



## Biomonitoring Equivalents (BE) dossier for trihalomethanes

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### ABSTRACT

Measurements of whole blood concentrations of trihalomethanes (THMs) have been reported in persons in the general population. Risk assessments based on administered doses of THMs have been conducted for both cancer and non-cancer health endpoints by the US Environmental Protection Agency; however, no health-based standards exist for interpreting measured blood concentrations of THMs. Existing physiologically based pharmacokinetic models for laboratory rats, dogs, and humans were used to estimate the average blood concentrations consistent with the points of departure, reference doses (RfDs), and, where applicable, cancer potency estimates to provide biomonitoring equivalents (BEs) for these exposure guidance values. The models were also used to characterize the short term variations in blood concentrations that could result from various exposure regimens, even when exposures remain consistent with the underlying RfDs. The BE values derived in this exercise can be used as one component of a screening-level assessment of future population biomonitoring THM data.

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### 1. Introduction

The benefits of disinfecting drinking water as a means of protecting the public from disease-causing microorganisms such as typhoid, hepatitis, *Giardia* and cholera are clear (USEPA, 2006a). At the same time, the reaction of drinking water disinfectants with naturally occurring organic matter in the water supply produces disinfection byproducts (DBPs). The most widely used disinfectant – chlorine – produces DBPs such as trihalomethanes (THMs, which for the purposes of this paper include chloroform [trichloromethane], bromoform [tribromomethane or TBM], bromodichloromethane [BDCM], and dibromochloromethane [DBCM]) as well as other classes of compounds (e.g., haloacetic acids) (USEPA, 2006a). Toxicological studies of THMs have consistently demonstrated that liver and kidney toxicity are the most sensitive endpoints in laboratory animals (USEPA, 2005). At doses above those producing liver and kidney toxicity, effects on reproductive and developmental endpoints and increases in tumor incidence in several target organs (liver, kidney, and large intestine) have been observed (USEPA, 2005). A variety of ecological and cross-sectional studies of human populations have examined possible associations between exposure to these compounds in drinking water and certain adverse health effects, such as specific cancers or reproductive

effects (reviewed in USEPA, 2005; see also King et al., 2000; Nieuwenhuijsen et al., 2000; Dodds et al., 2004; Toledano et al., 2005; Villanueva et al., 2007a). The US Environmental Protection Agency (USEPA) has set limits on allowable levels of THMs in drinking water supplies, recognizing that DBPs are the unwanted but unavoidable consequence of treating drinking water, and the risks associated with exposures to DBPs must be considered in light of the important public health benefits associated with disinfection.

Numerous investigations have provided data on exposures to THMs from activities such as water consumption, showering, and bathing. However, because of the pharmacokinetic and chemical characteristics of THMs (rapidly eliminated, high volatility) and the fluctuating nature of human exposures (due to variation in human activities and to the variable concentrations of THMs in water at any given time), reliable dose estimates are difficult to obtain. Sophisticated exposure analysis coupled with physiologically based pharmacokinetic (PBPK) models has provided evaluations of the relative contributions of various exposure pathways to internal doses of THMs (Haddad et al., 2006; USEPA, 2006c). With the availability of analytical methods for measuring THMs in human blood (Bonin et al., 2005), researchers have sought to use biomonitoring data to better determine exposures to THMs on a population basis. However, there are no readily available methods for interpreting biomonitoring data in a public health risk context because the tolerable exposure guidelines established by USEPA and other agencies are based on external air concentration or daily dose.

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Screening criteria for evaluation of biomonitoring data would ideally be based upon data from robust epidemiological studies that evaluate a comprehensive set of health endpoints in relationship to measured levels of chemicals in biological media. However, development of such epidemiologically-based screening values is a resource- and time-intensive effort. As an interim effort, the development of Biomonitoring Equivalents (BEs) has been proposed (Hays et al., 2007). A BE is defined as the concentration or range of concentrations of chemical in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline. Chemical-specific pharmacokinetic data are used to estimate biomarker concentrations associated with the Point of Departure (PODs; such as No Observed Effect Levels [NOELs], Lowest Observed Effect Levels [LOELs], or Benchmark Doses [BMDs]) and to estimate biomarker concentrations that are consistent with the guidance value. BEs can be estimated using human or animal pharmacokinetic data. Guidelines for the derivation and communication of BEs are available in (Hays et al., 2008). BEs are designed to be screening tools to gauge which chemicals have large, small or no margin of safety compared to existing health-based exposure guidelines. BEs are only as robust as are the underlying health-based exposure guidelines that they are based upon and the underlying animal toxicology studies and pharmacokinetic data used to derive these health-based exposure guidelines. BEs are not designed to be diagnostic for potential health effects in humans, either individually or among a population.

The value of the development of BEs for THMs and other environmental chemicals is that the method directly addresses the problem noted by the National Research Council (NRC, 2006), that “We do not know how to convey the biomarker-presence-does-not-indicate-health-effects message effectively.” THMs present a case in which substantial data on mechanism of action and detailed pharmacokinetic models are available. Application of the BE approach, using forward dosimetry, provides a relatively straightforward method for providing a set of screening values for an initial evaluation of human biomonitoring data from a public health risk perspective. Reported concentrations of THMs in human blood can be compared to BEs to evaluate whether population blood concentrations are above, below, or close to blood concentrations that are consistent with exposure guidance values as determined by USEPA.

This BE dossier describes the scientific basis for and derivation of BE values for THMs and discusses issues that are important for the interpretation of biomonitoring data using BEs. This BE dossier is not designed to be a comprehensive compilation of the available hazard, dose–response or risk assessment information for THMs.

### 1.1. Current health-based exposure guidance values

Health-based exposure guidance and toxicity values have been established for many chemicals for the general population by the USEPA (Reference Doses or Reference Concentrations [RfDs or RfCs]), the Agency for Toxic Substances and Disease Registry (ATSDR) (Minimal Risk Levels or MRLs), and various organizations outside the US including Health Canada and the World Health Organization (WHO) (Tolerable Daily Intakes or TDIs). Although these health-based guidance values have different labels and slightly different definitions, they all generally describe an approximation (with uncertainty spanning an order of magnitude) of daily intake rates (or air concentrations) for a chemical expected to be without adverse effects in the general population, including sensitive subpopulations.<sup>1</sup> For chemicals considered to be carcinogenic,

the USEPA also establishes estimates of cancer potency by assigning a quantitative estimate of the upper bound of potential increased cancer risk associated with a unit of intake or air concentration (unit cancer risks, or UCRs).

USEPA has established RfDs for non-cancer toxicity for the four THM compounds. These RfDs are estimates of oral exposure levels (in terms of  $\text{mg kg}^{-1} \text{d}^{-1}$ ) that are anticipated to be without appreciable risk of adverse health effects over a lifetime of exposure based on extrapolation from animal studies. Table 1 presents a summary of the existing USEPA RfDs for the THMs including a description of the studies used, the most sensitive endpoints, and the identified POD used to estimate RfDs for each compound. The RfDs are based on hepatic effects for all four compounds, with the critical study being in rats for DBCM, BDCM, and TBM and from a study in dogs for chloroform.

USEPA has concluded that the carcinogenicity of chloroform observed in animal studies occurs as a result of repeated cytotoxicity and cytolethality resulting from high peak tissue concentrations and high rates of metabolism following repeated dosing (USEPA, 2006a,b). Based on this determination of mode of action for carcinogenicity, USEPA has concluded that exposures to chloroform below the RfD set for non-cancer endpoints will be protective for the cancer endpoint. EPA has not made a similar determination regarding the mode of action or cancer risks from DBCM, BDCM or TBM, relying instead on the default linear, non-threshold extrapolation approach to estimate cancer risks. In the recent assessment of brominated trihalomethanes conducted by the USEPA Office of Water, dose–response assessments of cancer bioassay data for the three brominated trihalomethane compounds were presented (USEPA, 2005). Table 2 gives an overview of the estimates of human equivalent benchmark doses for a 10% increase in tumor risk at the responding tumor sites and of the selected cancer slope factors (derived using the linearized multistage model and scaling to bodyweight to the  $\frac{3}{4}$  power) for the three THM compounds other than chloroform (USEPA, 2005).

