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Biomonitoring Equivalents for benzene

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ABSTRACT

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 such as a reference dose (RfD) or tolerable daily intake (TDI). BE values can be used as a screening tool for the evaluation of population-based biomonitoring data in the context of existing risk assessments. This study reviews available health based risk assessments and exposure guidance values for benzene from the United States Environmental Protection Agency (US EPA), Texas Commission on Environmental Quality (TCEQ), California's Office of Environmental Health Hazard Assessment (OEHHA) and the Agency for Toxic Substances and Disease Registry (ATSDR) to derive BE values for benzene in blood and urine. No BE values were derived for any of the numerous benzene metabolites or hemoglobin and albumin adducts. Using existing physiologically based pharmacokinetic (PBPK) models, government risk assessment values were translated into corresponding benzene levels in blood assuming chronic steady-state exposures. BEs for benzene in urine were derived using measured correlations between benzene in urine with benzene in blood. The BE values for benzene in blood range from 0.04 to 1.29 μg/L, depending upon the underlying non-cancer risk assessment used in deriving the BE. Sources of uncertainty relating to both the basis for the BE values and their use in evaluation of biomonitoring data, including the transience of the biomarkers relative to exposure frequency, are discussed. The BE values derived here can be used as screening tools for evaluation of population biomonitoring data for benzene in the context of the existing risk assessment and can assist in prioritization of the potential need for additional risk assessment efforts for benzene relative to other chemicals.

1. Introduction

Large biomonitoring studies such as those conducted as part of the US National Health and Nutrition Examination Survey (NHANES) and other national biomonitoring efforts such as those conducted in Canada and in Germany are providing valuable data on the prevalence and concentrations of chemicals in biological media such as blood or urine from individuals in the general population. These measured concentrations provide an integrated reflection of exposures that may occur via multiple routes and pathways, and biomonitoring is increasingly being relied upon as a state-of-the-art tool for exposure assessment of environmental chemicals (Sexton et al., 2004). The potential significance of the measured concentrations of chemicals in the context of existing toxicology data and risk assessments can be assessed if chemical-specific quantitative screening criteria are available. Such screening criteria would ideally be based on robust datasets relating potential adverse effects to biomarker concentrations in human populations (see, for example, the US Centers for Disease Control and Prevention (CDC) blood lead level of concern; see http://www.cdc.gov/nceh/lead/). However, development of such epidemiologically-based screening criteria is a resource- and time-

Abbreviations: ADI, acceptable daily intake; AEGL, acute exposure guideline level; AML, acute myologenous leukemia; ATSDR, Agency for Toxic Substances and Disease Registry; BE, Biomonitoring Equivalent; BE_{POD}, Biomonitoring Equivalent point of departure; BMDL, benchmark dose lower limit; BO, benzeneoxide; Bz, benzene; ESL, effects screening level; MRL, Minimal Risk Level; MW, molecular weight; NOAEL, no observed adverse effect level; 1,4-BQ, 1,4-benzoquinone; POD, point of departure; RfD, reference dose; SPMA, s-phenyl mercapturic acid; TCEQ, Texas Commission of Environmental Quality; TD_{05}, The tumorigenic dose05, the dose level that causes a 5% increase in tumor incidence over background; TDI, tolerable daily intake; tt-MA, trans, trans-muconic acid; UF, uncertainty factor; USEPA, United States Environmental Protection Agency; WHO, World Health Organization.

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intensive effort, and in practice, data to support such assessments exist for only a few chemicals. As an interim approach, the concept of Biomonitoring Equivalents (BEs) has been developed (Hays et al., 2007), and guidelines for the derivation and communication of these values have been prepared (Hays et al., 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; available at www.biomonitoringequivalents.net). 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 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 for a population.

This manuscript presents the background and derivation of BE values for benzene (CAS #71-43-2). Benzene is a ubiquitous environmental chemical that is also present in cigarette smoke and various petroleum derived products including gasoline. Cigarette smoke, and second hand smoke, are the largest sources of exposures among the general population, and are estimated to be an order of magnitude greater than exposures from all other sources (Wallace, 1996). However, exposures to benzene can occur via multiple routes (inhalation, oral and dermal) and from many different sources. As a result, biomonitoring has been used as a potential tool for better assessing integrated exposures to benzene. The BEs derived here can be used as a tool to help regulators and risk managers interpret benzene biomonitoring data in a public health risk context.

