daily average	The same 106 workers reported by Eisen et al. (1991)	Significant increased incidences measured by OR: Nasal > breathlessness > eye > throat > cough	Controlled for smoking, age and presence of the common cold. Particle size data might be limited due to the alteration of the borate hydration/ dehydration status in the desiccation process since particle size is not measured in samples that are dessicated, this does not apply	Wegman et al. (1994)

Table 7
Probability of nasal irritation categorized by exposure in each 15 min interval Hu et al. (1992).

Exposure level (mg inorganic borate dust/m^3)	Exposure level (actual inspirable mass)	Probability (TWA-6)
<1.0	<2.5	0.005
1–4	2.5–10	0.01
5–9	12.5–22.5	0.042
10–14	25–35	0.076
15-	37.5-	0.068

Note: the probability values were estimated based on a dose–response bar graph from original publication Hu et al. (1992). The exposure levels reported reflect the values reported by the authors as collected using 37 mm collection filters for total aerosol. The actual inhalable mass collected using an IOM would be 2.5 times higher than the values reported Shen et al. (1991), Werner et al. (1996), Katchen et al. (1998), Teikari et al. (2003), Vincent (2007).

potential POD magnitudes higher than those identified through the Cain et al. (2004) data, but the resulting OEL is much higher (~6-fold higher; see Fig. 1).

For the sensory irritation endpoint, a composite UF value of 1 is appropriate. This reflects the conclusion that the concentration–response estimate from Cain et al. (2004) represents a lower bound estimate of response for a sensitive population. A factor of 1 to account for human variability in response is appropriate when the POD is derived from a NOAEL or NOAEL surrogate (such as the BMCL) and for when the sensitive population serves as the basis for the POD (Haber et al., 2001). This use of a factor of 1 does not infer that there is no variability in human response, rather that sensitive individuals were already accounted for in the estimation of the POD. This conclusion was supported by several considerations. First, in worker populations, the degree of variability based on toxicokinetic or toxicodynamic considerations is expected to be lower than for the general population, since the occupational population is only a subset of the general population. Second, a reduced factor for intraspecies variability is often used for sensory irritants, based on the principle that there is lower variability for direct contact effects than other systemic responses, and that only dynamic, not kinetic variability, is relevant for such effects. A third consideration reflects the nature of the study population in Cain et al. (2004) that consisted of non-smoking, young adults with no current active rhinitis or cold symptoms. The volunteers in the Cain et al. (2004) study represent a population that is at the sensitive end of the distribution for sensory irritants in a general population cohort of adults. Although interindividual variability is significant for chemosensory responses, analyses of controlled exposure studies suggests that younger age, presence of allergic rhinitis, and coincident odor stimuli tend to increase nasal sensitivity, while smoking tends to decrease sensitivity (Shusterman, 2002, 2007). Persons with respiratory infections might be more sensitive to some effects of respiratory toxicants, however multivariate logistic regression analysis indicates that smokers and borate workers with colds were less sensitive to irritation than nonsmokers and workers without colds (Eisen et al., 1991). The concordance in effect thresholds estimated from borate exposed workers to that derived from the studies (Cain et al., 2004, 2008) also suggests that the POD used for the OEL is sufficiently representative of a worker population NOAEL for sensory irritation and the use of a small UF for this consideration. Nevertheless, the number of subjects in the clinical studies was small and an argument could be made for increasing the factor for human variability as a result.

