OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Air Toxics Hot Spots Program

Ethylene Glycol mono-n-Butyl Ether

Reference Exposure Levels

Technical Support Document for the Derivation of Noncancer Reference Exposure Levels

Appendix D1

Scientific Review Panel Review Draft
January 2016

Air, Community, and Environmental Research Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

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Appendix D1

Prepared by the

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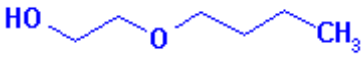
Ethylene Glycol mono-n-Butyl Ether

(2-butoxyethanol; butoxyethanol; butyl cellosolve; ethylene glycol mono-n-butyl ether; butyl glycol)

CAS 111-76-2



1. Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)). OEHHA developed a Technical Support Document (TSD) in response to this statutory requirement that describes methodology for deriving acute, 8-hour and chronic Reference Exposure Levels (RELs) (OEHHA, 2008). RELs are airborne concentrations of a chemical that are not anticipated to result in adverse noncancer health effects for specified exposure durations in the general population, including sensitive subpopulations. In particular, the methodology explicitly considers possible differential effects on the health of infants, children and other sensitive subpopulations, in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, Chapter 731, Statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*). The methods described in the TSD were used to develop the RELs for ethylene glycol mono-n-butyl ether (EGBE) presented in this document; this document will be added to Appendix D of the TSD.

Ethylene glycol mono-n-butyl ether (EGBE), commonly called 2-butoxyethanol (2-BE), has gained widespread use in industrial and consumer applications due to its properties as a solvent. It is well-known for its hemolytic properties in rodents (i.e., red blood cell (RBC) damage resulting in regenerative anemia) and the secondary effects from hemolysis including splenic congestion and liver Kupffer cell pigmentation. However, airborne exposures in humans are more often associated with eye, nose, and upper respiratory tract irritation, with no or minor hematologic effects only occurring at high concentrations. Major exposure routes of EGBE in humans are through inhalation and skin contact. The critical effects of EGBE in humans resulting from short to long term exposures are eye irritation, respiratory irritation and epithelial degeneration of upper respiratory airways. High oral doses in adult humans may result in metabolic acidosis and other symptoms.

1.1 EGBE Acute REL

Reference exposure level	4.7 mg/m^3 (1 part per million (ppm))
Critical effect(s)	Ocular and nasal irritation (sensory irritation)
Hazard index target(s)	Eyes and respiratory system

1.2 EGBE 8-Hour REL

Reference exposure level	0.15 mg/m^3 (0.032 ppm)
Critical effect(s)	Nasal hyaline degeneration of olfactory epithelium
Hazard index target(s)	Eyes and respiratory system

1.3 EGBE Chronic REL

Reference exposure level	0. 077 mg/m^3 (0. 016 ppm)
Critical effect(s)	Nasal hyaline degeneration of olfactory epithelium
Hazard index target(s)	Eyes and respiratory system

List of Acronyms

ADH	Alcohol Dehydrogenase	NTP	National Toxicology Program
AIC	Akaike Information Criterion	NIOSH	National Institute for Occupational Safety and Health
AIDS	Acquired Immune Deficiency Syndrome	OECD	Organisation for Economic Co-operation and Development
BAA	2-butoxyacetic Acid	OEHHA	Office of Environmental Health Hazard Assessment
BAL	Butoxyacetaldehyde	PBPK	Physiologically Based Pharmacokinetic
BCH	Basal Cell Hyperplasia	POD	Point of Departure
2-BE	2-butoxyethanol	ppm	Parts per million
$BMCL_{05}$	the 95% lower confidence interval at the 5% response rate	RBC	Red Blood Cell
BMD	Benchmark Dose	RD50	Dose resulting in a 50% depression of respiratory rate
$BMDL_{05}$	BMD 95% lower confidence limit	REL	Reference Exposure Level
BMDS	Benchmark Dose Modelling Software	RGDR	Regional Gas Dose Ratio
BPH	Benign Prostatic Hyperplasia	SA	Surface Area
CE	Carboxylesterase	SA_A	Surface Area for Animal
CI	Confidence Interval	SA_H	Surface Area for Human
CNS	Central Nervous System	TSD	Technical Support Document
EG	Eosinophilic Globules	TWA	Time-weighted Average
EGBE	Ethylene Glycol mono-n-Butyl Ether	UF	Uncertainty factor
ER	Endoplasmic Reticulum	UF_{A-d}	Toxicodynamic portion of the interspecies uncertainty factor
EU	European Union	UF_{A-k}	Toxicokinetic portion of the interspecies uncertainty factor
GD	Gestational Day	UF_{H-d}	Toxicodynamic portion of the intraspecies uncertainty factor
HEC	Human Equivalent Concentration	UF_{H-k}	Toxicokinetic portion of the intraspecies uncertainty factor
Hgb	Hemoglobin	UF_L	LOAEL uncertainty factor
Ig	Immunoglobulin	VOC	Volatile Organic Compound
IV	Intravenous	U.S. EPA	United States Environmental Protection Agency
LOAEL	Lowest Observed Adverse Effect Level		
MCH	Mean Corpuscular Hemoglobin		
MV	Minute Volume		
MV_A	Minute Volume for Animal		
MV_H	Minute Volume for Human		
NOAEL	No Observed Adverse Effect Level		

2. Physical & Chemical Properties (HSDB, 2005)

Description	Colorless liquid
Molecular formula	C_4H_9-O-CH_2CH_2-OH ($C_6H_{14}O_2$)
Molecular weight	118.2 g/mol
Density	0.90 g/cm^3 @ 20 °C
Boiling point	171 °C
Melting point	-70 °C
Vapor pressure	0.88 mm Hg @ 25°C
Odor threshold in air	0.10 ppm (geometric mean) (AIHA, 1989) Sweet, ester-like, musty
Water Solubility	Miscible, but soluble in most organic solvents
Log Kow	0.81
Henry's law constant	2.08 x 10^{-7} – 10^{-8} atm-m^3/mole @ 25°C
Flash point	62°C (close cup); 70°C (open cup)
Conversion factor	1 ppm = 4.83 mg/m^3; 1 mg/m^3 = 0.207 ppm

