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Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide

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ABSTRACT

An approach is presented for ethylene oxide (EO) to derive endogenous equivalent (EE) values, which are endogenous levels normally found within the body expressed in terms of exogenous exposures. EE values can be used to support risk assessment and risk management decisions for chemicals such as EO that have both endogenous and exogenous exposure pathways. EE values were derived using a meta-analysis of data from the published literature characterizing the distribution for an EO biomarker of exposure, hemoglobin N-(2-hydroxyethyl)-valine (HEV), in unexposed populations. These levels are compared to the those reported in exposed populations (smokers, workers). Correlation between the biomarker of exposure and external exposures of EO were applied to this distribution to determine corresponding EE values, which range from 0.13 to 6.9 ppb for EO in air. These values are orders of magnitude higher than risk-based concentration values derived for EO using default methods, and are provided as a pragmatic, data-driven alternative approach to managing the potential risks from exogenous exposures to EO.

1. Introduction

Assessing and managing the potential risks associated with chemicals that have both exogenous and endogenous exposure pathways pose a challenge to the risk assessment community. For example, ethylene oxide (EO, CAS RN 75-21-8) has been identified as a carcinogen based upon increases in multiple tumor types in laboratory rodents (hematopoietic/lymphopoietic system, brain, lung, uterus, and peritoneal cavity; Snellings et al., 1984; Lynch et al., 1984; NTP, 1987), and increases in specific cancers in highly exposed workers (hematopoietic cancers, and possibly breast cancer; Steenland et al., 2003, 2004; Teta et al., 1999). EO is used in the production of chemicals and polymers, and as a disinfectant (e.g., sterilization medical equipment). Accordingly, exogenous exposures to EO can occur to workers in industries that make or use this chemical. However, EO is also produced endogenously in the body due to oxidation of ethylene, which is produced from the oxidation of lipid, methionine, and hemoglobin, and from intestinal bacteria (Wu et al., 2011; Liberman and Mapson, 1964; Sagai and Ichinose, 1980; Clemens et al., 1983; Shen et al., 1989; Tornqvist et al., 1989; Kessler and Remmer, 1990). The relative contribution of exogenous and endogenous pathways to total exposure, as well as their contribution to potential risks, is typically not well characterized.

This problem shares some of the same issues associated with assessing the potential risk from exposure to metals that also occur naturally in environmental media. Standard risk assessment practices can result in the derivation of risk-based concentrations for a chemical in environmental media that are below naturally occurring background levels. For example, naturally occurring background levels of arsenic, aluminum, iron and manganese in soil exceed risk-based screening levels. For arsenic, a known human carcinogen, many states in the U.S. rely upon naturally occurring background soil arsenic levels for cleanup decisions, with upper background concentrations ranging from 7 to 40 mg/kg. On the other hand, risk-based cleanup levels for arsenic used by some states can be up to two orders of magnitude lower than this range (Teaf et al., 2010). Reliance upon background concentration levels to support risk management decisions by some states and regions reflects a pragmatic approach that considers the possibility that resources spent on removing/treating marginally increased concentrations in soil might not produce a meaningful change in risk to human health (e.g., replacement soils may likely contain similar levels of arsenic).

Like risk-based concentrations for arsenic in soil, standard risk assessment practices applied to EO result in risk-based exposure concentrations for EO in air that are extremely low. In USEPA's Draft IRIS Toxicological Review for EO (USEPA, 2014), USEPA derived an inhalation unit risk value of 0.0018 per $\mu g/m^3$ based on epidemiology data for exposed workers. This unit risk value can be used to calculate a *de minimis* (1×10^{-6}) risk-based concentration of 0.00031 ppb.

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Meanwhile, because of endogenous production of EO in the body, it is expected to be present in human blood at steady-state concentrations ranging from 0.04 to 017 nmol/L (Filser et al., 1992; Csanády et al., 2000). Based upon blood:air partition coefficients (Filser et al., 2013), these blood levels are predicted to correspond to exhaled breath concentrations of approximately 0.01–0.05 ppb. In short, standard risk assessment practices result in the calculation of risk-based concentrations for EO in air that are approximately two orders of magnitude lower than levels predicted in exhaled breath of humans with no exogenous EO exposure.

As an alternative to reliance on standard risk-based concentrations, a pragmatic approach is presented here for the derivation of endogenous equivalent (EE) values, which can be used to support risk assessment and risk management decisions for chemicals like EO that have both endogenous and exogenous exposure pathways.

2. Methods

Literature searches were conducted using publically available databases (Pubmed, TOXNET) using appropriate search terms (ethylene oxide, biomonitoring, biomarker, adducts, hemoglobin, protein, DNA, 2-hydroxyethyl valine, 2-hydroxyethyl guanine, blood, urine) to identify studies that provide biomarkers of exposure for EO in human populations to supplement those identified by Wu et al. (2011). The reference lists for review articles and recent publications were also used as secondary sources of relevant studies. Endogenous equivalents were determined for EO using the following steps: (1) Identify an appropriate biomarker of exposure; (2) Characterize the biomarker distribution in humans; and (3) Establish quantitative relationship between biomarker of exposure and external exposure. Resulting EE values reflect endogenous EO levels expressed in terms of equivalent exogenous exposure levels (e.g., ppm EO in air).