Human variability has already been addressed in the concentration response assessment by the selection of the POD estimate. The use of a minimal composite UF reflects the POD selection approach. Several decisions were made in the modeling process to assure that a sensitive response threshold was identified for the test subjects included in the study. A reduced factor is supported by the use of several health-protective assumptions in conducting the concentration–response modeling that were chosen to increase the overall margin of safety in the assessment. The effect level used as the POD is the lower bound estimate of the sensory response (i.e., $BMCL_{10}$) rather than the maximum likelihood estimate (i.e., BMC) – reflecting subject response and experimental variability. We selected 15% CO_2 as the cut point for deriving the OEL even though a value of 17.7% may have been the best estimate (mean response) for the onset of irritation, based on a subset of test subjects (Cain et al., 2008). Additionally, we used a 5% CO_2 response to represent the control response, although a lower background response of 2.5% response may have been suitable. All of these modeling decisions resulted in a lower bound estimate of the point of departure that was meant to ensure that the data are representative of the sensitive human population. Despite these decisions, the POD was developed using a small number of subjects and is not a direct estimate of overall worker variability. To the degree that the risk assessment does not consider that POD as reflective of a sensitive population NOAEL a larger factor for human variability in response could be applied. For the reasons noted above to be concordant with current risk assessment practice, such a factor would need to be 3 or less.

3.4. Preliminary OEL based on evaluation of animal and human studies

Based on these limited data, an OEL for irritant and systemic effects could be derived using the $BMCL_{10}$ for nasal sensory irritation in humans (derived from Cain et al., 2004) or the $BMDL_{05}$ for developmental effects in animals (US EPA, 2004). In comparing the effect levels across endpoints, it was determined that the effects on the male reproductive tract occurred at higher or equal doses than the doses that caused developmental effects and the studies for the developmental endpoints were more reliable for characterizing dose–response (US EPA, 2004). Therefore, in the context of setting an OEL, protection from developmental toxicity should also be adequate to protect from reproductive toxicity as well as toxicity to other systemic target organs. Each of these critical effect levels is adjusted using appropriate uncertainty factors to determine the best OEL estimate (see Fig. 1) per IPCS (2005) CSAF methods.

The OEL for protection against systemic effects (based on developmental toxicity as the critical effect) can be calculated as follows: 10.3 mg B/kg-day (the critical effect level for developmental effects) $\times$ 58 kg body weight for a female worker/9.1 m^3 of air inhaled per 8-h work shift/40 (the UF) = 1.6 mg B/m^3 (ICRP, 1975). Body weight and air intake rate default values used by other OEL-setting organizations would yield even higher OEL estimates for the systemic effect. Since the various borate compounds all form boric acid in the body, the appropriate dose metric for systemic toxicity is based on boron equivalents. The OEL for protection against sensory irritation is estimated to be 1.4 mg B/m^3, as shown in Fig. 1, which is essentially the same as that based on developmental toxicity, after consideration of uncertainties (and the degree of precision afforded by risk assessment methods). Thus, the final OEL recommendations show consistency in the prevention of sensory irritation and systemic effects. Irritation, being the more sensitive and least variable of the two endpoints, was selected as the basis for the OEL. Because of the slope of the irritation response, it is possible that less sensitive individuals will have no indications of irritation at this value. Therefore, borates do not necessarily have strong warning properties and the presence of irritation, or lack thereof, should not be used to ensure that acceptable exposure levels are maintained.