3. Occurrence and Major Uses

Due to their excellent solvency, chemical stability and water compatibility, ethylene glycol mono-butyl ether (EGBE) and other glycol ethers are good solvents for many applications and often act as coupling agents to stabilize immiscible ingredients. Consumer products and building materials that may contain EGBE include liquid wax and wax strippers, varnish removers and lacquers, surface cleaner and coatings, water-based paints, nail enamel remover, permanent hair colorants, caulking and sealants, and resilient floorings (Andersen, 1996; Fang et al., 1999; Zhu et al., 2001; IWMB, 2003; HSDB, 2005). EGBE has been estimated to range in concentration from 1 to 30% (volume/volume) in some industrial and commercial products (Vincent et al., 1993). The Organisation for Economic Cooperation and Development (OECD, 1997) has estimated the air concentrations of EGBE associated with various occupations and consumer activities. Silk screening with a product containing 50% EGBE resulted in the highest dose estimate (18.2 mg/kg-day), followed by cleaning with a product containing 30% EGBE (13.7 mg/kg-day), while painting for 6 hours with a coating containing 1.5% EGBE resulted in an estimated dose of 1.05 mg/kg-day (OECD, 1997; ATSDR, 1998).

EGBE is a high production volume chemical with an estimated 180,000 tons produced in the United States in 1992 (NTP, 2000) and 150,000 tons in the European Union (EU)

(SCHER, 2008; OECD, 2012). Others have estimated world production to be 200,000 to 500,000 tons per year, of which 75% is for paints and coatings (Rebsdat and Mayer, 2001) and 18% for metal cleaners and household cleaners (NLM, 2014). The California statewide emissions of EGBE, reported under the Air Toxics Hot Spots Program, were 282,760 pounds in 2011 (ARB, 2011). EGBE is one of the major indoor volatile organic compounds (VOCs) in some newly constructed homes resulting in sensory irritation. The EGBE indoor air concentrations are thought to originate from water-based paints or adhesives. Brown (2002) measured EGBE levels in one new home on days 2, 19, 72, and 246 post-construction. The highest geometric mean EGBE concentration (81 $\mu g/m^3$) was found on day 19, but decreased to 4 $\mu g/m^3$ on post-construction day 246 (Brown, 2002). Microorganisms or molds have also been identified as possible emission sources for EGBE in buildings (McJilton et al., 1990). The National Institute for Occupational Safety and Health (NIOSH) (NOES Survey 1981-1983) has statistically estimated that 2,139,297 workers (585,932 of these are female) are potentially exposed to EGBE in the US. (HSDB, 2015).

4. Toxicokinetics

4.1 Absorption and Distribution

EGBE is absorbed and rapidly distributed in humans following inhalation, ingestion, or dermal exposure. In four healthy male research subjects who inhaled 25 ppm EGBE for 10 minutes, the mean uptake was 80% in the last 5 minutes of EGBE respiration (Kumagai et al., 1999).

Varied estimates of human EGBE dermal absorption have been published. Johanson and Boman (1991) exposed four male subjects to 50 ppm EGBE by mouth-only inhalation for two hours, followed by a one hour rest period, and then a two hour exposure to 50 ppm EGBE in a whole body exposure chamber, with 0 ppm EGBE breathing air supplied from a respiratory protection mask. Blood samples were taken via a finger-prick method and analyzed for EGBE. Each subject was exposed twice, with at least a two week interval between exposures. One exposure was carried out at what the authors described as "normal" (23°C, 29% relative humidity) environmental conditions, and one at “raised" (33°C, 71% relative humidity) air temperature and humidity in the chamber. The authors found that the average blood concentration and the calculated EGBE uptake rate were higher during dermal exposure compared to inhalation exposure (2-3-fold higher, respectively). The authors also found that dermal uptake of EGBE accounted for about 75% of the total EGBE uptake during whole body exposure (Johanson and Boman, 1991).

In contrast, in a whole-body human exposure scenario, the absorption through the skin was about 21% of total EGBE (skin permeability coefficient of 3 cm/hr) (calculated using physiologically-based pharmacokinetic (PBPK) modeling) (Corley et al., 1994). The same investigators (Corley et al., 1997) conducted a human study in which one arm of each subject was exposed to 50 ppm $^{13}C_2$-EGBE for 2 hours. Blood samples were collected by finger-prick method from the exposed arm, and by intravenous (iv) catheter from the non-exposed arm of each subject. The concentrations of EGBE in blood drawn from the exposed arms via the finger-prick method were nearly 1,500-fold higher than that in blood drawn from the non-exposed arms via iv catheter. The authors concluded that the finger-prick sampling technique grossly overestimates systemic absorption of EGBE via the dermal route. The authors also suggested that the relatively high dermal EGBE uptake (75% of total uptake) reported by Johanson and Boman (1991) compared to that found in their study (21% of total uptake) was the result of sampling artifacts caused by use of the finger-prick sampling technique.

4.2 Metabolism and Elimination

The two main oxidative pathways of EGBE metabolism observed in rats are via alcohol dehydrogenase (ADH) and O-dealkylation by cytochrome P450 (primarily the CYP2E1 isozyme). Like other monoethylene glycol ethers, EGBE is a substrate for ADH, which catalyzes the conversion of the terminal alcohol to butoxyacetaldehyde (BAL). Aldehyde dehydrogenase then rapidly converts BAL to 2-butoxyacetic acid (BAA), a predominant urinary metabolite (Ghanayem et al., 1987b). Because BAA is excreted in the urine of both rats and humans following EGBE exposure, it has been suggested that the production of BAA through the formation of BAL by ADH is applicable to both rats and humans (Medinsky et al., 1990; Corley et al., 1997). However, there are significant differences in some major toxicological endpoints (e.g., hemolysis) between rats and humans, as well as other species. Species-specific phase II metabolism of EGBE may be responsible for species differences in toxicity. Sulfate and glucuronide conjugates of EGBE have been reported in rodents, while glycine and glutamine conjugates of BAA have only been found in humans (Medinsky et al., 1990; Corley et al., 1997). Approximately two-thirds of the BAA formed by humans is conjugated with glutamine and, to a lesser extent, glycine, while the BAA-glutamine and BAA-glycine conjugation pathways have not been detected in the rat (Corley et al., 1997) (Figure 1). Lesser amounts of the glucuronide and sulfate conjugates of EGBE have been observed in the urine of rats (Bartnik et al., 1987; Ghanayem et al., 1987a), but not humans (Corley et al., 1997).