### 1.2. Pharmacokinetics

The pharmacokinetics of THM compounds have been extensively investigated in laboratory rodents. The compounds are rapidly metabolized, volatile, and lipophilic, and toxicity is believed to arise due to the production of reactive metabolites (reviewed in Meek et al., 2002; USEPA, 2005). PBPK models have been developed for all four compounds based on experiments in laboratory rats and mice (Corley et al., 1990; Lilly et al., 1997, 1998; Lucieni da Silva et al., 1999 and extended to humans through the use of allometric scaling of metabolic parameters (Haddad et al., 2006). The pharmacokinetic models are discussed further in Section 2.1 below.

### 1.3. Biomarkers

The objective of using BEs is to provide a human health risk framework for screening-level evaluation of human biomonitoring data. The choice of the biomarker (analyte and medium) should be optimized to facilitate this objective. The key criteria for the choice of a biomarker are that it be as closely related to the appropriate dose to the target tissue as possible and that it be practical for collection in a biomonitoring study. This, in turn, means that the biomarker should be (i) the compound that causes the toxicity (parent or metabolite), or (ii) should be just upstream on the metabolic pathway from the toxic compound, and (iii) as closely related to the target tissue as possible.

Identification of relevant dose metrics depends upon the health endpoints that are the bases of the health-based screening values. The available health-based criteria presented in Table 1 focus on two health endpoints.

<sup>1</sup> See the definition of RfD at <http://www.epa.gov/iris/gloss8.htm>; definitions for ATSDR MRLs are included in ATSDR Toxicological Profiles at <http://www.atsdr.cdc.gov/toxpro2.html>. Definition of the TDI is available at [http://ptcl.chem.ox.ac.uk/MSDS/glossary/tolerable\\_daily\\_intake.html](http://ptcl.chem.ox.ac.uk/MSDS/glossary/tolerable_daily_intake.html).

**Table 1**  
Description of studies and endpoints used to establish the point of departure (POD) and the identified uncertainty factors (UFs) used in the derivation of the USEPA reference doses (RfDs) for four THM compounds

Compound	Description of study used as the basis for RfD	Effects observed	POD	UFs	RfD (mg kg <sup>-1</sup> d <sup>-1</sup> )
Chloroform	Chloroform administered to dogs in a toothpaste base in gelatin capsules, 15 or 30 mg kg <sup>-1</sup> d <sup>-1</sup> 6 d/wk for 7.5 yrs (Heywood et al. 1979)	Reversible elevations in SGPT (ALT) during treatment at both doses; increased fatty cysts in liver	BMDL <sub>10</sub> <sup>a</sup> : 1.2 mg kg <sup>-1</sup> d <sup>-1</sup>	10010 for interspecies 10 for intraspecies	0.01
DBCM	DBCM administered to rats via corn oil gavage, 0, 40, 80 mg kg <sup>-1</sup> d <sup>-1</sup> , 5 d/wk, 104 wks (NTP 1985 as reported in USEPA 2005)	Fatty changes in the liver of male rats	BMDL <sub>10</sub> : 1.6 mg kg <sup>-1</sup> d <sup>-1</sup>	10010 for interspecies 10 for intraspecies	0.02
BDCM	BDCM administered to male rats in diet at 6, 26, or 138 mg kg <sup>-1</sup> d <sup>-1</sup> , 24 months (Aida et al. 1992 as reported in USEPA 2005)	Fatty changes in liver of male rats	BMDL <sub>10</sub> : 0.8 mg kg <sup>-1</sup> d <sup>-1</sup>	30010 for interspecies 10 for intraspecies 3 to account for database uncertainty regarding potential reproductive effects	0.003
TBM	TBM administered to rats via corn oil gavage, 12, 25, 50, 100, or 200 mg kg <sup>-1</sup> d <sup>-1</sup> , 5 d/wk, 13 wks (NTP 1989 as reported in USEPA 2005)	Hepatocellular vacuolization	BMDL <sub>10</sub> : 2.6 mg kg <sup>-1</sup> d <sup>-1</sup>	10010 for interspecies 10 for intraspecies	0.03

RfD for chloroform from USEPA's Integrated Risk Information System (USEPA 2006b); information on RfDs for brominated THM compounds from USEPA (2005).

<sup>a</sup> BMDL<sub>10</sub>: statistical lower bound on the benchmark dose associated with a 10 percent increase in the occurrence of the critical response.

Exposures to THMs have been biomonitoring by quantifying the parent compounds in blood, exhaled air, and to a limited degree in urine. The most common matrix has been blood, and thus BEs are derived for THMs in whole blood in this paper.

## 2. BE derivation

In this analysis, we utilize the underlying PODs for health-based exposure guidance values (RfDs) for the four THMs to derive estimated blood concentrations (BEs) consistent with the derivation of the RfD values. We also estimate BE values based on the cancer risk assessments conducted by USEPA. We then compare these BEs to available data on THMs in human blood, describe the uncertainties in the BE derivation for THMs, and discuss interpretation of biomonitoring data sets for these compounds in the context of the BEs and the risk/benefit considerations for water disinfection.

### 2.1. Methods

Of the four THMs, the most extensive database for understanding the pharmacokinetic relationship between exposures and resulting blood levels is for chloroform. This is, to some degree, because of its historical use as an anesthetic during surgery (Poobalasingham and Payne, 1978). There are considerably fewer available data on the brominated THMs. However, efforts in recent

years to develop a family of PBPK models for the four THMs (Corley et al., 1990; Lilly et al., 1998; Luciene da Silva et al., 1999; Haddad et al., 2006) have provided a fairly robust and consistent means of estimating the relationship between THM exposures and resulting tissue and blood THM concentrations. Therefore, these PBPK models form the basis for derivation of the BEs.

#### 2.1.1. Models

The pharmacokinetics of chloroform has been studied extensively in animals and to a limited degree in humans, and a well-accepted PBPK model is available for chloroform (Corley et al., 1990). PBPK models for the other three THM compounds have been developed for rats (Lilly et al., 1998; Luciene da Silva et al., 1999) and recently these models have been adapted for humans (Haddad et al., 2006) through the use of allometric scaling of metabolic parameters. These are the same basic models used by USEPA in their examinations of exposure pathways for THMs (Teuschler et al., 2004) and by other researchers examining the relationship between biomonitoring levels of THM compounds and external exposure patterns (Tan et al., 2006, 2007). PBPK models were implemented in Microsoft Excel<sup>®</sup> for all four THM compounds for humans and rats and for chloroform in dogs. Physiological and chemical-specific metabolic parameters for the human models were taken from Haddad et al. (2006). These models have been used to predict blood levels in humans associated with exposures

**Table 2**  
Overview of benchmark dose assessment of point of departure (human equivalent LED<sub>10</sub>) and selected cancer slope factors (CSFs) for THM compounds (USEPA 2005)

Compound	Study description	Most sensitive endpoint	Human equivalent LED <sub>10</sub> <sup>a</sup> (mg kg <sup>-1</sup> d <sup>-1</sup> )	CSF <sup>b</sup> (mg kg <sup>-1</sup> d <sup>-1</sup> ) <sup>-1</sup>
Chloroform	"A dose of 0.01 mg kg <sup>-1</sup> d <sup>-1</sup> (equal to the RfD) can be considered protective against cancer risk" <sup>c</sup>			
DBCM	NTP (1985, as cited in USEPA 2005) study in B6C3F1 mice; 0, 50 or 100 mg kg <sup>-1</sup> d <sup>-1</sup> , 5 d/wk via corn oil gavage	Liver tumors in female mice	2.5	4.3 × 10 <sup>-2</sup>
BDCM	NTP (1987, as cited in USEPA, 2005) study in B6C3F1 mice; 0, 25, or 50 mg kg <sup>-1</sup> d <sup>-1</sup>	Kidney tumors in male mice	3.0	3.5 × 10 <sup>-2</sup>
TBM	NTP (1989, as cited in USEPA, 2005) study in Fisher 344/N rats; 0, 100, or 200 mg kg <sup>-1</sup> d <sup>-1</sup> , 5 d/wk via corn oil gavage	Tumors of the large intestine in female rats	22	4.6 × 10 <sup>-3</sup>

<sup>a</sup> LED<sub>10</sub>: human equivalent (scaled using bodyweight<sup>3/4</sup>) lower bound on the estimated dose associated with a 10% increase in tumor occurrence.

<sup>b</sup> Cancer slope factor derived using the linearized multistage model and bodyweight<sup>3/4</sup> scaling. Only the final CSF selected for each compound as assessed in the USEPA (2005) Drinking Water Criteria Document for Brominated Trihalomethanes is reported here.