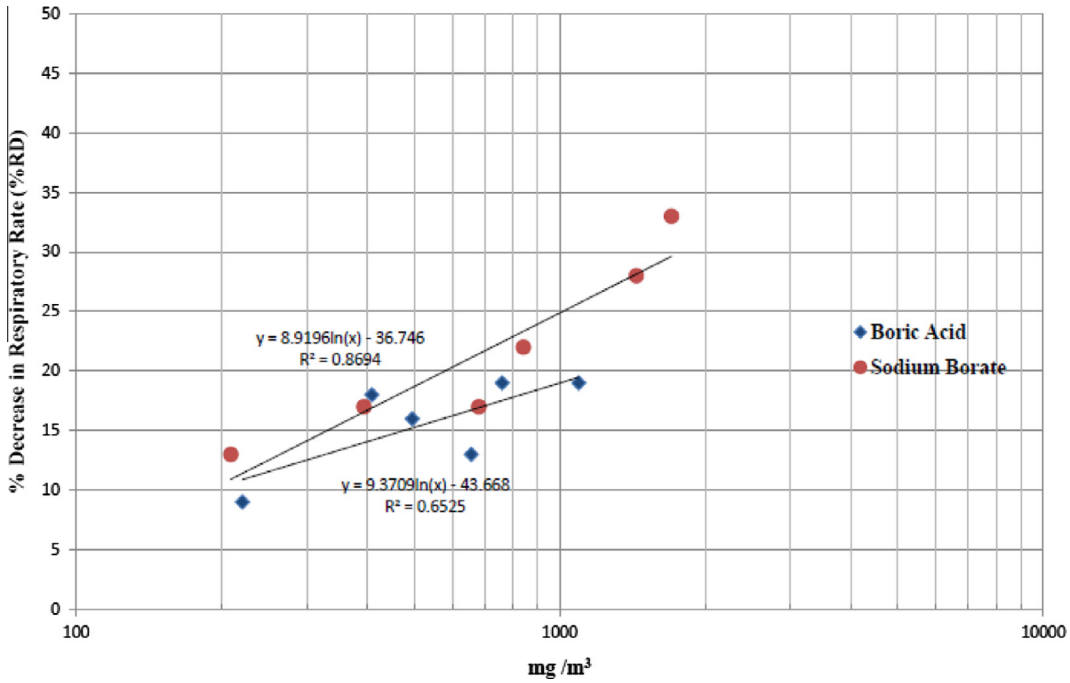

Fig. 3. Dose–response curves obtained for boric acid disodium tetraborate pentahydrate in male Swiss-Webster mice. Each data point represents the mean of four mice exposed simultaneously at each concentration. The concentration is given in mg/m^3 Kirkpatrick (2009; 2010).

4. Discussion

Inorganic borates remain an important focus of risk assessment activity. We evaluated current data in light of evolving risk methodologies (IPCS, 2005, 2007) to provide an updated OEL recommendation using a weight of evidence approach. As shown in Fig. 1, the data provide a cohesive picture supporting the conclusion that occupational exposures controlled to address potential developmental toxicity will also be adequate to protect worker populations from any significant irritant effects. Given the similarity in derived OEL values for irritation and developmental toxicity and the precision of the methods in OEL derivation, it cannot be concluded that inorganic borates have adequate properties to warn workers of potentially relevant systemic doses. Based on these considerations, we recommend an OEL of 1.4 mg B/m^3 as an 8-h TWA for inhalable particulate. The final OEL recommendation reflects the endpoint-specific analysis tempered by risk management considerations driven by limitations in the data. These include the active form of the compound, particle size characteristics, and the temporal response of adverse effects.

4.1. Form of the compound

Choosing the appropriate metric as the basis for the OEL requires evaluation of the chemical properties of each compound and the likely mechanism of toxicity. Systemic toxicity depends on boron dose, since the various borates are converted to boric acid when entering systemic circulation. Therefore, a metric based on boron equivalents is appropriate for deriving an OEL to protect against the sensitive systemic effects of concern (i.e., developmental toxicity). For portal of entry (i.e., upper respiratory tract sensory irritation) effects; however, the mode of action determines the nature of the appropriate OEL metric. Hypothesized irritant mechanisms for inorganic borates include local tissue pH change, physical irritation due to particle structures, local thermodynamic changes resulting from dissolution of the particles and formation of boric acid, or changes in tissue osmolarity (Cain et al., 2004, 2008; Woskie et al., 1998).

The various lines of evidence paint an inconclusive, and in some cases contradictory, picture of the relative potency of the inorganic borate compounds. Therefore, applying a single OEL on a simple per mass basis may not fully capture the range of irritant potency across all of the inorganic boron compounds. This uncertainty is highlighted by the finding that irritation responses above those of controls were observed beginning at 2.5 mg/m^3 for boric acid (equivalent to 0.45 mg B/m^3) and 5 mg/m^3 for sodium borate (equivalent to 1.5 mg B/m^3). Despite the concentration for the onset of reporting, the intensity of irritation (~16% CO_2 equivalent concentration which is close to experimental threshold for irritation detection) was similar for boric acid and sodium borate at 10 mg/m^3. Whether the differences reflect true potency differences, differences in variability among subjects for the two forms of inorganic borate, or other experimental variability is not clear.