Oral studies suggested that human stomach tissues would be less capable of accumulating and localizing BAA than rat stomach tissues because of the different distributions of EGBE metabolizing enzymes and different anatomy (Green et al., 2002).

Elimination of EGBE and BAA from blood in mice is faster than in rats or humans (NTP, 2000). The blood half-life in human, rat, and mouse are 0.53-0.95, 0.11-0.69, and 0.05-0.35 hours for EGBE and 3.3-4.3, 0.55-6.6, and 0.36-4.5 hours for BAA, respectively (EPA, 2010). Toxicokinetic studies performed by the National Toxicology Program (NTP) (Dill et al., 1998) found that BAA was eliminated in both rats and mice following dose-dependent, nonlinear kinetics. Gender-related differences in BAA elimination were significant in rats in that females were less efficient in clearing BAA from the blood than males.

There are also age-related differences in the metabolism and clearance of EGBE, at least in rodents. Compared to older rats (9-13 weeks old), young rats (4-5 weeks old)

eliminated a larger proportion of gavage-administered EGBE as CO_2 and in the urine as EGBE metabolites, resulting in lower plasma concentrations of EGBE and BAA (Ghanayem et al., 1990a). However, young rats had lower urinary excretion of BAA and higher butoxy-glucuronide conjugation compared to the older rats (Ghanayem et al., 1987).

In low dose exposures, the kinetics of EGBE and BAA were linear up to 100 ppm, following continuous inhalation exposure to EGBE at doses of 20 or 100 ppm for 12 days in 4-month-old male rats (Johanson, 1994). Daily analyses indicated that EGBE and BAA concentrations increased rapidly in blood, muscle, testis, and liver tissues during the first 1 to 3 days and then more slowly during the rest of the study. At these concentrations, there was no effect of exposure concentration on total blood clearance of EGBE (approximately 2.3 L/kg per hour) or the fraction of inhaled EGBE excreted in urine as BAA (approximately 65%) (Johanson, 1994). Compared to younger rats and mice, older rats and mice have lower peak blood levels of BAA at the same exposure dose of EGBE (Corley et al., 2005).

In human volunteers, the elimination half-life of EGBE in blood following inhalation is about 40 min and the elimination half-life of the primary metabolite (BAA) in urine is about 6 hours (Johanson, 1986b), while peak excretion of BAA in urine for occupational exposure to EGBE does not occur until 6-12 hours post-exposure (Jones and Cocker, 2003). PBPK modeling of EGBE in workers continually exposed indicates that elimination from the most poorly perfused organs is rapid and that EGBE does not appear to accumulate in the body (Johanson, 1986b). However, small amounts of free and conjugated BAA were found in urine of EGBE-exposed workers the following morning after a work shift, indicating slight accumulation of the metabolite in the body (Sakai et al., 1994). EGBE exposure levels (breathing zone Time-Weighted Average (TWA)) during a work week were mostly between 0.2 and 0.8 ppm, with urinary elimination of the metabolite almost complete over the weekend.

A case report by Gualtieri et al. (2003) described an 18-year-old male who ingested 360–480mL of a glass cleaner which contained 22% EGBE and then again ingested approximately 480 ml of the same cleaner 10 days later. The authors reported serum concentrations of EGBE and BAA for both ingestion incidents. The highest BAA serum concentration noted during the first ingestion was 4.86 mmol/L, collected approximately 16 hours post-ingestion and 7 hours prior to hemodialysis. The highest BAA serum concentration noted during the second ingestion was 2.07 mmol/L, collected approximately 22 hours post-ingestion and 2 hours after the start of hemodialysis.

Corresponding EGBE serum concentrations were substantially lower than the corresponding BAA serum concentrations at the time points listed above (0.00038 mM and 0.108 mM for the first and second ingestion, respectively). However, no statistical analysis was provided by the authors.

Some chemicals have a protective effect against the hemolytic effects of EGBE, known as heteroprotection. For example, a priming dose of phenylhydrazine protected the rats from the hemolytic and lethal effects of BAA, which may be due to phenylhydrazine treated rats having lower renal and hepatic BAA levels and about 3-fold higher urinary excretion of BAA compared to the control rats (Palkar et al., 2007). Hepatic alcohol and aldehyde dehydrogenase activities were unaltered, indicating that bioactivation of EGBE to BAA was unaffected by phenylhydrazine. The higher erythropoietin levels, reticulocyte count, and resiliency of RBCs in phenylhydrazine-primed rats indicated that the newly formed RBCs are resistant to the hemolytic action of BAA (Palkar et al., 2007). Young rodent erythrocytes have been found to be less sensitive to BAA than older erythrocytes (Ghanayem et al., 1992).