<sup>c</sup> From USEPA IRIS, further discussion is provided: "...the RfD for non-cancer effects is derived from the most sensitive endpoint in the most sensitive species. The RfD is based on fatty cysts [sic] formation (fat accumulation) in the liver and elevation of SGPT in dogs (Heywood et al., 1979). Hepatic fat accumulation and elevated SGPT are considered early signs of impaired liver function resulting from chloroform-induced cytotoxicity. This effect occurs at doses at or below those that cause increased labeling index, morphological changes, or cellular necrosis, so protection against this effect is believed to protect against cytolethality and regenerative hyperplasia. Accordingly, the RfD of 0.01 mg kg<sup>-1</sup> d<sup>-1</sup> presented in Section 1.A.1 can be considered protective against increased risk of cancer."

to THMs via inhalation and ingestion (Tan et al., 2006, 2007) but have undergone limited validation against human experimental data. Parameters for the rat PBPK models for DBCM, BDCM, and TBM were taken directly from Luciene da Silva et al. (1999); for chloroform, the rat model parameters from Corley et al. (1990) were used. These models have been more extensively validated against rat pharmacokinetic data. Finally, the rat and human PBPK models were extended to the dog by Meek et al. (2002) in order to assess the liver toxicity data from Heywood et al. (1979), which is the basis for the chloroform RfD. The dog model as parameterized by Meek et al. (2002) was implemented here to estimate blood levels in dogs at the POD used to derive the chloroform RfD. However, that model has not been validated against experimental pharmacokinetic data in dogs, but instead includes physiological and anatomical parameters specific for dogs in combination with metabolic parameters averaged from those used in the rat and human models.

### 2.1.2. Non-cancer

The approach to estimating blood concentrations consistent with the USEPA RfDs for the four THMs is illustrated in Fig. 1. The critical effects observed in animal studies in response to exposure to all four THMs were effects on liver (summarized in Table 1). Although the specific mechanism(s) of action for these effects are not known, they likely involve production of reactive metabolites that result in hepatotoxicity. The critical dose metric may be related to either rate of production or peak or average concentration of metabolites in liver tissue (USEPA, 2006c). For the purposes of the modeling conducted here, the following assumptions were made:

- Daily metabolite production in the liver ( $\text{mg L}^{-1}$  per day) is a relevant dose metric for the critical effect.
- Exposures in the range encountered in the environment will not result in saturation of the metabolic capability for individual

compounds, nor are combined exposures sufficiently high to result in metabolic interactions/inhibitions among THM compounds (Tan et al., 2007; USEPA, 2006c).

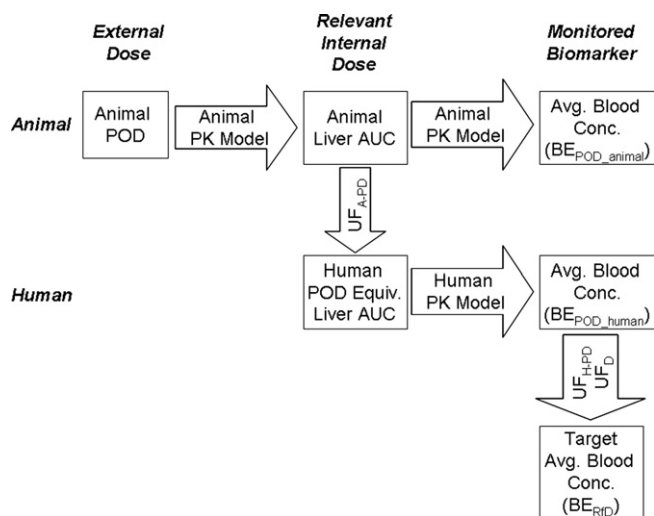
As a consequence of the model structure, daily area under the curve (AUC) of the concentration of the parent THM compound in liver is directly proportional to daily metabolite production when metabolism is not saturated. Thus, hepatic AUC of the parent compound was selected as a biologically relevant dose metric for the critical non-cancer effects used as the bases for derivation of the RfDs. The relationship between the relevant dose metric, hepatic AUC, and average blood concentrations (the biomarker likely to be measured in humans) was investigated under different exposure scenarios (all oral, all inhalation, or mixed oral and inhalation) using the human PBPK models to confirm that blood concentration could be reliably used as a surrogate for hepatic AUC. Based on the results of that assessment, the following steps were taken:

- The 24-h hepatic AUC in the laboratory animals at the POD for each THM was estimated using the animal PBPK models.
- The 24-h hepatic AUC at the POD was extrapolated to the corresponding human equivalent hepatic AUC by applying an uncertainty factor of one-half an order of magnitude, representing the pharmacodynamic component of the interspecies default uncertainty factor (UFA-PD). The pharmacokinetic component of the interspecies UF was not applied because the extrapolation is conducted using a relevant internal dose metric.
- The human PBPK models were used to evaluate the relationship between hepatic AUC and 24-h average blood concentration, and a value for 24-h average blood concentration consistent with the human equivalent hepatic AUC POD was estimated.

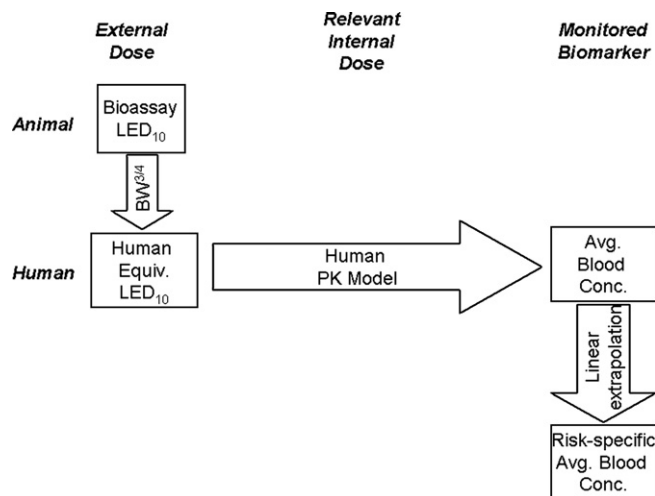
The resulting human 24-h average blood concentration at the POD was combined with the intraspecies uncertainty factor for pharmacodynamic variability (UFH-PD) and, where designated by USEPA, the uncertainty factor for database uncertainties selected by USEPA (UFD), to identify target average blood concentrations consistent with the derivation of the RfD. The pharmacokinetic component of the intraspecies UF was not applied because measured blood concentrations in humans are the endpoint metric. Pharmacokinetically “sensitive” humans will display higher blood concentrations for the same external dose; thus, blood concentrations measured in a sample population will directly reflect this component of variability and no additional UF needs to be applied to the calculated target blood concentrations to account for this factor. In essence, humans are the perfect PBPK “model” and the pharmacokinetic variability present will be reflected in the sampling results.

### 2.1.3. Cancer

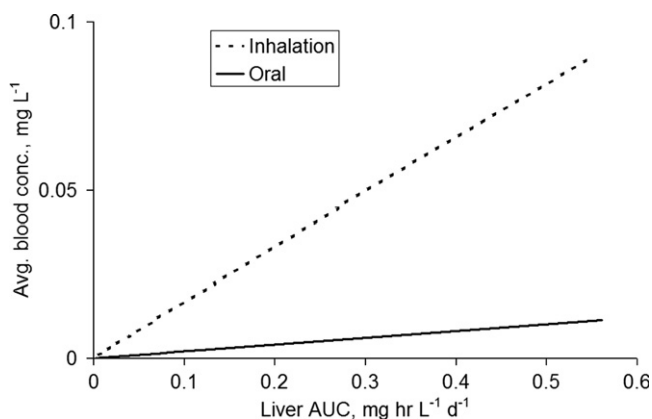
Fig. 2 illustrates the approach to the derivation of BE values based on the cancer risk assessment by USEPA. The starting point for the derivation is the lower bound on the estimated dose associated with a 10% increase in tumor frequency ( $\text{LED}_{10}$ ) from the animal bioassays. Because increases in tumors were observed in several tissues and because the mechanism or mode of action for the tumor responses are not known, no specific internal dose metric could be selected as most relevant. However, blood concentrations are directly related to tissue concentrations throughout the body based on the organ-specific partition coefficients and are thus at least reflective of the relative magnitude of internal concentration within a given tissue. Because no data have been generated to validate mouse PBPK models for the two compounds (DBCM and BDCM) with cancer slope factors based on mouse tumor response data, animal PBPK modeling was not conducted for the POD. Instead, the human equivalent to the POD (the  $\text{LED}_{10}$  scaled



**Fig. 1.** Flowchart of approach for deriving BE values for the THM compounds for non-cancer endpoints. Effects on hepatic tissue were the most sensitive endpoint observed in animal studies for each of the THM compounds. Based on this, for each compound, the hepatic area under the curve (AUC) resulting from the external dose point of departure (POD) was estimated using the animal pharmacokinetic (PK) model. An equivalent human POD in terms of liver AUC was estimated by applying the default uncertainty factor for animal to human pharmacodynamic differences ( $U_{FA-PD}$ ). The human PK model was used to estimate the average blood concentration associated with this hepatic AUC. Finally, remaining uncertainty factors for human variability in pharmacodynamics ( $U_{FH-PD}$ ) and database uncertainties (where designated by USEPA) were applied to estimate target average blood concentrations. See text for further discussion of uncertainty factors and approach.