In the absence of a clear mechanistic rationale for setting the irritation-based OEL, there are practical reasons to favor using a boron equivalent OEL approach. First, typical industrial hygiene sampling will not distinguish between the various inorganic borates or mixed exposures, so the measurement of total boron is a more pragmatic sampling method. Second, systemic effects are caused by the internal concentration boron, so using a boron equivalent is a simpler method for estimating a boron-internal concentration and does not require back-extrapolation for each boron-containing substance. Moreover, presentation of an OEL on a boron-equivalent basis allows easy comparison of exposures relevant to both sensory irritation and developmental toxicity because developmental effects are an endpoint of interest. Finally, presentation of the OEL in the form of boron equivalents still provides the user the flexibility to calculate gravimetric equivalents if they have well-defined borate speciation for a specific exposure situation.

4.2. Particle size considerations

Concern for endpoints of potential significance for occupational exposures to borates – systemic toxicity and sensory irritation - are both best represented by the inhalable fraction of the distribution

of aerosols to which workers might be exposed. Soluble borates may be absorbed across any portion of the respiratory tract or be swallowed after deposition in the upper respiratory tract with potential absorption via the gastrointestinal tract. Sensory irritant response predominates in the upper respiratory tract, where larger size particles, predominately those 10 μm or larger (U.S. EPA, 1994), are most likely to be deposited. The relationship between the masses collected using total particulate sampling techniques versus those that would occur using inhalable mass samplers have been characterized (Werner et al., 1996). This type of analysis is particularly important for supporting dose–response analyses where conversion from older total sampling techniques is required. We applied such a conversion to the older epidemiology database for inorganic borates. The inhalable fraction adjustment was not needed for the data modeled from Cain et al. (2004) due to the small correction that would result from the aerosol distributions used in their controlled-exposure experiments. Use of developmental toxicity following oral dosing of rodents as the basis for the OEL calculation for protection from systemic effects following inhalation exposure in the workplace requires careful consideration of route-dependent kinetics and dynamics. In this case, such an extrapolation is appropriate because complete systemic absorption and distribution of the deposited dose is a reasonable assumption for a soluble particulate that is widely distributed in tissue without significant tissue deposition or metabolism.

4.3. Appropriate time weighted averaging of the OEL (TWA versus STEL)

Typically, a full-shift TWA OEL is established to protect against effects that occur as a result of repeated and longer-duration exposures, as is the case for developmental toxicity for inorganic borates. A TWA approach is recommended, since developmental toxicity is the most significant endpoint of concern in terms of effect severity. Often a STEL is established to protect against effects that arise from acute exposures – in this case sensory irritation. It is often the case that acute effects occur at higher concentrations than those that generate longer-term effects. For the inorganic borates, the OEL estimates for developmental toxicity are very similar to the OEL derived for significant sensory irritation (see Fig. 1) and are not distinguishable within the precision of the methods used to derive an OEL for systemic effects. Because the OELs for both relevant endpoints are similar, but the nature of the time for response is much shorter for sensory irritation, setting a TWA at the most protective level for developmental effects may not assure the absence of sensory irritation in some workers where significant peak exposures could occur. One approach to address this residual concern for peak exposures above the TWA is through the use of an excursion rule that is a multiplier of the TWA for evaluating acceptability of short-term exposures (ACGIH, 2012). Use of the excursion approach should consider that exceeding the TWA value for short periods might cause slight to moderate irritation responses, and thus practices to control peaks should be considered in application of the recommended OEL. An alternative approach would be to set the final OEL as a STEL based on the sensory irritation effect alone. If this approach where selected for occupational risk management the remaining hazard communication surrounding developmental toxicity would need to be highlighted.

