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Biomonitoring Equivalents for inorganic arsenic

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ABSTRACT

This paper presents Biomonitoring Equivalents (BEs) for inorganic arsenic. Biomonitoring Equivalents (BEs) are defined as the concentration or range of concentrations of a chemical or its metabolite in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline, and are derived by integrating available data on pharmacokinetics with existing chemical risk assessments. This study reviews available health-based exposure guidance values for arsenic based on recent evaluations from the United States Environmental Protection Agency (US EPA), US Agency for Toxic Substances and Disease Registry (ATSDR) and Health Canada (HC). BE values corresponding to the Reference Dose (RfD) or risk-specific doses for cancer endpoints from these agencies were derived based on kinetic data (urinary excretion) from controlled dosing studies in humans. The BE values presented here provide estimates of the sum of inorganic arsenic-derived urinary biomarkers (inorganic arsenic, monomethylated arsenic, and dimethylated arsenic). The BE associated with the United States Environmental Protection Agency's Reference Dose and the Agency for Toxic Substances and Disease Registry's Minimal Risk Level is 6.4 μg arsenic/L urine. The BEs associated with the various cancer risk assessments are significantly lower. These BE values may be used as screening tools for evaluation of biomonitoring data for inorganic arsenic in a public health risk context.

1. Introduction

Interpretation of measurements of concentrations of chemicals in samples of urine or blood from individuals in the general population is hampered by the general lack of screening criteria for evaluation of such biomonitoring data in a health risk context. Without such screening criteria, biomonitoring data can only be interpreted in terms of exposure trends, but cannot be used to evaluate which chemicals may be of concern in the context of current risk assessments. Such screening criteria would ideally be based on robust datasets relating potential adverse effects to biomarker concentrations in human populations (see, for example, the U.S. Centers for Disease Control and Prevention (CDC) blood lead level of concern; http://www.cdc.gov/nceh/lead/). However, development of such epidemiologically-based screening criteria is a resource- and time-intensive effort. As an interim approach, the development of Biomonitoring Equivalents (BEs) has been proposed, and guidelines for the derivation and communication of these values have been developed (Hays et al., 2007, 2008; LaKind et al., 2008).

A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or Tolerable Daily Intake (TDI). Existing chemical-specific pharmacokinetic data are used to estimate biomarker concentrations that are consistent with the Point of Departure (POD) used in the derivation of an exposure guidance value (such as the RfD or TDI), and with the exposure guidance value itself. BEs can be estimated using available human or animal pharmacokinetic data (Hays et al., 2008), and BEs have been derived for numerous compounds including acrylamide, cadmium, 2,4-dichlorophenoxyacetic acid, toluene, and others (reviewed in Hays and Aylward 2009). BEs are intended to be used as screening tools to provide an assessment of which chemicals have large, small, or no margins of safety compared to existing risk assessments and exposure guidance values. BE values are only as robust as are the

Abbreviations: ADI, acceptable daily intake; As, arsenic; iAs, inorganic arsenic; BE, Biomonitoring Equivalent; BE_{POD}, Biomonitoring Equivalent point of departure; DMA, dimethylarsinic acid (cacodylic acid) ; FAO, Food and Agricultural Organization of the United Nations; HC, Health Canada; LOAEL, lowest observed adverse effect level; MAC, maximum allowable concentration; MMA, methylarsonic acid; MRL, minimal risk level; NOAEL, no observed adverse effect level; PBPK, physiologically based pharmacokinetic; PMRA, Pest Management Regulatory Agency; POD, point of departure; RfD, reference dose; TDI, tolerable daily intake; USEPA, United States Environmental Protection Agency; UF, uncertainty factor; WHO, World Health Organization.

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Table 1
Available exposure guidance values for inorganic arsenic based on non-cancer endpoints. All of the available chronic exposure guidance values are based on data from studies of human populations exposed to arsenic in drinking water (or contaminated soy sauce in the case of ATSDR's acute MRL). Different agencies have selected different points of departure for their derivations.

Organization, criteria (year of evaluation)	Study description	Critical endpoint and dose	Uncertainty factors	Guidance value
US EPA, RfD (1993), Health Canada, TDI (2008) [Inorganic arsenic][a]	Human cohort exposed to arsenic in drinking water Tseng et al. (1968) and Tseng (1977)	• Hyperpigmentation, keratosis and possible vascular complications • NOAEL: 0.009 mg/L converted to 0.0008 mg/kg-d	3	3×10^{-4} mg/kg-d
ATSDR, chronic MRL (2007) [inorganic arsenic]	Human cohort Tseng et al. (1968) and Tseng (1977)	• Human cohort: dermal effects in Taiwanese farming population • NOAEL 0.0008 mg/kg-d	3	3×10^{-4} mg/kg-d
ATSDR, acute MRL (2007) [inorganic arsenic]	Human cohort Mizuta et al. (1956)	• Human cohort: facial edema and gastrointestinal effects • Cohort exposed to contaminated soy sauce for 2–3 weeks • LOAEL 0.05 mg/kg-d	10	5×10^{-3} mg/kg-d

RfD: reference dose, for chronic exposure.
MAC: maximum acceptable concentration.
MRL: minimal risk level.
[a] US EPA value adopted by Health Canada (http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2008-08/index-eng.php).

underlying exposure guidance values and pharmacokinetic data used to derive the values. BE values are not intended to be diagnostic for potential health effects in humans, either individually or among a population.