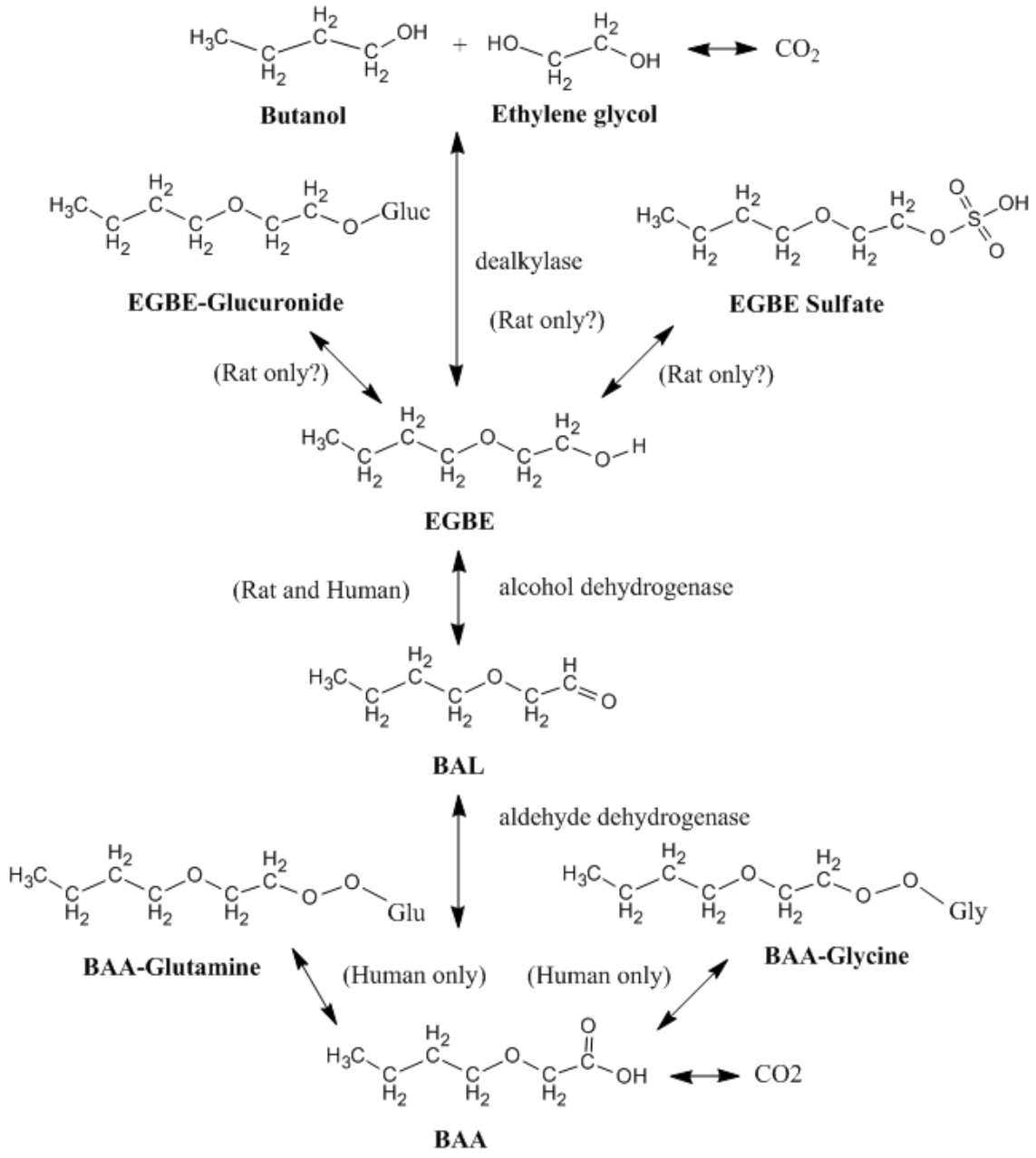


Figure 1. EGBE Metabolism in Rats and Humans - adapted from (Medinsky et al., 1990; Corley et al., 1997)

5. Acute Toxicity of EGBE

5.1 Acute Toxicity to Adult Humans

EGBE is an irritant of the eyes and upper respiratory tract in humans. Accidental exposures of humans to high levels of EGBE vapors originating from misuse of concentrated EGBE cleaning products has resulted in immediate intense eye and respiratory irritation, marked dyspnea, nausea, and faintness (Raymond et al., 1998). Long-term effects attributed to high acute exposures include recurrent eye and respiratory irritation, dry cough and headache (Raymond et al., 1998). The appearance of cherry angiomas were also reported to occur in 6 of 7 workers (mean age: 36 yrs) 4 months following the high acute EGBE exposure. Cherry angiomas can appear spontaneously usually after age 50, but have been observed in workers following exposure to other irritating gases. The authors suggested cherry angiomas may represent a nonspecific response in some persons to inhalation of noxious agents.

EGBE concentrations near silk screening equipment that resulted in complaints of odor and sensory irritation during use were found to range from 13 to 169 ppm (Kullman, 1987). Respiratory irritation due to EGBE exposure could trigger asthmatic episodes in people with asthma and also pose risks for people with chronic obstructive pulmonary disease, emphysema, and other respiratory diseases and conditions (Bello et al., 2009; Burns, 2010). Epidemiological investigations have shown an association between exposure to cleaning products and respiratory dysfunction, including exacerbation of asthma (Zock et al., 2007; Siracusa et al., 2013; Folletti et al., 2014). Although EGBE has been implicated as a potential irritant in cleaning products that lead to respiratory problems, the presence of other VOC irritants in cleaning products and the lack of quantitative assessments of exposure during cleaning activities makes it difficult to characterize EGBE's role as a respiratory irritant in these products (Bello et al., 2009; Bello et al., 2013; Fromme et al., 2013; Gerster et al., 2014).

For the hemolytic effects of EGBE, rats, mice and rabbits are highly susceptible, but not humans, monkeys, dogs and guinea pigs (Carpenter et al., 1956). In sensitive mammalian species, hemolytic anemia and increased erythrocyte osmotic fragility are primary toxic endpoints of EGBE exposure. However, simultaneous chamber exposures of rats and men to EGBE (113 ppm for 4 hours) have shown humans to be insensitive to these toxic endpoints at this dose level compared to rats (Carpenter et al., 1956). *In vitro* studies have also shown considerably less risk of hemolysis in human erythrocytes compared to rat erythrocytes when blood is incubated with BAA (Corley et al., 1994; Udden, 2002). After comparing *in vivo* and *in vitro* studies for several species,

including monkeys, Carpenter et al. (1956) stated "the in vivo response of erythrocytes to butyl Cellosolve (EGBE) is more closely correlated to the in vitro response to sodium butoxyacetate (BAA) than to the in vitro response to butyl Cellosolve. This suggests that butoxyacetic acid is more directly responsible for in vivo erythrocyte fragility or hemolysis than is butyl Cellosolve." Physiologically-based pharmacokinetic (PBPK) modeling for exposures to saturated atmospheres of EGBE showed that the maximum blood concentration of BAA is below that needed to produce this effect in the human (Corley et al., 1997). PBPK modeling simulations have also found that the maximum venous blood concentration of BAA in adult humans is similar to or below that of rats and mice (Corley et al., 2005). The resistance of RBC's in healthy adults to the hemolytic effects of BAA *in vitro* extends to erythrocytes from elderly individuals, children, and individuals with sickle cell disease or hereditary spherocytosis (Udden and Patton, 1994; Udden, 2002). Nevertheless, anecdotal reports of hemoglobinuria and anemia have been reported following exposure to very high concentrations of EGBE (Carpenter et al., 1956; Raymond et al., 1998).