**Fig. 2.** Flowchart of approach to estimating cancer risk-specific average blood concentrations. No specific internal dose metric was identified as most relevant due to the variability in tumor sites observed and the lack of a validated PBPK model in mice (the most sensitive species for carcinogenic responses to DBCM and BDCM). LED<sub>10</sub>: lower bound on the estimated dose associated with a 10 percent increase in tumor incidence, as estimated by benchmark dose modeling conducted by USEPA (2005). BW<sup>3/4</sup>: interspecies dose scaling via bodyweight to the 3/4 power.



**Fig. 3.** Relationship between chloroform blood concentration and liver AUC in humans estimated using a PBPK model for inhalation-only exposure and oral-only exposure. Mixed exposures result in values of average blood concentration for a given hepatic AUC that are intermediate between those from the oral- and inhalation-only scenarios.

to bodyweight<sup>3/4</sup>, as identified by USEPA [2005]) was entered as an input into the human PBPK models for each of the three compounds with cancer slope factors to estimate daily average blood concentrations at this human equivalent POD. In addition, the risk-specific doses for risks from  $1 \times 10^{-6}$  to  $1 \times 10^{-4}$  were calculated based on the oral cancer slope factors estimated by USEPA (2005) (Table 2) for the three brominated THMs. Human blood

concentrations were modeled assuming daily bolus doses at these risk-specific doses to identify the average and estimated repeated peak blood concentrations consistent with these doses.

## 2.2. Results of modeling and identification of BE values

### 2.2.1. Relationship between hepatic AUC and average blood concentrations

Using the human PBPK model for each compound, the relationship between hepatic AUC and average blood concentrations was assessed under oral-only and inhalation-only exposure scenarios. The relationship between the two metrics was linear but route-specific (Fig. 3 for chloroform; other THMs give similar results). Under conditions of oral exposure, hepatic AUC is much greater for a given blood concentration than under conditions of inhalation exposure. This is consistent with the underlying physiology, as oral exposures result in direct absorption of compound from the gastrointestinal (GI) tract into the liver, with subsequent distribution to the venous blood supply. In contrast, inhalation exposures result in direct uptake to blood from the lungs, and subsequent distribution to liver is controlled by blood flow into the liver. For the purposes of using blood concentrations as a surrogate for liver AUC, an assumption of oral-only exposure results in the most conservative (i.e., lowest) estimates of blood concentration consistent with a target hepatic AUC, and this assumption was used in the BE derivation. Under conditions of mixed exposure routes or all inhalation exposure, higher average blood concentrations would be required to result in the target hepatic AUC.

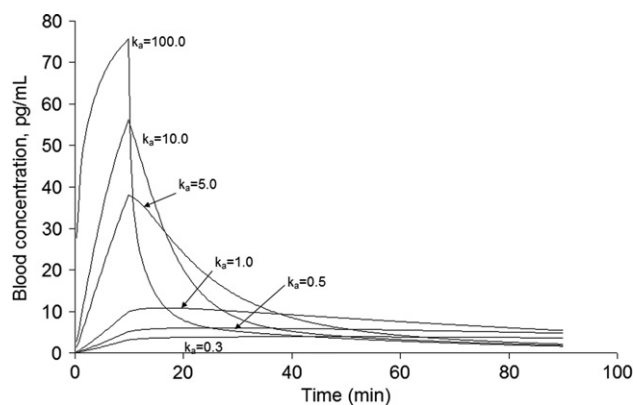
### 2.2.2. Non-cancer endpoints

The hepatic AUC associated with the POD for each THM compound using the PBPK models for dogs (chloroform) and rats (the brominated THMs) are reported in Table 3. The corresponding human equivalent hepatic AUC POD and corresponding average human blood concentrations (estimated from the human PBPK models for each THM) are also reported. Finally, the estimated average blood concentration consistent with the derivation of the RfD (BE<sub>RfD</sub>) for each compound is presented. Because of the rapid elimination kinetics and highly volatile nature of these compounds, blood concentrations at any given time point during a day can deviate substantially from the average estimate presented here and yet still be consistent with exposures not exceeding the critical hepatic AUC dose metric. For example, ingestion of a single dose of a THM equal to the RfD (through drinking water consumption, for example) can result in a rapid rise in blood concentration to a peak more than five times higher than the 24-h average concentration that would be associated with that same dose. Inhalation of THM compounds also results in a rapid rise and then fall in blood concentrations upon removal of the airborne exposure source.

Estimation of the magnitude of such peaks can be made using PBPK modeling by accounting for numerous sources of variability including variations in oral absorption rate and characteristics of the exposure episode. However, estimates of such peaks are far less certain than the 24-h average blood concentrations, which are relatively stable, and essentially insensitive to the oral absorption rate

**Table 3**  
Estimated internal dose metrics and 24-h average human blood concentrations consistent with the derivation of the RfD for each THM (see Fig. 1)

Compound	POD mg kg <sup>-1</sup> d <sup>-1</sup>	BE <sub>POD,animal</sub> Animal avg. blood conc., pg ml <sup>-1</sup>	Animal hepatic AUC mg h L <sup>-1</sup> d <sup>-1</sup>	UF <sub>A-PD</sub>	Human equivalent hepatic AUC mg h L <sup>-1</sup> d <sup>-1</sup>	BE <sub>POD,human</sub> Corresponding human avg. blood conc., pg ml <sup>-1</sup>	UF <sub>H-PD</sub>	UF <sub>D</sub>	BE <sub>RfD</sub> pg ml <sup>-1</sup>
Chloroform	1.2	4,400	0.12	3.2	0.038	750	3.2	1	230
DBCM	1.6	2,200	0.056	3.2	0.019	270	3.2	1	80
BDCM	0.8	670	0.019	3.2	0.006	190	3.2	3	20
TBM	2.6	2,900	0.074	3.2	0.025	420	3.2	1	130



**Fig. 4.** PBPK model simulations showing the impact of varying  $k_a$  (the rate of absorption of chloroform from the GI tract) following an oral dose of 20  $\mu\text{g}$  of chloroform in tap water over a ten minute period. The PBPK model of Haddad et al. (2006), used in this evaluation, incorporated an allometrically scaled  $k_a$  equivalent to approximately 0.7 for a 70-kg individual.

and exposure episode characteristics. But evaluation and interpretation of biomonitoring data for THMs must recognize that at any given time during the course of a day, concentrations in an individual several times higher than the target daily average concentration can occur without necessarily indicating exposures in excess of those considered to be tolerable. Conversely, concentrations below the daily average concentration would also be encountered depending on when sampling occurred in relation to exposure.

Fig. 4 illustrates the impact that varying only the oral absorption rate parameter in the PBPK model has on predicted blood concentrations following a single oral exposure. Because of the uncertainty associated with accurately predicting peak levels of biomarkers associated with a once daily exposure, experts at a recent workshop addressing technical and communications challenges in deriving biomonitoring equivalents recommended that for short-lived compounds, estimates of daily average blood concentrations were more reliable than estimates of peaks and are best used as a screening tool to evaluate average measured concentrations in a population (Hays et al., 2008). However, in individuals, the existence of transient peaks substantially above the BE should be recognized as potentially consistent with the BE values (Hays et al., 2008).

