Regulatory Toxicology and Pharmacology 92 (2018) 55–66

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Development of an inhalation reference concentration for diethanolamine

Joseph T. Haney Jr.*, Darrell McCant, Michael E. Honeycutt, Sabine Lange

Texas Commission on Environmental Quality (TCEQ), Toxicology Division, MC-168, P.O. Box 13087, Austin, TX, 78711, United States

ARTICLE INFO

Keywords:
Diethanolamine
DEA
Regulatory
Laryngeal squamous metaplasia
Liver
Toxicity
Inhalation

ABSTRACT

An inhalation reference concentration (RfC) was developed for diethanolamine (DEA), based principally on evaluation of three animal studies (Gamer et al., 1993, 1996, 2008). The RfC (25 μg/m^3) was based on statistically significantly increased relative liver weight in female rats in Gamer et al. (2008) as the critical effect. The lower confidence limit on the benchmark dose ($BMDL_{10}$ of 5.5 mg/m^3) was adjusted to a human equivalent concentration and to continuous exposure before dividing the final point of departure (2.3 mg/m^3) by a total factor of 90 that considered standard key areas of uncertainty (intrahuman variability, potential interspecies toxicodynamic differences, database limitations). While laryngeal effects observed in Gamer et al. (2008) were also considered as candidate critical effects, evaluation of the adversity and human relevance of rat laryngeal squamous metaplasia and concomitant effects at the various exposure levels resulted in identifying a LOAEL for laryngeal squamous hyperplasia and chronic inflammation that was much higher than the liver weight LOAEL identified. The RfC of 25 μg/m^3 is considered health protective for the general population and can be used to evaluate the potential health effects of long-term environmental exposure of the general public (i.e., long-term, ambient air dispersion modelling or monitoring data).

1. Introduction

Ethanolamines have been of steadily growing commercial importance as chemical intermediates since the 1940's because of the large-scale production of ethylene oxide, with the economical production of very pure ethanolamines being possible since the 1970's (IARC, 2000). Annual world-wide capacity for ethanolamines was estimated at 1.5 million tons (for 2005), with more than half attributable to North and South America, including multiple facilities in the United States (US) (OECD, 2007; IARC, 2013). Diethanolamine (DEA) is produced by reacting ethylene oxide with ammonia in a batch process that yields a mixture of monoethanolamine (MEA), DEA, and triethanolamine (TEA). Individual compounds can then be separated and purified by distilling this mixture (Edens and Lochary, 2004).

DEA is used widely in the production of diethanolamides and diethanolamine salts of long-chain fatty acids that are formulated into soaps and surfactants used in liquid laundry and dishwashing detergents, cosmetics, shampoos, and hair conditioners. It is also used in the production of lubricants in the textile industry, in industrial gas purification, as an emulsifier and dispersing agent in agricultural chemical preparations, in metalworking fluids and die-casting operations as a corrosion inhibitor and antimicrobial agent, and as a chemical intermediate in the manufacture of resins and plasticizers. Hair products such as shampoos and dyes may contain DEA as a component and/or a contaminant of fatty acid alkanolamides in the range of ≈0.1–10% (Bailey, 2007; IARC, 2013; ACGIH, 2009). Major use estimates of DEA in the US are: surfactants (39%), gas purification (30%), textile processing (15%), metalworking fluids (10%), laundry detergents (2%), and agricultural chemicals (2%) (Knaak et al., 1997). The US Food & Drug Administration (USFDA) allows DEA for various uses (e.g., as a component of certain food packaging products) and as an indirect food additive (IARC, 2013; ACGIH, 2009).

DEA is not monitored in ambient air by the Texas Commission on Environmental Quality's (TCEQ) monitoring program because standard analytical methods cannot measure all chemicals. However, it is important for the TCEQ to derive a chronic inhalation toxicity factor (e.g., reference concentration or RfC, termed a chronic reference value or ReV in Texas) for DEA for several reasons:

- Although a recent scientific literature search identified chronic inhalation toxicity factors derived by other agencies for use in the protection of public health (i.e., OEHHA, 2001; USEPA, 2012), those toxicity factors are based on an endpoint (i.e., laryngeal lesions in rats) for which critical recent guidance and information regarding adversity is now available but was not considered in the dose-response assessments (e.g., Mowat et al., 2017; Kaufmann et al., 2009;

* Corresponding author.
E-mail addresses: Joseph.Haney@tceq.texas.gov (J.T. Haney), Darrell.McCant@tceq.texas.gov (D. McCant), Michael.Honeycutt@tceq.texas.gov (M.E. Honeycutt), Sabine.Lange@tceq.texas.gov (S. Lange).

https://doi.org/10.1016/j.yrtph.2017.11.011
Received 21 June 2017; Received in revised form 14 November 2017; Accepted 16 November 2017

Tepper et al., 2016);

- The Texas Clean Air Act (Chapter 382 of the Texas Health and Safety Code (THSC)) specifically mandates the TCEQ to conduct air permit reviews of all new and modified facilities to ensure that the operation of a facility will not cause or contribute to a condition of air pollution (THSC §382.0518 and 382.085), which includes comparing modelled emissions of air pollutants to TCEQ-derived health-protective air concentrations; and
- Most importantly, DEA is emitted by various facilities in Texas (i.e., per the emission limits contained in their respective air permits based on air dispersion modelling of off-site, ground-level concentrations), and therefore the derivation of an RfC will help ensure the protection of public health.