In acute oral exposure case reports, two women who ingested window cleaner containing about 12% EGBE (dose range 391 – 933 mg/kg) developed severe respiratory effects including pulmonary edema and obstructive respiration that required a ventilator (Rambourg-Schepens et al., 1988; Gijsenbergh et al., 1989). One 50-year-old woman had moderate hemoglobinuria on the third day, which lasted until the sixth day, inducing progressive erythropenia (RBC 3 $x10^{12}$/L, hematocrit 28.6%, hemoglobin (Hgb) 9.7 g/L on the 10th day) (Rambourg-Schepens et al., 1988). Another 23-year-old woman had a fall in Hgb from 11.9 g/dL on admission to 8.9 g/dL on the second day, together with the appearance of hematuria (Gijsenbergh et al., 1989). Both patients recovered and were discharged in good condition after 8 to 10 days.

A case report described an 18-year-old male who ingested 360–480mL of a glass cleaner which contained 22% EGBE (Gualtieri et al., 2003). Approximately 10 hours after the first ingestion, the patient developed severe central nervous system (CNS) depression, metabolic acidosis, hematuria, and mild elevation of hepatic enzymes. He was treated initially with ethanol therapy but continued to deteriorate and was started on hemodialysis. Approximately 10 days after discharge, the patient ingested 480mL of the same product and received ethanol and hemodialysis within four hours of ingestion. During his second admission the patient did not develop the delayed severe CNS depression or profound metabolic acidosis. Clinically significant hemolytic anemia, oxaluria, ethylene glycol production, and renal failure were not noted in either episode. The patient recovered on both occasions without sequelae.

In whole-body chamber studies, volunteers were exposed to 98 ppm (two men and one woman) or 195 ppm (two men and two women) EGBE for a total of 8-hours (Carpenter et al., 1956). Even at the lower exposure level, eye, nose, and throat irritation, taste disturbances, headache, and nausea were reported. Two men exposed to 113 ppm EGBE for 4-hours reported similar effects. Erythrocyte osmotic fragility and urinalysis were normal in the subjects during and after exposure.

In a chamber study conducted to investigate the toxicokinetics of EGBE, seven healthy male adults were exposed to 20 ppm EGBE for 2 hours during light exercise on a bicycle ergometer. There were reportedly no complaints or any other adverse effects from exposure. No changes in pulmonary ventilation, respiratory frequency or heart rate were seen. However, this study was primarily a toxicokinetic study and was not designed to collect detailed information on potential sensory irritant effects. In another toxicokinetic study, whole body 2-hour exposure of four volunteers to 49 ppm EGBE did not result in physiological changes in breathing rate, pulse rate, skin surface temperature or skin resistance (Jones and Cocker, 2003; Jones et al., 2003b). Although an odor was noted on entering the chamber and some volunteers found it initially unpleasant, perception of the smell diminished over time during exposure (electronic communication from K. Jones, 2005).

5.2 Acute Toxicity to Infants and Children

No studies of children exposed to airborne EGBE were located. However, acute ingestion of EGBE in cleaning solutions by 24 children (aged from 7 months to 9 years) from a regional poison control center have been reviewed (Dean and Krenzelok, 1992). These reports included the ingestion of 5-300 mL of liquid glass cleaning products containing 0.5 to 9.9% EGBE. All ingestions were reported within 5 minutes of ingestion, and all 24 children, including two who were hospitalized for 24 hours following gastric emptying and gastric lavage, were asymptomatic at the time the ingestions were reported. The five month retrospective review of the two hospitalized children failed to find symptoms consistent with hemolysis, nervous system depression, acidosis, or renal compromise. EGBE at these concentrations appears to have low acute toxicity by the oral route.

5.3 Acute Toxicity to Experimental Animals

Substantial species differences exist among experimental animals in their acute responses to EGBE. Rats and mice are especially susceptible to the hemolytic effects

of EGBE, while guinea pigs, canines, and primates are more resistant to these effects (Ghanayem and Sullivan, 1993; Gingell et al., 1998).

Male and female rats were exposed by inhalation to EGBE for 4 hours at concentrations of 867, 523, and 202 ppm. All of the rats in the 867 ppm group died within 24 hours of exposure. The estimated LC_{50} was 486 ppm for males and 450 ppm for females. These rats exhibited loss of coordination, rapid shallow breathing, and red discharge from the urogenital region (Dodd et al., 1983).

In a subsequent study, rats were exposed for 9 days (6 hr/day) to EGBE concentrations of 245, 86, 20, or 0 (control) ppm. The authors found EGBE exposure significantly reduced RBC count, Hgb, mean corpuscular Hgb (MCH) concentration, and body weight gain, while increases in nucleated erythrocytes, reticulocytes, lymphocytes, and liver weights were observed in both male and female rats. A 14-day post-exposure recovery showed substantial reversal of the affected blood parameters. Similar hematologic effects were observed in the 86 ppm group, but not in the 20 ppm group. In a 90-day study, rats were exposed to EGBE at 77, 25, 5, or 0 ppm, 6 hours/day, 5 days/week. Significant decreases in RBC (13% below control) and Hgb, accompanied by an increase in MCH (11% above control) were observed in the 77 ppm-exposed females after 6 weeks. There were no significant biological effects in rats exposed subchronically to 5 or 25 ppm of EGBE (Dodd et al., 1983).

Whole body inhalation exposure of guinea pigs for 1 hour to 633 ppm (5 males) and 691 ppm (5 females) resulted in no mortality or clinical signs of toxicity, either immediately or for up to 14 days following exposure (Gingell et al., 1998).

In a comparison study of hematological parameters, a single gavage administration of EGBE (250 mg/kg) to rats caused an early increase (1 hour post-treatment) in mean corpuscular volume and hematocrit (HCT), which declined over a 24 hour period. This was associated with hemolysis, and a decline in Hgb and numbers of RBCs. However, this same treatment in guinea pigs had no similar effect (Ghanayem and Sullivan, 1993).

Kane et al. (1980) estimated an RD50 (an airborne concentration of a chemical that produces a 50% decrease in respiratory rate) of 2825 ppm in mice. The RD50 bioassay measures decreases in respiratory frequency in mice as a result of stimulation of the trigeminal or laryngeal nerve endings. However, the RD50 needed to be extrapolated for EGBE because the authors were unable to generate a high enough EGBE

concentration to directly determine the RD50. Although not specified by the authors, this could be a result of the exposures reaching the saturated vapor pressure (about 1000 to 1600 ppm, depending on the temperature and humidity) prior to reaching the RD50. EGBE was categorized as a weak sensory irritant by Kane et al. (1980) when compared to the RD50 of potent sensory irritants such as chlorine, acrolein, formaldehyde and toluene diisocyanate (Kane et al., 1980).