### 2.2.3. Cancer risk

Using the approach described in Fig. 2, the human equivalent POD and risk-specific doses associated with cancer risks of  $1 \times 10^{-6}$  to  $1 \times 10^{-4}$  were identified, and the daily average blood concentrations associated with daily exposure at these risk-specific doses were modeled (Table 4). The PBPK models implemented here were also used to predict peak blood concentrations associated with single daily dose exposures at the risk-specific doses to

provide an indication of the degree of variation that might plausibly be attributed to different exposure scenarios (Table 4). As discussed above, transient peak blood concentrations several times the averages presented in Table 4 are also consistent with exposure at these risk-specific doses, but it is difficult to obtain a reliable estimate of such peaks. However, for rapidly metabolized compounds, it is important to recognize and reflect the substantial variation in measured blood concentrations that may result from equivalent daily exposures under differing temporal patterns (Hays et al., 2008).

### 2.3. Discussion of sources of variability and uncertainty

A number of issues affect the interpretation of, and confidence in, the BEs developed for the four THMs. These factors include the impact of temporal variations in exposure patterns for rapidly eliminated compounds, uncertainties regarding the pharmacokinetic models used, mechanistic considerations related to the carcinogenicity of the THMs, interpreting blood levels above the BEs, and methods for addressing simultaneous exposures to four THM compounds. These issues are discussed below.

#### 2.3.1. Temporal variations: exposure, sampling, and short half-life

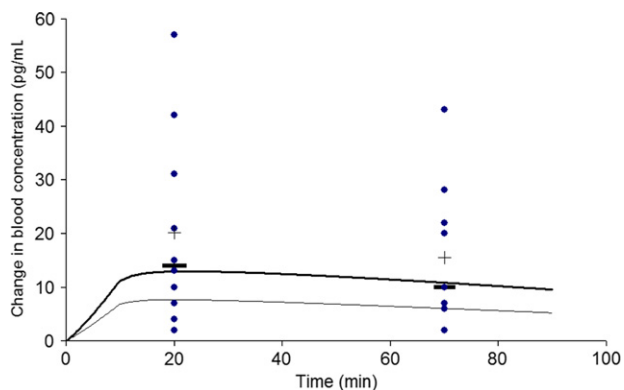
For compounds with very short elimination half-lives such as the THMs, both the variability in recent exposure behaviors and the longer term exposure profiles are relevant to interpreting blood levels with respect to BE values. Activities of an individual have implications for understanding whether measured levels in that individual represent a peak exposure (e.g., did the study participant shower immediately prior to sample collection? Were levels of THMs in the tap water at peak levels when the activity occurred?) or more typical exposures. Researchers are working to evaluate the relationships between exposure patterns and pathways and note the significant changes in blood concentrations that follow usage of THM-containing water (Backer et al., 2008; Ashley et al., 2005; Villanueva et al., 2007b). However, this type of information is not necessarily captured by questionnaire data or available for use in interpreting cross-sectional population-based biomonitoring data. Interpretation is further complicated by the fact that the concentrations of THMs in drinking water fluctuate (Ashley et al., 2005), with concentrations depending on such factors as the season, water temperature, amount of chlorine added by the treatment facility, and the amount of organic matter in the source water (USEPA, 2006a). The RfD and other health-based chronic exposure guidelines are set at levels designed to be protective for exposures over a specified period of time (e.g., one week, several months, or a lifetime), while biomonitoring data provide only a snapshot at a particular point in time. This will necessarily limit the interpretation of cross-sectional biomonitoring data for such compounds in terms of chronic health risks without substantial additional data on current and ongoing exposure characteristics.

**Table 4**

Human equivalent LED<sub>10</sub> estimates for cancer endpoints (USEPA, 2005), corresponding average and peak blood concentrations at the LED<sub>10</sub> estimated using the human PBPK models, and extrapolated average and peak modeled human blood concentrations for the  $10^{-6}$  to  $10^{-4}$  risk range for three THM compounds

Compound	Human equivalent LED <sub>10</sub> , $\text{mg kg}^{-1} \text{d}^{-1}$	Modeled human blood concentrations associated with LED <sub>10</sub> , $\text{pg ml}^{-1}$		Range of modeled human blood concentrations (BEs) associated with $10^{-6}$ to $10^{-4}$ risk-specific doses, $\text{pg ml}^{-1}$	
		Average	Peak	Average	Peak
DBCM	2.5	16,000	120,000	0.16–16	1.2–120
BDCM	3.0	15,000	120,000	0.15–15	1.2–120
TBM	22	740,000	5,000,000	7.4–740	50–5000

Chloroform is not included in this table because USEPA has determined that the non-cancer RfD is protective for cancer in humans.



**Fig. 5.** Comparison of chloroform PBPK model predictions (solid lines) with experimental data on blood levels resulting from water ingestion (closed circles). Data from Backer et al. (2000) represent measured change from baseline chloroform concentrations in whole blood following ingestion of 1 L of water (measured water concentrations ranging from 18 to 23  $\mu\text{g l}^{-1}$ ) over 10 min. Measurements were taken 10 and 60 min following end of ingestion. Horizontal lines and crosses represent median and mean measured values for 10 individuals at each time point, respectively. Modeled profiles demonstrate predicted blood concentrations following ingestion of the water at that range of concentrations using the model of Haddad et al. (2006). The model results are within the range of the measured data, but the model under-predicts the median measured changes in blood concentrations by a factor of about 2, and there is significant inter-individual variability in the observed changes in blood concentrations following ingestion of water.

### 2.3.2. Pharmacokinetic variability and uncertainties in PBPK models

The PBPK models implemented here represent a central estimate of the metabolic and elimination behavior of these compounds in adult humans. Previous modeling studies of the variability in physiological or metabolic parameters in the general population demonstrate differences in elimination profile on the order of 2- to 3-fold for volatile organic compounds (Pelekis et al., 2001) (for example, due to differences in metabolic capability between adults and children [Nong et al., 2006]). Few data are available from controlled exposure studies to assess the performance of these pharmacokinetic models for THMs in humans. Fig. 5 presents a small data set on changes in blood concentrations (measured minus baseline concentrations) following controlled ingestion of water with measured chloroform concentrations for ten individuals (data from Backer et al., 2000) and PBPK model simulations of the same exposures. The range of observed changes in blood levels of chloroform is significant, even though each individual was exposed to a similar amount of chloroform (however, no information on individual bodyweights was available). More recently, Backer et al. (2008) have reported that polymorphisms in metabolizing enzymes may also contribute to variability in THM pharmacokinetics.

Fig. 5 also highlights several other important issues. First, the PBPK model simulations using the mean parameter set predict changes in blood chloroform concentrations a factor of two to three lower than the median and mean of the observed changes. A Monte Carlo simulation incorporating variability in physiological and metabolic parameters (parameter distributions from Tan et al., 2007) produced estimates that encompassed the mean and median observed changes in blood concentrations, but the upper bound of the simulated changes were still more than a factor of two lower than the upper bound observed in this sample of ten individuals (results not shown). Second, changes in blood chloroform concentration from baseline varied by approximately a factor of 3 between the mean increase and the greatest observed increase in blood chloroform levels, even within this small sample of 10 individuals exposed to similar doses of chloroform under controlled conditions. These data suggest that although the models used in the derivation of the BE values produce results within the range of the observed data, the models tend to under-predict the average

and range of impacts of the bolus ingestion of chloroform. In contrast, an initial analysis of a recent data set published for BDCM (Leavens et al., 2007) suggests that the current published PBPK models may over-predict average blood concentrations associated with bolus ingestion of BDCM.

One consequence of the choice of target hepatic AUC following oral exposure as the critical dose metric is that many of the details of the PBPK models become irrelevant to the estimation of the human average blood concentration corresponding to the target hepatic AUC. That is, under conditions of linear kinetics (conditions which hold in the conceivable exposure ranges for humans exposed environmentally to THMs), the modeled relationship between daily hepatic AUC and daily average blood concentration depends solely on the partition coefficient between liver and blood. There are few published data on variability in partition coefficients among individuals. In one recent study, blood to air partition coefficients for six volatile organic compounds were relatively consistent across individuals, with coefficients of variation of less than 20% and less than 10% differences between males and females and between adults and children (Mahle et al., 2007). The model parameters for metabolism and oral absorption rate do not affect the relationship between daily hepatic AUC and estimated average blood concentration for compounds such as these that undergo nearly complete metabolism and elimination over the course of a day. In contrast, estimates of peak concentrations in liver or blood are highly sensitive to metabolic and absorption rate parameters. However, the BE values derived here for cancer endpoints, which translate external exposures at risk-specific doses directly to predicted average blood concentrations, are sensitive to the metabolic parameters of these models. Additional data sets involving controlled exposures should be conducted to refine and parameterize the human models for these compounds.