2.1. Identification of reliable biomarkers of exposure

Based upon animal studies, EO is well absorbed following exposures, and is rapidly distributed to all organs and tissues (USEPA, 2014). In tissues, EO is subject to metabolism by hydrolysis (yielding 1,2-ethanediol, hydroxyacetaldehyde, glycolic acid, glyoxylic acid, formic acid, oxalic acid, and carbon dioxide) or glutathione conjugation pathways (yielding mercapturic acids), both of which are considered to be detoxifying steps, and whose products are excreted in the urine. Some of the EO that is absorbed is eliminated unchanged in exhaled breath. As an epoxide, EO is capable of reacting with cellular macromolecules, including hemoglobin and DNA. Based upon a review of the published literature, potential biomarkers of exposure for EO include a consideration of the following: (1) EO in exhaled breath; (2) DNA adducts; and (3) hemoglobin adducts (Fig. 1). The primary advantage of using EO levels in exhaled breath for this assessment would be that it simplifies comparisons to risk-based concentrations for EO in air. Unfortunately, direct measurements for EO in exhaled breath are not available, and instead can only be estimated and/or predicted from toxicokinetic models (Filser et al., 2013; Csanády et al., 2000; Fennell and Brown, 2001).

As an alkylating agent, EO reacts with DNA to produce adducts including the major N7-2-hydroxyethylguanine (N7-HEG), which although a non-mutagenic adduct is a useful biomarker of exposure. N7-HEG adducts have been quantified in tissues in rodents exposed to ethylene, which is metabolized to EO in tissues (Wu et al., 1999; Walker et al., 2000; Rusyn et al., 2005) and rodents exposed to exogenous EO (van Sittert et al., 2000; Rusyn et al., 2005; Marsden et al., 2007, 2009; Zhang et al., 2015). N7-HEG adducts have also been used to characterize endogenous exposures in human lymphocytes (Wu et al., 1999). HEG levels in granulocytes have been reported as a useful biomarker in exposed workers (Yong et al., 2007). Similarly, N7-HEG adducts that have undergone repair via depurination are excreted in urine, which has been reported as a useful biomarker in smokers (Huang et al., 2008) and exposed workers (Huang et al., 2011). The primary disadvantages to relying upon N7-HEG adducts are: (1) the data are limited to just a few studies in humans; and (2) N7-adducts are chemically unstable (Boysen et al., 2009), and therefore may only be reflective of very recent exposures; and (3) N7-HEG adducts are not mutagenic and do not block DNA replication (Boysen et al., 2009; Philippin et al., 2014).

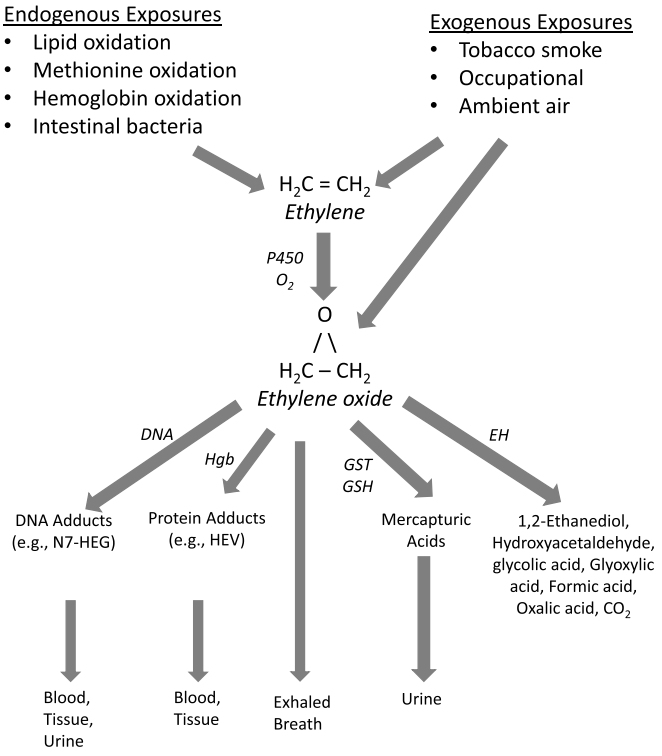

Fig. 1. Metabolism and Biomarkers for Ethylene Oxide. P450 = cytochrome P450; O2 = oxygen; DNA = deoxyribonucleic acid; Hgb = hemoglobin; EH = epoxide hydrolase; GSH = glutathione; GST = glutathione-S-transferase; N7-HEG = N7-hydroxyethyl guanine; HEV = N-2-hydroxyethyl valine.

Importantly, EO also forms adducts on the terminal valine of hemoglobin, N-(2-hydroxyethyl)-valine (HEV). These adducts are relatively stable, considerably more so than DNA adducts of EO (Wu et al., 2011), and are readily measurable in erythrocytes. Because of the half-life of EO hemoglobin is expected to reflect erythrocyte turnover in humans (approximately 120 days), HEV adducts reflect cumulative exposures to EO that occurred during the previous months. Since EO is widely distributed in the body, the levels of HEV in erythrocytes are expected to be proportionate to levels of HEV in other tissues (including tissues that are targets of EO toxicity), which in turn is expected to be proportionate to tissue exposures to free EO. HEV adducts have been well studied, including characterization by many studies in human populations with no known and/or negligible exogenous exposures (Table 1). EO and ethylene are both components of tobacco smoke. Accordingly, HEV adduct burdens are generally higher in smokers compared to non-smokers. HEV adducts have also been characterized in populations with significant exogenous exposures to EO, including smoking and occupational exposures (Table 2).

Based upon the review of the available biomarker data for EO, and based upon a consideration of data availability and stability of the biomarker, HEV adducts were selected as the most appropriate basis to support the derivation of EE values for EO.

2.2. Characterize biomarker distribution

The HEV adduct data in Tables 1 and 2 were used to support meta-