Because of the comprehensiveness of the language in the THSC, the TCEQ develops inhalation toxicity factors (e.g., ReVs, unit risk factors) for as many air contaminants as possible, even for chemicals with toxicity data more limited than that which would be required by other agencies' programs that conduct hazard identification and dose-response assessment (e.g., the US Environmental Protection Agency's (USEPA's) Integrated Risk Information System program). The development of scientifically-defensible inhalation toxicity factors under the TCEQ toxicity factor guidelines (TCEQ, 2015) includes the consideration of the standard key uncertainties associated with extrapolating laboratory animal data to humans (e.g., potential interspecies toxicodynamic differences, database limitations), and is consistent with TCEQ's goal of protecting human health and the environment. The purpose of this paper is to document the derivation of an RfC for DEA (referred to as a chronic ReV in TCEQ, 2015), which may be used in the protection of public health (e.g., in the TCEQ air permitting process).

2. Materials and methods

The TCEQ guidelines (TCEQ, 2015) employ the 4-stage risk assessment process formalized by the National Research Council (NRC, 1983, 1994) and procedures recommended in numerous USEPA risk assessment guidance documents and the scientific literature (e.g., USEPA, 1994, 2002). Briefly, the basic steps of our toxicity factor derivation include:

(1) Reviewing essential data (e.g., physical/chemical properties) and searching the literature to identify potential key studies (e.g., those with a dose-response and the most conservative lowest-observed-adverse-effect-levels (LOAELs) and no-observed-adverse-effect-levels (NOAELs));
(2) Considering mode of action (MOA) data relevant to appropriate low-dose extrapolation procedures (e.g., threshold non-carcinogenic responses versus linear low-dose extrapolation when conducting a carcinogenic dose-response assessment for chemicals with a mutagenic carcinogenic MOA);
(3) Selecting the best available dose metric (frequently air concentration for inhalation studies);
(4) Conducting appropriate dosimetric modelling (e.g., animal-to-human) to produce human equivalent concentrations (HECs) for points-of-departure (PODs) that potentially identify the critical adverse effect (e.g., relatively low study LOAELs), as well as exposure regimen/duration adjustments;
(5) Identifying the critical adverse effect based on the lowest HEC for an adverse, human-relevant effect (e.g., the lowest HEC based on a study LOAEL ($LOAEL_{HEC}$) may be used); and
(6) Extrapolating from the most appropriate POD_{HEC} for the critical effect (e.g., a POD_{HEC} corresponding to the $BMDL_{10\text{-}HEC}$) to lower exposures, which for chronic non-carcinogenic effects typically entails dividing the duration-adjusted POD_{HEC} by applicable uncertainty factors (TCEQ, 2015).

For non-carcinogenic effects, consistent with standard methods used for toxicity factor derivation by other agencies (e.g., USEPA, ATSDR), the central elements of this process entail identifying the POD_{HEC} for the critical adverse effect and dividing it by appropriate safety factors that consider relevant key areas of uncertainty (e.g., intrahuman variability, potential interspecies differences in toxicodynamics, database limitations) [see TCEQ 2015 for more detailed information]. The focus of this manuscript is to document these key elements with the associated methods and rationale for a DEA RfC derivation, based on a critical toxicological evaluation of the results reported in three animal inhalation studies by Gamer et al. (1993, 1996, 2008) as well as other relevant information (e.g., criteria relevant to endpoint adversity, TCEQ guidance, developmental/reproductive toxicity results for other exposure routes). Additional details are provided in the sections that follow.

3. Identification and discussion of key studies

A scientific literature search was conducted for DEA to identify relevant studies via online databases (i.e., PubMed, Toxline, Hazardous Substances Data Bank, Registry of Toxic Effects of Chemical Substances, Screening Information Datasets for High Volume Chemicals). For example, the initial PubMed search for “diethanolamine” (June 2016) yielded approximately 500 articles simply related to DEA in some regard. Review of the abstracts resulted in the exclusion of studies that were not relevant for a chronic RfC dose-response assessment of the potential toxic effects of DEA inhalation (e.g., those involving chemical synthesis). Exclusion criteria (for purposes of dose-response assessment and toxicity factor derivation) included:

- Studies that did not assess health effects;
- Unpublished studies that were unavailable (only abstract available);
- Reports not in English;
- Lack of exposure data or original data (e.g., while review articles were examined to gain familiarity with previous assessments, they often do not contain the actual dose-response data required for derivation of toxicity factors);
- Irrelevant exposure route (e.g., intraperitoneal);
- Mixture studies (i.e., wherein any effects observed are not attributable specifically to DEA); and
- Endpoints (e.g., severe effects like mortality) and exposure durations irrelevant for RfC derivation (e.g., acute, < 24-h exposure studies).

Upon review of the abstracts, however, the vast majority of the studies initially identified for DEA did not concern inhalation exposure (e.g., chemical synthesis papers). Furthermore, only three studies were identified with inhalation dose-response data relevant to derivation of an RfC. While human studies are preferred for RfC derivation under the TCEQ (2015) guidelines, as noted elsewhere (e.g., IARC, 2013) and confirmed by our updated scientific literature search, no human data are available from which to assess the potential for long-term, non-carcinogenic toxic effects attributable to DEA inhalation. In fact, use of the exclusion criteria narrowed down the number of potentially relevant studies for RfC derivation to three animal inhalation studies by Gamer et al.: two subchronic studies (Gamer et al., 1996, 2008) and a 10-day gestational exposure study (Gamer et al., 1993). The studies used two different strains of Wistar rats: Chbb:THOM was used in Gamer et al. (1993, 1996) and the Study 1 portion of Gamer et al. (2008), while the CrlGlxBrIHan:WI strain was used in the Study 2 portion of Gamer et al. (2008, 1993) is relevant for RfC derivation as it evaluated developmental/reproductive effects following subacute gestational exposure and an RfC should be protective against these potential effects. However, as described in Sections 3.2 and 4, ultimately Gamer et al. (1993) was not chosen as the key study to derive the DEA RfC because it did not identify the critical effect (i.e., it did not identify