### 2.3.3. Mechanistic considerations related to the carcinogenicity of the THMs

The four THM compounds are considered by USEPA to be carcinogenic. However, USEPA has determined, based on well-studied mechanistic considerations, that chloroform is not likely to produce cancer in humans at exposures below the RfD (Schoeny et al., 2006). While no mode of action has been established for the other THMs (USEPA, 2005), a recent cancer bioassay for BDCM found no excess incidence of tumors in female mice and male rats exposed to BDCM via drinking water (NTP, 2006) at daily doses just below the lower end of the previous, positive, NTP gavage study dose range. The study protocol used three administered dose levels and a relevant route of administration (drinking water) at the maximum palatable concentrations of BDCM. No increases in tumors at any site in either species were observed, in contrast to the findings of liver, kidney, and large intestine tumors in the previous corn oil gavage bioassays (summarized in USEPA, 2005). Because the maximum doses used in this bioassay are approximately one half of the lowest doses used in the corn oil gavage studies, no clear conclusions regarding the effect of vehicle can be drawn. However, these data suggest the possibility that, as for chloroform, the carcinogenic response to BDCM in the corn oil gavage bioassay may be sensitive to peak concentrations resulting from bolus administration in corn oil gavage and perhaps of less relevance to human drinking water exposures.

### 2.4. Confidence assessment

Guidelines for the derivation of BE values (Hays et al., 2008) specify consideration of two main elements in the assessment of confidence in the derived BE values: Robustness of the available pharmacokinetic models and data, and understanding of the rela-

relationship between the measured biomarker and the critical or relevant target tissue dose metric.

#### 2.4.1. Robustness of pharmacokinetic data and models

In the case of the THMs, the pharmacokinetic data and models for rodents are based on substantial data sets, while those available for humans have not been assessed against much experimental data. In the case of the non-cancer BE derivations, the most sensitive parameter within the human PBPK model is the partition coefficient between liver and blood. This value is dictated largely by the physical/chemical properties of these compounds, which are reasonably well understood (Gargas et al., 1989) and available data indicate relatively low variability in partition coefficients among individuals (Mahle et al., 2007); therefore confidence in this aspect of the non-cancer BE values is high. The cancer risk-based BE values are more sensitive to metabolic parameters for the individual compounds, and as discussed above, the limited available human data sets suggest that the model predictions of average blood concentrations for a given risk-specific dose may be underestimates for chloroform and overestimate the actual average BDCM concentrations. In addition, the cancer risk-specific doses require extrapolation far below the range of observed data used to derive the basic model parameters in rodents and in humans. Thus, confidence in this aspect of the derivation of BE values for cancer is low.

#### 2.4.2. Relationship of measured biomarker to critical or relevant dose metric(s)

The non-cancer endpoint of interest for all four compounds is liver toxicity, which may be related to production of reactive metabolites. Thus, the critical dose metric will be related to metabolite production and could be related to either cumulative or peak metabolite concentrations. Hepatic AUC of the parent compound is directly related to daily cumulative metabolite production when linear metabolism conditions hold; however, peak metabolite concentration is not directly related to hepatic AUC of parent compound. As discussed above, modeling of actual peak liver concentrations is highly uncertain. For this reason, daily cumulative metabolite production was selected as the relevant dose metric. Daily average blood concentration, the biomarker metric used in the non-cancer BE derivation, is directly related to daily liver AUC, so confidence in this element of the non-cancer BE derivation is high. For cancer, various target organ sites are of interest based on the results of laboratory rodent studies, and the mechanism of action is not agreed upon for THM compounds other than chloroform, although reactive metabolites are likely to be important. Despite a lack of detailed mechanistic information for all four THM compounds, average blood concentrations are likely to be relevant for critical internal dose metrics for most cancer target sites observed, except potentially the intestinal tumors observed following gavage administration of TBM, which might indicate a local, portal of entry response not directly related to blood concentrations. Based on this assessment, confidence in this element of the cancer risk-specific BE values is medium.

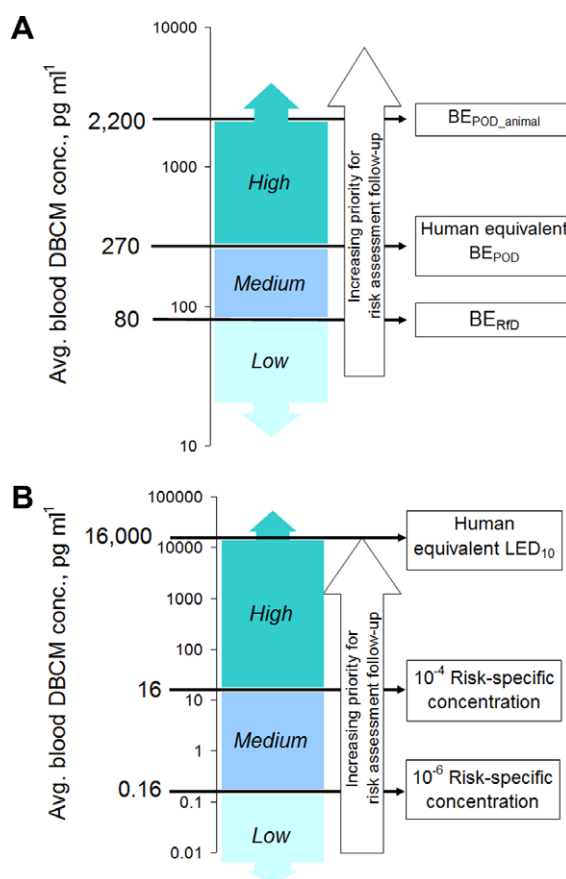
Overall, these assessments suggest high confidence in the non-cancer BE values, and low to medium confidence in the cancer risk-specific BE values.

### 3. Discussion and interpretation of BE values

The BE values presented here are screening values and can be used to provide a screening-level assessment of measured blood levels of THMs in population- or cohort-based studies. BE values do not represent diagnostic criteria and cannot be used to evaluate the likelihood of an adverse health effect in an individual or even among a population. BEs are not “bright lines” separating safe from

unsafe blood levels. Chronic RfD values are set at levels that are designed to be health-protective for daily exposure for a full lifetime of exposure. The BE values identified here are tied to daily average blood concentration. For short-lived compounds, transient blood concentrations several times higher (and lower) than these target daily average concentrations would be expected in individuals resulting from episodic use of drinking water under conditions in which the target average daily concentration was not exceeded. Thus, a measured blood concentration exceeding the corresponding BE value in a single sample of blood from an individual may or may not reflect continuing elevated exposure.

As discussed above, for short-lived compounds, BEs should be used as tools to evaluate biomonitoring data on a population basis, rather than for assessment of an individual person's biomonitoring levels. If the mean of the population-based biomonitoring data is below the BEs, then in general the population is experiencing exposures lower than those considered consistent with the RfD or a target cancer risk range, even though some of the blood samples may show higher concentrations. However, the potential for heterogeneous exposures within the population, combined with the transient nature of blood concentrations of these compounds, will limit the ability to interpret upper tails of the distribution of measured blood concentrations from cross-sectional studies. Fig. 6 illustrates the BE values derived for DBCM in this paper in a framework that can be useful for interpretation of biomonitoring data



**Fig. 6.** Example display of BE values for DBCM in accordance with the guidelines for BE communication (LaKind et al., in 2008). The BE values presented here are appropriate for evaluation of the central tendency of biomonitoring data from population studies, rather than for interpretation of data for individuals (see text discussion). Figures present the general demarcations between regions of low, medium, and high priority for risk assessment or risk management follow-up based on values from Tables 3 and 4. (A) Display of the non-cancer BE<sub>RfD</sub> and underlying derivation values. (B) Display of the cancer risk-based BE values.

according to guidelines developed for the interpretation and communication of BE values (LaKind et al., 2008).