6. Chronic (including Sub-chronic) Toxicity of EGBE

6.1 Chronic Toxicity to Adult Humans

Chronic exposure to EGBE can cause dermatitis and hematuria (NIOSH, 1992). A cross-sectional study included 31 male workers (22 - 45 years old) who had been employed for 1 to 6 years. Workers were exposed to low levels of EGBE at 0.59 ± 0.27 ppm (means ± standard deviation) in a beverage packing plant. There was a good concentration correlation between EGBE in air and post-shift BAA in urine. A slight but significant effect on erythroid parameters (hematocrit, a 3.3% decrease; and MCH concentration, a 2.1% increase) suggested membrane damage in exposed workers, but no significant effect was found on other erythroid parameters (Haufroid et al., 1997). The US Environmental Protection Agency (EPA, 2010) noted that hematocrit and MCH concentrations were still within normal clinical ranges. Additional studies are needed to confirm if these changes represent early markers of EGBE toxicity in workers.

In another occupational study, the investigators evaluated the hematological status of nine parquet floorers exposed to a mean 8-hour concentration of 24.6 mg/m^3 (5.1 ppm) EGBE (max: 350 mg/m^3 (72 ppm)) by personal air sampling) for an average of 18.9 years (ranged 25 – 58 years). The workers' erythrocyte numbers showed a slight, but insignificant ($0.05 < p < 0.1$) decrease, but their Hgb concentrations were unaffected. Co-exposure to a number of other chemicals in the worker group also occurred (Denkhaus et al., 1986).

While some studies note a good correlation between EGBE in air and urinary BAA concentrations, one study measured high levels of urinary BAA in workers cleaning offices and cars with EGBE-containing products, even though air concentrations of EGBE were often lower than 0.5 ppm (Vincent et al., 1993). This finding suggested that skin penetration of EGBE-containing solution in unprotected workers could be a significant source of exposure. Dermal exposure studies in human volunteers show EGBE solutions are well absorbed dermally and could represent a dominant route of

exposure (Jakasa et al., 2004; Kezic et al., 2004). Based on urinary BAA levels in 'whole body' and 'skin only' EGBE chamber exposures, dermal absorption of EGBE vapors averaged 11% of the total body dose (Jones et al., 2003b). PBPK modeling estimations by Corley et al. (1997) under similar baseline conditions produced similar dermal absorption results (15% of total body dose) via vapor exposure. Wearing overalls during exposure actually increased dermal absorption, probably by forming a warmer, more humid microclimate next to the skin that promoted absorption (Jones et al., 2003b).

As noted in Section 3 of this document, EGBE is used in a variety of industrial and consumer products, including cleaning products. Exposure to substances in the workplace has been estimated to cause about 10% of all cases of adult-onset asthma (Blanc and Toren, 1999). A prospective study of 6837 participants from 13 countries in the EU found the population-attributable risk for adult asthma due to occupational exposures ranged from 10% to 25%, equivalent to an incidence of new-onset occupational asthma of 250–300 cases per million people per year. Asthma risk was also reported to be increased in participants who reported an acute symptomatic inhalation event such as fire smoke exposure, mixing cleaning products, or chemical spills (RR = 3.3, 95% CI 1.0–11.1, p = 0.051) (Kogevinas et al., 2007). Cleaning workers have been described as an exposure group at high risk of developing occupational asthma and asthma-like symptoms (Kogevinas et al., 2007). However, the determination of which health hazards are associated with exposure to cleaning agents is a complex issue, and the contribution of sensitization to specific agents or exposure to irritants in the pathogenesis of respiratory symptoms associated with cleaning is unclear (Quirce and Barranco, 2010). A European Academy of Allergy and Clinical Immunology task force consensus statement indicated cleaning sprays, bleach, ammonia, disinfectants, mixing products, and specific job tasks have been identified as specific causes and/or triggers of asthma (Siracusa et al., 2013). However, Siracusa et al. (2013) did not indicate that cleaning products containing glycol ethers (including EGBE) were specifically included as asthmagens in their assessment.

6.2 Chronic Toxicity to Infants and Children

(Choi et al., 2010) conducted a case-control study of exposure to common household chemicals and the resulting prevalence of allergic airway disease in Swedish pre-school age children. Cases were defined as children 3-8 years of age who were reported to have at least two symptoms of wheezing, rhinitis, or eczema without a cold during the preceding 12 months on either a baseline questionnaire or a follow-up questionnaire

(done 1.5-years after the baseline questionnaire). Controls were randomly identified from 1,100 symptom-free children from local primary care clinics. This resulted in a study population of 198 cases and 202 controls. Air and dust samples were collected from the bedrooms of the houses where the cases and controls lived, and analyzed for several classes of VOCs, including glycols and glycol ethers.

Of the original population of cases and controls, 18 cases and 9 controls were found to have EGBE indoor air concentrations greater than the EGBE functional detection limit (not specified). No significant differences in the geometric mean EGBE indoor air concentrations were noted between the controls (3.0 μg/m^3; 95% confidence interval (CI) 0.30-29.61) and the cases (3.11 μg/m^3; 95% CI 0.76-12.67).

6.3 Chronic Toxicity to Experimental Animals

The principal toxic effect of exposure to EGBE in sensitive species is a reversible hemolytic anemia. In rodents, the primary effect on the hematologic system was anemia characterized as macrocytic (rat), normocytic (mouse), normochromic, and regenerative in exposed rats and mice (NTP, 2000). More generally, EGBE also causes irritation and damage to epithelial tissues at portal of entry sites (i.e., eyes and respiratory airways).

The NTP (2000) conducted a 14-week whole-body EGBE inhalation exposure study in Fisher 344 rats and B6C3F$_1$ mice. Exposure (6 hours/day, 5 days/week) to 31, 62.5, 125, 250, and 500 ppm EGBE resulted in clinical findings that included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy, and increased salivation and/or lacrimation primarily at the three highest concentrations in rats, and at the highest concentration in mice. The most pronounced effect was a concentration-related hemolytic anemia in male rats and mice exposed to 125 ppm and above and, to a greater extent, in all exposed groups of female rats and mice. Exposure-related increases in the incidences of forestomach inflammation and epithelial hyperplasia, bone marrow hyperplasia (rats only), Kupffer cell pigmentation of the liver, splenic hematopoietic cell proliferation, and renal tubule pigmentation were observed in male and/or female rats and mice surviving to the end of the study. The latter three effects were secondary to red cell hemolysis and regenerative anemia, with female rats showing the greatest sensitivity. Statistically significant increases in Kupffer cell pigmentation and bone marrow hyperplasia were apparent in female rats at concentrations as low as 62.5 ppm (NTP, 2000).

