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Derivation of a No-Significant-Risk-Level (NSRL) for diethanolamine (DEA)

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ABSTRACT

Diethanolamine (DEA) has been listed on the State of California's Proposition 65 List. This listing is based in part on tumors reported in a National Toxicology Program (NTP) 2-year dermal carcinogenicity study in mice which found clear evidence of carcinogenic activity in B6C3F$_1$ mice based on increased incidences of liver neoplasms in both sexes, and increased incidences of renal tubule neoplasms in males. Although considerable controversy exists on the relevance of the NTP study to humans, industries are obligated to comply with the Proposition 65 labeling requirement and drinking water discharge prohibition, unless they are able to demonstrate that DEA levels in their products are below a specific No Significant Risk Level (NSRL). The State of California has not published an NSRL for DEA. In this article, a NSRL of 5.6 μg/day and a life-stage-adjusted NSRL$_{adj}$ of 1.4 μg/day are derived from the NTP carcinogenicity study using a benchmark dose modeling method based on the incidence of hepatocellular carcinomas in female mice, in accordance with the guidelines of California EPA.

Introduction

In 2012, DEA was listed by the State of California on the list of chemicals known to the state to cause cancer ("Proposition 65 List"), in part due to the International Agency for Research on Cancer (IARC)'s updated classification of DEA as a Group 2B possible human carcinogen. The IARC classification is based on a National Toxicology Program (NTP) 2-year dermal carcinogenicity study in mice (NTP, 1999). Scientific disagreements exist regarding the carcinogenic potential of DEA in humans; however, in order for industries to comply with California's Proposition 65 law, ToxServices calculated a NSRL for DEA.

As defined by the California Office of Environmental Health Hazard Assessment, carcinogen safe harbor levels are termed No Significant Risk Levels (NSRLs). For carcinogens or potential carcinogens, a NSRL is equivalent to an exposure level that results in 1 excess cancer in an exposed human population of 100,000, assuming lifetime exposure at the level in question (OEHHA, 2001, 2011). If an exposure subject to the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") can be shown to be less than the specific NSRL (or Maximum Allowable Daily Levels for chemicals that cause birth defects of other reproductive toxicities), the responsible person has "safe harbor" from the Proposition 65 warning requirement and drinking water discharge prohibition.

Use, chemical, and physical properties of DEA

DEA is produced by the reaction of ethylene oxide and ammonia. This batch process yields a crude mixture of ethanolamine, diethanolamine (DEA) and triethanolamine (TEA). These individual compounds are then separated and purified. The major uses of DEA in the U.S. are summarized in Table 1. Of particular relevance to the personal care products industry, DEA is widely used in the preparation 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. Shampoos and hair dyes may contain free DEA as a component and/or contaminant of fatty acid alkanolamides (0.2–10%). Free DEA is reported to be a contaminant in fatty acid-diethanolamine condensates (amides of coconut oil acid, oleic acid and lauric acid) at levels up to 19%. It is also a contaminant in TEA products (Bailey, 2007; IARC, 2012). The physical and chemical properties of DEA are listed in Table 2.

Comparative kinetics and metabolism of DEA

Studies in humans

Very limited human data are currently available. Dermal penetration studies were performed using human skin samples and ^{14}C-labelled DEA from cosmetic formulations (Kraeling et al., 2004). Approximately 0.1% of the applied dose of shampoo and hair dye formulations was absorbed into the receptor fluid after 5–30 min. In a 72-h repeated exposure study using a body lotion formulation,

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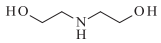
Table 1
Major uses of DEA in the U.S.A.

Applications	Percentage of production
Surfactants	39
Gas purification	30
Textile processing	15
Metal working fluids	10
Miscellaneous	8
Laundry detergents	2
Agricultural chemicals	2

Source: Knaak et al. (1997).

Table 2
Physical and chemical properties of DEA.

Property	Value
Molecular formula	C_4-H_{11}-N-O_2
CAS number	111-42-2
Chemical structure	
Molecular weight	105.136
Physical state	Crystalline solid or viscous liquid
Appearance	Colorless crystals or a syrupy, white liquid
Melting point	28 °C
Boiling Point	268.8 °C
Vapor pressure	2.80×10^{-4} mmHg (at 25 °C)
Water solubility	1.00×10^{6} mg/L (at 20 °C)
Taste/odor threshold	Mild ammonia-like odor
Dissociation constant	8.96
Density/specific gravity	1.0966 (at 20 °C/4 °C)
log K_{ow}	−1.43
Henry's law constant	3.87×10^{-11} atm-m^3/mole (at 25 °C)

Source: ChemIDplus (2013) and HSDB (2009).

almost 30% of the applied DEA accumulated in the skin while 1% was absorbed into the receptor fluid (Kraeling et al., 2004). In another study, DEA was absorbed by human liver slices and incorporated into phospholipids (Mathews et al., 1995). When a small group ($n = 3$) of human subjects were treated for one month with a dermal application of a commercially-available skin lotion containing 1.8 mg/g DEA, detectable DEA (up to 7 nmol/mL plasma) and dimethyldiethanolamine levels were found in the plasma of these subjects (Craciunescu et al., 2009). In this same publication, the authors pointed out that plasma DEA levels in exposed human subjects were 100–200 fold lower than the DEA levels associated with perturbed brain development in C57BL/6 mice.