Exposure guidance values from organizations other than USEPA, could also be used as the basis for derivation of BE values and interpretation of biomonitoring data. The Agency for Toxic Substances and Disease Registry (ATSDR) has established chronic oral MRL values for chloroform ( $0.01 \text{ mg kg}^{-1} \text{ d}^{-1}$ ), DBCM ( $0.09 \text{ mg kg}^{-1} \text{ d}^{-1}$ ), and TBM ( $0.02 \text{ mg kg}^{-1} \text{ d}^{-1}$ ) (ATSDR, 1997, 2005). In general, these values are based on similar toxic endpoints (and in most cases, the same toxicity studies) as are the USEPA values. Differences in the values are generally due to different methods for identifying a POD (benchmark dose modeling by the USEPA versus application of uncertainty factors for LOAEL to NOAEL by ATSDR) and different judgments regarding uncertainty factors required. In general, the BE values derived from the USEPA RfDs can be extrapolated linearly to derive BE values corresponding to the ATSDR MRL values.

### 3.1. Implications of simultaneous exposures to four THM compounds

THMs are regulated in drinking water as a combined group of four compounds with an MCL (maximum contaminant level) of  $80 \mu\text{g L}^{-1}$  (USEPA, 2006a). However, as indicated by the range of RfD values and related  $\text{BE}_{\text{RfD}}$  values, the toxic potency is not equivalent for these compounds, and equal exposures do not result in equal blood levels due to differences in metabolic rates, partition coefficients, etc. Thus, assessment of the concentration of THMs in blood by summing the concentrations of the four compounds may not be scientifically justifiable. One approach for combining available data for these compounds might involve a hazard quotient/hazard index approach, analogous to the approach used for risk screening across compounds in assessments of exposure to multiple chemicals at hazardous waste sites. In the case of THM compounds, all four compounds demonstrate liver toxicity as among the most sensitive non-cancer toxicological effects in animal studies, lending support to a hazard index approach. Specifically, the concentrations in blood of each THM could be related to that compound's  $\text{BE}_{\text{RfD}}$  value for an individual, with the resulting ratios summed to obtain the hazard index (HI):

$$\text{HI} = \sum_{i=1}^4 \frac{[\text{THM}_i]}{\text{BE}_{\text{RfD},i}} \quad (1)$$

The current mixtures risk assessment paradigm implies no excess risks when the HI is below 1. This method requires examination of biomonitoring data on an individual-by-individual basis, and thus may be limited to situations where the biomonitoring data for all of the individual compounds are available on an individual-by-individual basis. However, as discussed above, blood concentrations in an individual are likely to fluctuate widely due to the rapid absorption and elimination of these compounds, and hazard indices of greater than 1 may occur in an individual without necessarily indicating daily or long-term exposures in excess of those consistent with the RfD. Assessment of the impact of combined exposure to THMs on cancer risk estimates could theoretically proceed in an analogous manner, with estimated compound-specific risks summed across the three brominated THM compounds, similar to approaches used in assessing cancer risks from mixtures on an external exposure basis. However, the risk assessment paradigm for both cancer and non-cancer endpoints incorporates an assumption of constant exposure for a full lifetime. Conclusions regarding either cancer or non-cancer risks based on biomonitoring data derived from cross-sectional studies for rapidly metabolized compounds such as THMs must be tempered by the recognition that such biomonitoring efforts may not accurately reflect long term average blood concentrations in individuals.

### 3.2. Risk/benefit considerations for drinking water disinfection

As noted by EPA (USEPA, 2006a), DBPs present a case in which there are obvious trade-offs between decreasing the potential risks associated with DBPs and increasing risk from exposure to pathogens in drinking water and “[e]liminating or significantly decreasing disinfection to stop disinfection byproduct formation would seriously compromise overall public health protection” (USEPA, 2006a). Complicating attempts to quantify the risk/benefit “trade-off” is the lack of commonly used methods for comparing two distinctly different types of risks, i.e., a potential risk of cancer from lifetime exposure to DBPs versus health benefits associated with protection against acute illness from exposures to pathogens in untreated waters. One attempt to perform such an analysis focused on reduction of risk of infection by *Cryptosporidium parvum* compared with risk of renal cell cancer from exposure to bromate in water disinfected by ozonation (Havelaar et al., 2000). The authors used the concept of disability adjusted life-years (DALYs) and found a net health benefit associated with disinfection of drinking water, even though estimated bromate levels were above World Health Organization guidelines (Ashbolt, 2004). These results cannot be applied directly to this current assessment because the method of water treatment, and therefore the DBPs formed, differ. However, it is believed that the potential risks associated with DBP exposure are insignificant compared to the microbial risks that would transpire without disinfection (Bull et al., 1995).

## 4. Conclusions

The BE values developed and described here provide quantitative tools that can be used in a screening-level assessment of biomonitoring data for chloroform, DBCM, BDCM, and TBM in human blood. These levels do not represent a bright line between safe and unsafe exposure levels, nor can they serve as diagnostic values for application to individual measured levels. Instead, the BE values presented here can provide a health-based context for evaluating biomonitoring data sets and assist in prioritization of further research, risk characterization, and risk management activities. BE values do not represent diagnostic criteria and cannot be used to evaluate the likelihood of an adverse health effect in an individual or even among a population.

Interpretation of measured blood concentrations of THMs will continue to pose challenges due to the rapid metabolism and elimination of these compounds. While these BE values refer to long-term average concentrations of THMs in blood, biomonitoring results for individuals are generally based on single, snapshot measurements of compounds and are highly influenced by whether an exposure (for example, due to showering or drinking water) has occurred recently. Thus, the BE values derived here, which correspond to 24-h average blood concentrations consistent with exposure guidance values, are most appropriately applied to assess the central tendency and overall pattern of results for a sampled population, rather than extreme values or individual measurements. In addition, these BE values should be used in combination with other tools and information to evaluate and interpret biomonitoring data for the THMs. Further discussion of interpretation and communications aspects of BE values is presented in LaKind et al. (2008).

### Conflict of interest disclosure statement

The authors declare that they have no conflicts of interest.