This manuscript presents the background and derivation of BE values for interpreting biomarkers of exposure to inorganic arsenic. Arsenic is a naturally-occurring metal which occurs in both organic and inorganic forms (ATSDR, 2007; Hughes, 2006). It is found naturally in air, water, and soils, primarily in the inorganic form. It exists in the +5 oxidation state in oxygenated water sources, whereas it exists in the +3 oxidation state in low oxygen, reducing water sources. Arsenic can be released into the environment due to activities associated with mining and smelting of metal ores, and due to coal-burning energy production. It is used in a variety of pesticides, medical and veterinary antiparasitic treatments, and in the manufacture of semiconductors and other products. Inorganic arsenic is found in grains and produce, while organic arsenic species (primarily arsenobetaine) is found in seafood (fish and seaweed) (ATSDR, 2007).

2. Available data and background

2.1. Exposure guidance values, critical effects, and mode of action

Derivation of BE values requires both an exposure guidance value (such as an RfD, TDI, or cancer risk-specific dose) and pharmacokinetic data or models sufficient to estimate corresponding biomarker values. Tables 1 and 2 present the available exposure guidance values from US and Canadian Agencies derived for inorganic arsenic, including information regarding the toxicological endpoint of interest, the underlying datasets, and, where applicable, the point of departure (POD) and the applied uncertainty factors. All of the available exposure guidance values for inorganic arsenic are based on human cohort data, so interspecies extrapolations are not relevant.

The health endpoints of most concern following inorganic arsenic exposures include skin changes, peripheral neuropathy, blackfoot disease, and lung, bladder, liver, and skin cancers. It is not understood which oxidation state or degree of methylation is responsible for these effects. Early hypotheses considered inorganic arsenic the causative agent for most effects (Schwerdtle et al., 2003), with methylation considered to represent a deactivation step. Recently, the methylated species of arsenic have been implicated in the cancer effects, in particular the trivalent monomethylated arsenic (MMA^{III}) (Cohen et al., 2006; Schwerdtle et al., 2003). Thus, metabolism of inorganic arsenic to the methylated species is currently thought to be important for the mechanisms of arsenic toxicity (Schuhmacher-Wolz et al., 2009; Rossman, 2003). However, it is not conclusive which critical dose metric (iAs, MMA, DMA, or which oxidation state) is most relevant for the various effects observed with inorganic arsenic poisoning.

Table 2
Exposure guidance values based on cancer risk estimates. All of the available estimates of cancer potency are based on human cohort datasets. Estimated risk-specific dose levels associated with a cancer risk of 1 in 100,000 are presented. Both Health Canada and US EPA derived cancer slope factors for inhalation exposures (lung tumors being the effect of interest). However, since the predominant exposures of interest in the environment are from oral exposures, and because lung tumors following occupational exposures (by inhalation) are likely heavily influenced by the route of entry, BEs are not derived and the values are not summarized here.

Organization, criteria (year of evaluation)	Critical endpoint and cohort	Risk-specific exposure level (1×10^{-4} cancer risk) (mg/kg-d)	Risk-specific exposure level (1×10^{-6} cancer risk) (mg/kg-d)
Health Canada, Water Quality and Health Bureau (2006)	Lung, bladder and liver cancers based on Taiwanese cohort data Tseng et al. (1968) and Tseng (1977)	5.6×10^{-5}	5.6×10^{-7}
Health Canada, Foods Division (2007)	Bladder cancer based on a meta-analysis of data from Taiwan, Chile, Argentina, Finland, California, and Utah Chu and Crawford-Brown (2006)	3.3×10^{-3}	3.3×10^{-5}
US EPA (2008a) and Health Canada PMRA (2008)[a]	Lung and bladder cancers among Taiwanese population exposed via drinking water Morales et al. (2000)	2.7×10^{-5}	2.7×10^{-7}

[a] US EPA Office of Prevention, Pesticides, and Toxic Substances in 2008 adopted the cancer slope factor derived in 2001 by the US EPA Office of Water (US EPA, 2001). Health Canada's Pest Management Regulatory Agency (PMRA) conducted a review in 2008 and adopted the US EPA (2001) cancer risk assessment; available at http://www.hc-sc.gc.ca/cps-spc/pubs/pest/_decisions/rev2008-08/index-eng.php.