Studies in animals

In F344 rats and B6C3F_1 mice, the percentage of absorbed DEA increased with dose 48 h after a single dermal dose of 2.1–27.5 mg/kg and 8–81 mg/kg ^{14}C-labelled DEA in 95% ethanol, respectively (Mathews et al., 1997). The percentage of absorption was 10–20% in rats and 30–40% in mice. In this study, oral exposure through grooming activities was prevented by gluing a wire mesh over the area of skin application (Mathews et al., 1997). In a comparative *ex vivo* skin penetration study, the permeability rate constant for an aqueous solution of DEA (37% w/w) through mouse skin was approximately 10 times higher than that through rat skin, and 20 times higher than that through human skin (Sun et al., 1996). DEA is well absorbed after oral exposure in rats, but excreted very slowly. After a single oral dose of ^{14}C-DEA at 7 mg/kg, about 20–30% of the recovered dose at 48 h was excreted in the urine and approximately 60% remained in the tissues (Mathews et al., 1997). Based on the data above, route-specific absorption factors could be applied as part of a cancer risk assessment of DEA, according to OEHHA principles.

Available data indicate that tissue distribution of DEA is similar after oral, intravenous and dermal administration in rats and mice. Forty-eight hours after a single dermal administration of ^{14}C-labelled DEA, tissue/blood ratios of ^{14}C were substantially greater than 1 for adipose tissue, brain, heart, kidney, liver, lung, muscle, skin and spleen, and the greatest accumulation (tissue/blood > 100) was found in the liver and kidney of rats and mice. Repeated daily oral exposure to DEA at 7 mg/kg led to high tissue concentrations of the compound during 4–8 weeks of treatment and the concentration in the liver reached 0.3 mg/kg tissue. The oral elimination half-life of DEA was about 1 week in rats (Mathews et al., 1997).

The majority of absorbed DEA remained as the parent compound in the tissues and in the urine in rats, although upon repeated exposure, the extent of methylation and the accumulation of methylated metabolites increased. DEA is known to be incorporated into membrane phospholipids (IARC, 2000). It can be O-phosphorylated and N-methylated to metabolites that are incorporated into polar head groups as aberrant membrane phospholipids via the ethanolamine metabolic pathway (Mathews et al., 1995). N-nitrosodiethanolamine, a hepatocarcinogen, was not detected in the urine, blood or gastric contents of B6C3F_1 mice given DEA at the dose of 160 mg/kg/day via dermal application or oral gavage with and without sodium nitrite in the drinking water for 2 weeks (Stott et al., 2000). These results indicate that liver tumor formation in mice is unlikely the result of nitrosation of DEA to this mutagenic nitrosamine (IARC, 2012).

After a single oral or intravenous dose of DEA, rats predominantly excreted the parent compound in the urine. The parent compound was still the major urinary species after repeated oral administration, although N-methylated metabolites were also detected (Mathews et al., 1997). In tissues such as the liver and brain in rats, the parent compound was the major species found, and two minor metabolites were also identified as N-methyldiethanolamine and N,N-dimethyldiethanolamine (Mathews et al., 1995).

Method

Derivation of NSRL

Specific steps to derive a NSRL are outlined in Title 27, Division 4, Chapter 1: Safe Drinking Water and Toxic Enforcement Act of 1986, Article 7. No Significant Risk Levels, Proposition 65, Section 25703 (Quantitative Risk Assessment) (OEHHA, 2011). Briefly, the principles for deriving an NSRL for a carcinogen or potential carcinogen are identified below:

- The NSRL is based on data from the most sensitive study of sufficient quality, and may be applied to all relevant routes of exposure.
- The NSRL assumes that there is no carcinogenic threshold; a no-threshold model (i.e., linearized multistage model) shall be utilized for extrapolation from high to low doses, with the upper 95% confidence limit of the linear term assigned as the upper bound of carcinogenic potency. If data are available on the time of appearance of individual tumors, time-to-tumor models may be appropriate, particularly when survival is poor due to competing toxicity.
- Carcinogenic potency may be based on human or animal data, and shall be expressed in reciprocal milligrams of chemical per kilogram of bodyweight per day ((mg/kg-day)$^{-1}$). If animal data are used, animal cancer potency is converted to human cancer potency by multiplying by the following surface area scaling factor: $(BW_{human}/BW_{animal})^{1/4}$.
- Available physiologic, pharmacokinetic and metabolic data may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations, if of acceptable quality.