In the subsequent NTP 2-year study, Fisher 344 rats and B6C3F$_1$ mice were exposed to 31.2 (rats only), 62.5, 125, and 250 (mice only) ppm of EGBE via inhalation for 6-hours/day, 5 days/wk. In rats, anemia occurred in females starting at 31.2 ppm, and in males starting at 62.5 ppm. The anemia was considered mild and persisted with no apparent progression or amelioration of severity from 3 months to 12 months (final blood collection). Incidences of hyaline degeneration of the olfactory epithelium were increased in 62.5 or 125 ppm groups of both sexes, although the severity of this lesion was minimal (incidence presented in Table 1). No evidence of carcinogenicity was found in male rats, and equivocal evidence of carcinogenicity was found in female rats, based on increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla.

In mice, survival of males was reduced at 125 and 250 ppm. Anemia was observed following 3, 6, or 12 months of exposure at 125 and 250 ppm in both male and female mice. Incidences of forestomach ulcer and hyperplasia, nasal hyaline degeneration of olfactory and respiratory epithelium were increased in all exposed female mice. In male mice, there was an increased incidence of forestomach ulcer at 125 ppm. All groups of exposed males showed increased incidence of forestomach hyperplasia. A mouse urologic infection syndrome was apparent in males, and appeared to be exacerbated by EGBE exposure at 125 and 250 ppm. Effects secondary to hemolysis were also observed including splenic congestion and hemosiderin deposition in Kupffer cells of livers in both rats and mice (incidence presented in Table 1). The principal non-cancer toxic endpoints not linked to RBC hemolysis were nasal olfactory epithelial lesions (hyaline degeneration), forestomach epithelial hyperplasia, and forestomach ulcers (incidence presented in Table 1). NTP found that there was some evidence of carcinogenic activity of 2-BE in male B6C3F$_1$ mice based on increased incidences of hemangiosarcoma of the liver. A marginal increase in the incidences of forestomach squamous cell papilloma and an increase in the incidences of hepatocellular carcinoma may have been exposure related. NTP also found some evidence of carcinogenic activity of 2-BE in female B6C3F$_1$ mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma) (NTP, 2000).

Table 1. Incidence of nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, forestomach epithelial hyperplasia and ulcer in rats and mice following 2-year EGBE inhalation study (NTP, 2000)

Endpoints	Exposure Doses (ppm)				
	0	31.2	62.5	125	250
Nasal Olfactory Epithelial Hyaline Degeneration					
Male Rats	13/48	21/49	23/49*	40/50***	--------
Female Rats	13/50	18/48	28/50**	40/49***	--------
Total Rats	*26/98*	*39/97**	*51/99****	*80/99****	--------
Male Mice	1/50	--------	2/50	3/48	1/48
Female Mice	6/50	--------	14/50*	11/49	12/50*
Total Mice	*7/100*	--------	*16/100**	*14/97*	*13/98*
Liver Kupffer Cell Pigmentation					
Male Rats	23/50	30/50	34/50*	42/50***	--------
Female Rats	15/50	19/50	36/50***	47/50***	--------
Total Rats	*38/100*	*49/100*	*70/100****	*89/100****	--------
Male Mice	0/50	--------	0/50	8/49**	30/49***
Female Mice	0/50	--------	5/50*	25/49***	44/50***
Total Mice	*0/100*	--------	*5/100**	*33/98****	*74/99****
Forestomach Epithelial Hyperplasia					
Male Mice	1/50	--------	7/50*	16/49***	21/48***
Female Mice	6/50	--------	27/50***	42/49***	44/50***
Total Mice	*7/100*	--------	*34/100****	*58/98****	*65/98****
Forestomach Ulcer					
Male Mice	1/50	--------	2/50	9/49**	3/48
Female Mice	1/50	--------	7/50*	13/49***	22/50***
Total Mice	*2/100*	--------	*9/100**	*22/98****	*25/98****

Note: Statistically significant differences compared to the control group were measured with the Chi-square (X^2) or Fisher exact test, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (statistical analysis performed by OEHHA).

Chronic contact irritation by EGBE, and in particular the EGBE metabolites BAA and 2-butoxyacetaldehyde, have been implicated in the damage to the forestomach in mice (Green et al., 2002; Poet et al., 2003). Metabolism of EGBE by ADH to BAA in the rodent forestomach is thought to play a role in the development of epithelial hyperplasia and ulcers. A similar mechanism of action in rat and mouse nasal olfactory epithelium also likely occurs (Gift, 2005). Intravenous, oral and inhalation studies have shown accumulation of EGBE and BAA in the mouse forestomach (Boatman et al., 2004). Thus, systemic blood circulation, grooming of contaminated fur, and clearance of mucus from the respiratory tract are all factors in the accumulation of EGBE in the forestomach (NTP, 2000). In the chronic REL development of EGBE, we are focusing on the endpoint of upper respiratory tract irritation and nasal hyaline degeneration of the olfactory epithelium.

Similar concentration-response results for anemia in rodents were observed in earlier studies. In a 9-day exposure (6 hours/day, 5 days/week) study in rats, Dodd et al. (1983) reported a No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) of 20 and 86 ppm, respectively, based on the anemia endpoint. In a subsequent 90-day EGBE exposure study (6 hours/day, 5 days/week), the same authors reported a NOAEL and LOAEL of 25 and 77 ppm, respectively, for anemia in male and female rats. The severity of RBC depression in the 90-day study was not increased compared to the 9-day study (Dodd et al., 1983).

In a series of experiments using both rodent and non-rodent species, rats, guinea pigs, mice, dogs, and monkeys were exposed to EGBE via inhalation for 7 hours/day, 5 days/week for up to 90 exposures (Carpenter et al., 1956).