4.4. Differences from other OEL estimates

The toxicity of boron and various inorganic boron compounds have been the subject of recent analyses for the purpose of deriving environmental exposure criteria for protection of human health (See Table 8 for proposed OELs from other agencies). The current threshold limit value time-weighted average (TLV-TWA)® (ACGIH, 2005) appears to rely heavily on the occupational epidemiology studies (Garabrant et al., 1985; Wegman et al., 1994) as the under pinning for the OEL recommendation. Our proposed OEL differs from the TLV-TWA estimate for multiple reasons. Considerations of data quality and relevance led us to give greater weight to controlled human exposure studies (Cain et al., 2004, 2008) as the preferred basis for the dose–response analyses for the sensory irritation endpoint based on overall confidence in the concentration–response data achievable in a controlled study. Limitations in precise estimation of concentration response from epidemiology studies are a common challenge in quantitative risk assessment (Hertz-Picciotto, 1995; Nurminen et al., 1999) and the studies available for borates are no exception. Because multiple critical epidemiological studies (e.g., Wegman et al., 1994; Garabrant et al., 1984, 1985; Whorton et al., 1994) are based on samples collected with a 37 mm filter cassette, they likely underestimate actual exposures, based on side-by-side measurements for inorganic borates. An approximate difference of 2.5-fold is suggested by comparisons of sampling efficiencies for 37 mm cassettes and the IOM sampling method (Shen et al., 1991; Werner et al., 1996; Katchen et al., 1998; Teikari et al., 2003; Vincent, 2007). Thus, use of the epidemiology studies needs to correct for the differences in sampling techniques as we have done in the current analysis.

Other OEL derivation activities (e.g., MAK, 2011) have considered the study by Cain et al. (2004) as the most appropriate basis for identifying a POD, but have selected physiological endpoints, such as nasal secretion, as the best measure of sensory irritation. We choose not to use this endpoint for our OEL recommendation. While it is a physiological response to trigeminal nerve stimulation consistent with early events in the onset of irritation, in this case data from the same study are available for the actual adverse effect we are setting an OEL to prevent (i.e., sensory irritation). Direct data on this endpoint as reported by exposed subjects was judged a better metric for risk assessment purposes for the data available for inorganic borates. In the Cain et al. (2004) study, the amount of secretion correlated with area under the curve estimates for chemosensory response, but not irritation. However, in the Cain et al. (2008) study, the correlation was not significant. The relative merits of using objective physiological measures (e.g., nasal secretion) versus subjective responses, or the two methods in combination, has been described in the literature (Arts et al., 2006). The

Table 8
A comparison of the proposed occupational limits from multiple agencies and organizations.

Compound	ACGIH[a]	OSHA[b]	CAL OSHA[b]	NIOSH[b]	MAK[a]	AGW[a]
Boric acid	2 mg/m^3	–	–	–	1.8 mg B/m^3	0.5 mg B/m^3
Boric oxide	–	15 mg/m^3	10 mg/m^3	10 mg/m^3	–	–
Sodium borate anhydrous	2 mg/m^3	–	5 mg/m^3	1 mg/m^3	0.75 mg B/m^3	0.5 mg B/m^3
Sodium borate pentahydrate	2 mg/m^3	–	5 mg/m^3	1 mg/m^3	0.75 mg B/m^3	0.5 mg B/m^3
Sodium borate decahydrate	2 mg/m^3	–	5 mg/m^3	5 mg/m^3	0.75 mg B/m^3	0.5 mg B/m^3

[a] Measured as inhalable dust.
[b] Measured as total dust.

Cain et al. (2004, 2008) studies did not suffer from common limitations regarding use of subjective symptoms for dose–response such as poor control of exposures, lack of responder calibration, and concerns about the impacts of coincident odor responses stimulated by the test agent. In addition, the nasal secretion response, in the absence of reported irritation was not considered adverse in the context of risk assessment (U.S. EPA, 1994). The relationship between nasal secretion and signs of irritation is complex, and as a minimum is not currently well characterized. The lack of clear correlations between early physiological signs and actual reported irritant symptoms might reflect the well documented phenomenon that sensory irritant response is an integration of physiological and psychological factors (Dalton, 2001, 2003; Dalton and Jaen, 2010).