2. Methods

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

The hematopoietic toxicity of benzene exposure has been recognized for decades and has been consistently observed in both experimental studies and epidemiological evaluations of worker populations (ATSDR, 2007). Chronic, high-level occupational exposures to benzene have been positively associated with bone marrow failure and aplastic anemia as well as an increased risk of various subtypes of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) (Pyatt, 2004). Chronic occupational exposure to high levels of benzene is also an established cause of various cytopenias observed in the peripheral circulation (reductions in specific cell lineages) including pancytopenia (a reduction in all three major cell lines) (Green et al., 1981; Rozen et al., 1984; Snyder et al., 1978). Peripheral cytopenias, in particular lymphocytopenia, are generally believed to be the most sensitive manifestation of benzene toxicity. As such, lymphocytopenia forms the basis for most non-cancer regulatory limits set for benzene (Rothman et al., 1996).

Exposures to benzene may occur due to: (1) the production of benzene in combustion processes (e.g., forest fires, cigarette smoking), (2) the natural presence of benzene in foods, (3) proximity to industrial sources (e.g., refineries, petrochemical manufacturing, service stations), (4) pumping and potentially storing gasoline and (5) emissions from gasoline and other types of engines. Exposure to benzene can occur via the oral, dermal and/or inhalation routes, although due to benzene's high vapor pressure, inhalation is the most important exposure pathway, especially in occupational environments.

A robust body of experimental evidence supports the hypothesis that benzene must be metabolized to be hematotoxic (Gad-El Karim et al., 1985; Ross, 1996; Snyder et al., 1981, 1983; Valentine et al., 1996). The primary step in benzene metabolism is oxidation to benzene oxide (see Fig. 1) via the 2E1 isozyme of the cytochrome P-450 system (CYP2E1). Benzene oxide undergoes enzymatic or non-enzymatic rearrangement to phenol or is metabolized by epoxide hydrolase (Parke and Williams, 1950, 1953). Although the primary site of benzene's oxidation by CYP2E1 occurs mainly in the liver, additional metabolism also occurs in the bone marrow (Andrews et al., 1979). Human bone marrow lacks detectable levels of CYP2E1, but is a rich source of myeloperoxidase (MPO) (Ross, 1996; Ross et al., 1996). MPO, which has been measured in high concentrations in granulocytic precursor cells, can further oxidize various polyphenolic metabolites of benzene and is thought to play an important role in the hematopoietic toxicity of benzene (Gad-El Karim et al., 1985; Kalf, 1987; Rana and Verma, 2005; Ross, 1996).

The mechanism of action for benzene's hematopoietic toxicity is largely unknown. However, there are a few well-defined steps that seem to be required for benzene to exert its toxicity. These steps can be used to describe the more general mode of action (MOA) (Meek and Klaunig, 2010). Benzene must be absorbed into the systemic circulation and metabolized into its various phenolic metabolites. These metabolites must be stable enough to persist into the peripheral circulation and possibly to the bone marrow, where they likely undergo additional metabolic conversion. As discussed above, the exact metabolite or combination responsible for hematopoetic toxicity has not been determined with certainty. However, hydroquinone and *p*-benzoquinone are likely candidates. Once in the bone marrow, and perhaps in the peripheral circulation as well, it appears that the various metabolites interact with either mature blood cells or early precursor cells that would ultimately produce mature blood cells (Baarson et al., 1984). The toxicity of benzene has been shown to be greater in rapidly dividing cells, where more actively dividing cells are targeted but quiescent hematopoietic stem cells are spared (Dempster and Snyder, 1990, 1991; Green et al., 1981; Irons, 1981; Irons et al., 1979a; Keller and Snyder, 1988; Longacre et al., 1980). Additional evidence indicates that benzene metabolites can induce a block in cell cycle as well as induce apoptosis in precursor cells (Ross et al., 1996; Yoon et al., 2001). Other studies have shown that benzene metabolites alter important signaling pathways in hematopoietic cells that may also result in cytotoxicity (Irons et al., 1992; Pyatt et al., 1998, 1999a,b; Renz and Kalf, 1991, 1992).

As with peripheral cytopenias, the precise molecular mechanism underlying benzene's ability to induce AML has not been identified. Hypotheses include topoisomerase inhibition and/or hyper-responsiveness to various growth factors (Dempster and Snyder, 1990, 1991; Huff et al., 1989; Irons et al., 1992; Lindsey et al., 2005; Mondrala and Eastmond, 2010). The MOA on the other hand, has generally been described and there are several steps that have general acceptance (Meek and Klaunig, 2010). As with the hematopoietic toxicity described above, the first steps in the MOA for AML are absorption, metabolism and distribution to the bone marrow. Once in the marrow, the various benzene metabolites either create or provide a selective advantage for initiated target cells. These cells harboring specific mutations (perhaps evidenced by common cytogenetic markers) likely achieve a selective growth advantage over