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## References

- Agency for Toxic Substances and Disease Registry (ATSDR), 1997. Toxicological Profile for Chloroform. Accessed on the web at: <[www.atsdr.cdc.gov](http://www.atsdr.cdc.gov)>.
- Agency for Toxic Substances and Disease Registry (ATSDR), 2005. Toxicological Profile for Bromoform and Dibromochloromethane. Accessed on the web at: <[www.atsdr.cdc.gov](http://www.atsdr.cdc.gov)>.
- Ashbolt, N.J., 2004. Risk analysis of drinking water microbial contamination versus disinfection by-products (DBPs). *Toxicology* 198, 255–262.
- Ashley, D.L., Blount, B.C., Singer, P.C., Depaz, E., Wilkes, C., Gordon, S., Lyu, C., Masters, J., 2005. Changes in blood trihalomethane concentrations resulting from differences in water quality and water use activities. *Arch. Environ. Occup. Health* 60, 7–15.
- Backer, L.C., Ashley, D.L., Bonin, M.A., Cardinali, F.L., Kieszak, S.M., Wooten, J.V., 2000. Household exposures to drinking water disinfection by-products: whole blood trihalomethane levels. *J. Expo. Anal. Environ. Epidemiol.* 10, 321–326.
- Backer, L.C., Lan, Q., Blount, B.C., Nuckols, J.R., Branch, R., Lyu, C.W., Kieszak, S.M., Brinkman, M.C., Gordon, S.M., Flanders, W.D., Romkes, M., Cantor, K.P., 2008. Exogenous and endogenous determinants of blood trihalomethane levels after showering. *Environ. Health Perspect.* 116, 57–63.
- Bonin, M.A., Silva, L.K., Smith, M.M., Ashley, D.A., Blount, B.C., 2005. Measurement of trihalomethanes and methyl *tert*-butyl ether in whole blood using gas chromatography with high-resolution mass spectrometry. *J. Anal. Toxicol.* 29, 81–89.
- Bull, R.J., Birnbaum, L.S., Cantor, K.P., Rose, J.B., Butterworth, B.E., Pegram, R., Tuomisto, J., 1995. Water chlorination: essential process or cancer hazard? *Fundam. Appl. Toxicol.* 28, 155–166.
- Corley, R.A., Mendrala, A.L., Smith, F.A., Staats, D.A., Gargas, M.L., Conolly, R.B., Andersen, M.E., Reitz, R.H., 1990. Development of a physiologically based pharmacokinetic model for chloroform. *Toxicol. Appl. Pharmacol.* 103, 512–527.
- Dodds, L., King, W., Allen, A.C., Armson, B.A., Fell, D.B., Nimrod, C., 2004. Trihalomethanes in public water supplies and risk of stillbirth. *Epidemiology* 15, 179–186.
- Gargas, M.L., Burgess, R.J., Voisard, D.E., Cason, G.H., Andersen, M.E., 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. *Toxicol. Appl. Pharmacol.* 98, 87–99.
- Haddad, S., Tardif, G.C., Tardif, R., 2006. Development of physiologically based toxicokinetic models for improving the human indoor exposure assessment to water contaminants: trichloroethylene and trihalomethanes. *J. Toxicol. Environ. Health A* 69, 2095–2136.
- Havelaar, A.H., De Hollander, A.E., Teunis, P.F., Evers, E.G., Van Kranen, J., Versteegh, J.F., Van Koten, J.E., Slob, W., 2000. Balancing the risks and benefits of drinking water disinfection: disability adjusted life-years on the scale. *Environ. Health Perspect.* 108, 15–21.
- Hays, S.M., Becker, R.A., Leung, H.W., Aylward, L.L., Pyatt, D.W., 2007. Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. *Reg. Toxicol. Pharmacol.* 47, 6–109.
- Hays, S.M., Aylward, L.L., LaKind, J.S., Bartels, M.J., Barton, H.A., Boogaard, P.J., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Lipscomb, J., Kilpatrick, M.E., Krewski, D., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.-M., Viau, C., Yager, J.W., 2008. Guidelines for the derivation of biomonitoring equivalents: Report from the Biomonitoring Equivalents Expert Workshop. *Reg. Toxicol. Pharmacol.* 51, S4–S15.
- Heywood, R., Sortwell, R.J., Noel, P.R.B., Street, A.E., Prentice, D.E., Roe, F.J.C., Wadsworth, P.F., Worden, A.N., Van Abbe, N.J., 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. *J. Environ. Pathol. Toxicol.* 2, 835–851.
- King, W.D., Marrett, L.D., Woolcott, C.G., 2000. Case-control study of colon and rectal cancers and chlorination by-products in treated water. *Cancer Epidemiol. Biomarkers Prev.* 9, 813–818.
- LaKind, J.S., Aylward, L.L., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Kilpatrick, M.E., Krewski, D., Bartels, M.J., Barton, H.A., Boogaard, P.J., Lipscomb, J., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.-M., Viau, C., Yager, J.W., Hays, S.M., 2008. Guidelines for the communication of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents expert Workshop. *Reg. Toxicol. Pharmacol.* 51, S16–S26.
- Leavens, T.L., Blount, B.C., Demarini, D.M., Madden, M.C., Valentine, J.L., Case, M.W., Silva, L.K., Warren, S.H., Hanley, N.M., Pegram, R.A., 2007. Disposition of bromodichloromethane in humans following oral and dermal exposure. *Toxicol. Sci.* 2007 99, 432–445.
- Lilly, P.D., Andersen, M.E., Ross, T.M., Pegram, R.A., 1997. Physiologically based estimation of *in vivo* rates of bromodichloromethane metabolism. *Toxicology* 124, 141–152.
- Lilly, P.D., Andersen, M.E., Ross, T.M., Pegram, R.A., 1998. A physiologically based pharmacokinetic description of the oral uptake, tissue dosimetry, and rates of metabolism of bromodichloromethane in the male rat. *Toxicol. Appl. Pharmacol.* 150, 205–217.
- Luciene da Silva, M., Charest-Tardif, G., Krishnan, K., Tardif, R., 1999. Influence of oral administration of a quaternary mixture of trihalomethanes on their blood kinetics in the rat. *Toxicol. Lett.* 106, 49–57.
- Mahle, D.A., Gearhart, J.M., Grigsby, C.C., Mattie, D.R., Barton, H.A., Lipscomb, J.C., Cook, R.S., 2007. Age-dependent partition coefficients for a mixture of volatile organic solvents in Sprague-Dawley rats and humans. *J. Toxicol. Environ. Health A* 70, 1745–1751.
- Meek, M., Beauchamp, R., Long, G., Moir, D., Turner, L., Waker, M., 2002. Chloroform: exposure estimation, hazard characterization, and exposure-response analysis. *J. Toxicol. Environ. Health B* 5, 283–334.
- Nieuwenhuijsen, M.J., Toledano, M.B., Eaton, N.E., Fawell, J., Elliott, P., 2000. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. *Occup. Environ. Med.* 57, 73–85.
- NRC (National Research Council), 2006. Human Biomonitoring for Environmental Chemicals. Committee on Human Biomonitoring for Environmental Toxicants, National Research Council. National Academies Press.
- NTP (National Toxicology Program), 2006. NTP Toxicology and carcinogenesis studies of bromodichloromethane (CAS No. 75-27-4) in male F344/N rats and female B6C3F1 mice (Drinking Water Studies). *Natl. Toxicol. Program Tech. Rep. Ser.* 532, 1–248.
- Nong, A., McCarver, D.G., Hines, R.N., Krishnan, K., 2006. Modeling interchild differences in pharmacokinetics on the basis of subject-specific data on physiology and hepatic CYP2E1 levels: a case study with toluene. *Toxicol. Appl. Pharmacol.* 214, 78–87.
- Pelekis, M., Gephart, L.A., Lerman, S.E., 2001. Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. *Regul. Toxicol. Pharmacol.* 33, 12–20.
- Poobalasingham, N., Payne, J., 1978. The uptake and elimination of chloroform in man. *Br. J. Anaesth.* 50, 325–329.
- Schoeny, R., Haber, L., Dourson, M., 2006. Data considerations for regulation of water contaminants. *Toxicology* 221, 217–224.
- Tan, Y.M., Liao, K.H., Conolly, R.B., Blount, B.C., Mason, A.M., Clewell, H.J., 2006. Use of a physiologically based pharmacokinetic model to identify exposures consistent with human biomonitoring data for chloroform. *J. Toxicol. Environ. Health A* 69, 1727–1756.
- Tan, Y.M., Liao, K.H., Clewell, H.J., 2007. Reverse dosimetry: interpreting trihalomethanes biomonitoring data using physiologically based pharmacokinetic modeling. *J. Expo. Sci. Environ. Epidemiol.* 17, 591–603.
- Teuschler, L.K., Rice, G.E., Wilkes, C.R., Lipscomb, J.C., Power, F.W., 2004. A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. *J. Toxicol. Environ. Health A* 67, 755–777.
- Toledano, M.B., Nieuwenhuijsen, M.J., Best, N., Whitaker, H., Hambly, P., de Hoogh, C., Fawell, J., Jarup, L., Elliott, P., 2005. Relation of trihalomethane concentrations in public water supplies to stillbirth and birth weight in three water regions in England. *Environ. Health Perspect.* 113, 225–232.
- USEPA, 2005. Drinking Water Criteria Document for Brominated Trihalomethanes. Office of Water. EPA-822-R-05-11.
- USEPA, 2006a. Stage 2 Disinfectants and Disinfection Byproduct Rule (Stage 2 DBP rule). Available from: <<http://www.epa.gov/safewater/disinfection/stage2/basicinformation.html#ten>>.
- USEPA, 2006b. Integrated Risk Information System. Chloroform. Last updated on Wednesday, March 8th, 2006. Available from: <<http://www.epa.gov/iris/subst/0025.htm>>.
- USEPA, 2006c. Exposures and Internal Doses of Trihalomethanes in Humans: Multi-Route Contributions from Drinking Water. National Center for Environmental Assessment, Office of Research and Development, Cincinnati, OH, EPA 600/R-06/087.
- Villanueva, C.M., Cantor, K.P., Grimalt, J.O., Malats, N., Silverman, D., Tardon, A., Garcia-Closas, R., Serra, C., Carrato, A., Castano-Vinyals, G., Marcos, R., Rothman, N., Real, F.X., Dosemeci, M., Kogevinas, M., 2007a. Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. *Am. J. Epidemiol.* 165, 148–156.
- Villanueva, C.M., Gagniere, B., Monfort, C., Nieuwenhuijsen, M.J., Cordier, S., 2007b. Sources of variability in levels and exposure to trihalomethanes. *Environ. Res.* 103, 211–220.