Our analysis also includes new standard animal toxicology studies, not incorporated in currently published OEL recommendations. The results from new animal studies are considered in our analysis, but given less weight than the human volunteer study by Cain et al. (2004). This reflects uncertainty and extrapolation from the animal responses, particularly for RD50 studies (Bos et al., 2002, 1992). However, despite the uncertainties in extrapolation, 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 RD50 values are used as a basis, at least partially, for OELs set by several organizations, including the ACGIH (Kuwabara et al., 2007).

Overall, the results obtained from the modeling of the Cain et al. (2004) sensory response data were consistent with those from both the occupational epidemiology (see Table 6) studies and the recent RD50 studies in mice (Ball et al., 2012) when the nature of the endpoint examined and uncertainties inherent in data extrapolation were considered. The resulting OEL for sensory irritation is very similar to that derived based on developmental toxicity. As a result, the recommended OEL should reflect the co-critical nature of these endpoints. There is a potential hazard communication concern with deriving an OEL based on sensory irritation, that over emphasizes the severity of this response, in light of the systemic effects that might arise at a similar level of exposure. Thus, an OEL based on very subtle indicators of sensory irritant response was avoided in our analysis, due to the concern that workers would infer a lack of concern for systematic effects in the absence of significant sensory irritation.

4.5. Research needs

Although the data are sufficiently robust to have confidence in the exposure limit, there are a number of remaining uncertainties related to setting OELs for sensory irritants. The characterization of human variability in irritation responses is not fully understood; how this variability impacts selecting uncertainty factors for OEL development, while described as an important issue in the OEL literature, remains unresolved. Of particular use for the current OEL would be better data on the range of human response for different segments of the potentially-exposed working population (including asthmatics, age-and gender-related differences, and impacts on naïve subjects versus those with repeat exposures). Nevertheless, the current analysis does take into account individuals in the most responsive range for sensory irritation (e.g., young, naive, non-smokers) in the controlled exposure studies (Cain et al., 2004, 2008) and the epidemiology studies of boron mine workers did not exclude asthmatics (Wegman et al., 1994 and related studies).

Additional uncertainties are introduced when deriving the OEL on the basis of boron equivalent exposure. This recommendation is largely based on practical grounds, because the data are mixed with regard to the issue of whether equal mass, pH flux, or some other metric would most accurately describe the relative sensory irritant potency of inorganic borates. Experiments to test the relative irritant potency of inorganic borates directly in a controlled setting, based on changes in nasal pH tissue thermodynamic changes, or other biochemical metrics would be needed to resolve this issue.

Cain et al. (2004) developed a kinetic model to estimate dissolved versus total deposited borate in the upper respiratory tract to evaluate the mode of action for irritant induction for different forms of inorganic borates. We did not extend the use of his model directly in our analyses, since the mode of action remains unclear and traditional approaches were sufficient for the setting OELs under typical exposure scenario definitions. However, there are advantages of using the kinetic model for OEL development since potential irritant response for alternative workplace scenarios can be derived using such models. In addition, the systemic impacts of different durations or temporal patterns of exposure can be compared directly if the excretion rates are properly modeled.

Overall, the analysis provides an example of applying current risk methods for OEL development and highlights approaches and considerations to inform OEL setting. Many of the concepts addressed in our analyses can be applied to OEL development for other chemicals in the very common situation where alternative OELs for systemic effects and sensory irritation must be weighed.

5. Conflict of interest

We wish to acknowledge the funding of Rio Tinto Minerals who supported the development of this manuscript. The sponsors were asked to review the material and provide technical comment. However, the results and conclusions presented represent those of the authors.

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