In rats, groups of males and females were exposed to 54, 107, 203, 314, or 432 ppm EGBE for 30 exposures (7 hours/day, 5 days/week for 6 weeks). Deaths occurred at 314 ppm and higher, and evidence of hemoglobinuria was evident at concentrations of 203 ppm and higher. A dose-dependent increase in erythrocyte osmotic fragility was observed at all exposure levels.

Groups of 10 male guinea pigs exposed to 54, 107, 203, 376, or 494 ppm EGBE for 30 exposures did not show evidence of RBC hemolysis at any concentration. Lung congestion and kidney damage were the only findings among the three animals that died at 376 ppm or higher.

Groups of mice exposed to 112, 200 or 400 ppm EGBE for 30 to 90 exposures exhibited transient hemoglobinuria at the highest concentration and increased RBC fragility at all concentrations. No mortality occurred and no gross pathology of organs was observed 42 days after cessation of exposure.

Carpenter et al. (1956) observed decreased hematocrit values and increased leucocyte count in dogs (one male, one female/study, no controls) after exposure to 100 or 200 ppm EGBE for up to 90 and 31 exposures, respectively. In addition to these findings, two dogs (one male, one female, no controls) exposed repeatedly to 385 ppm also exhibited nasal and ocular infection, generalized weakness, apathy, anorexia, emesis and death following the 8th exposure in the female and the 28th exposure in the male.

In two monkeys exposed to 100 ppm EGBE (90 exposures) and one rhesus monkey exposed to 210 ppm EGBE (30 exposures) (no controls used in either study), increased RBC fragility was observed at both concentrations and emesis at the highest concentration. Pulmonary tuberculosis was found in the monkeys at autopsy, but no other noteworthy histopathological findings were observed (Carpenter et al., 1956).

7. Developmental and Reproductive Effects

EGBE is not listed as a developmental or reproductive toxicant under California Proposition 65 (OEHHA, 2015). Unlike some structurally-similar glycol ethers listed under Proposition 65, EGBE exposure did not cause significant effects in the reproductive organs, including testes (Dodd et al., 1983; NTP, 2000). Quantitative Structure Toxicity Relationship (QSTR) models also predicted that EGBE has no developmental toxicity (Ruiz et al., 2011).

In a developmental toxicity investigation, rats and rabbits were exposed to 25, 50, 100, or 200 ppm EGBE for 6 hours/day on gestational day (GD) 6-15 for rats and GD 6-18 for rabbits. In rats, maternal toxicity included decreased body weight gain, decreased food consumption, and evidence of anemia in the 100 and 200 ppm groups. Embryotoxicity (as increased number of totally resorbed litters and decreased number of viable implantations) was seen at the highest concentration and delayed skeletal ossification in offspring was observed at 100 and 200 ppm. In rabbits, toxicity included maternal deaths, spontaneous abortions and decreased body weight at 200 ppm, while hematological parameters were normal. Embryotoxicity indicated by reduced gravid uterine weight and a concomitant reduction in total and viable implantations was

observed at 200 ppm (Tyl et al., 1984). In another developmental study, rats were exposed to 150 or 200 ppm EGBE for 7 hours/day on GD 7-15. Maternal evidence of hematuria was observed only on the first day of exposure at both concentrations, and no fetotoxicity was seen in the offspring (Nelson et al., 1984).

In a two-generation reproductive toxicity study, mice of both sexes were exposed to EGBE at doses of 0, 700, 1300, and 2100 mg/kg-day for 7 days prior to and during a 98-day cohabitation period (Heindel et al., 1990; EPA, 2010). Six of 20 and 13 of 22 F_0 female mice in the mid- and high-dose groups, respectively, died during the cohabitation period. Both the mid- and high-dose EGBE groups had fewer litters/pair and pups/litter as well as smaller pup weight, while decreased body weight was also reported in F_0 female mice. There were no significant differences for testes and epididymis weights, as well as sperm number and motility between exposure and control groups. For the second generation reproductive study, no effects were found. The authors reported that the reproductive toxicity of EGBE was only evident in the female mice with large doses (usually >1000 mg/kg-day) (Heindel et al., 1990; EPA, 2010).

In an oral gavage study, pregnant mice were exposed to EGBE at doses of 0, 350, 650, 1000, 1500, and 2000 mg/kg-day (6 animals per group) during GD 8-14 (sacrificed at GD18). Hemolytic effects in the dams were observed starting at 650 mg/kg-day. At 1500 mg/kg-day and 2000 mg/kg-day, the maternal mortality rate was 3/6 and 6/6, respectively. Increased resorption rates and a reduced number of viable fetuses were observed at exposures of 1000 and 1500 mg/kg-day. Four (all in the same litter) of 43 fetuses at 1000 mg/kg-day and one of 25 fetuses at 1500 mg/kg-day had cleft palates. For this study, the NOAEL for maternal toxicity was 350 mg/kg-day and the NOAEL for developmental toxicity was 650 mg/kg-day (Wier et al., 1987; SCCP, 2007). Since only some of the offspring of pregnant mice exposed to very large doses of EGBE by gavage had cleft palates, it was concluded that EGBE is not significantly toxic to the reproductive organs of adult males or females, or to the developing fetuses of laboratory animals (ATSDR, 1998; EPA, 2010).

8. Derivation of Reference Exposure Levels

RELs are based on the most sensitive and relevant health effects reported in the medical and toxicological literature. Acute RELs are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Noncancer REL TSD (OEHHA, 2008).

8.1 EGBE Acute Reference Exposure Level

Study	(Carpenter et al., 1956)
Study population	2 to 4 human subjects per study
Exposure method	Whole body exposure, 98, 113 and 195 ppm
Exposure duration	8 hours (98 and 195 ppm in chamber) or 4 hours (113 ppm in room)
Critical effects	Subjective ocular and respiratory irritation
LOAEL	98 ppm (474 mg/m^3)
NOAEL	None
Time- adjusted exposure	None
Human equivalent concentration (HEC)	None
LOAEL uncertainty factor (UF_L)	10
Subchronic uncertainty factor (UF_S)	N/A
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1
Toxicodynamic (UF_{A-d})	1
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	1 (site of action; no systemic effects)
Toxicodynamic (UF_{H-d})	10 (potential asthma exacerbation in children; small sample size)
Cumulative uncertainty factor	100
Reference Exposure Level	4.7 mg/m^3 (1 ppm)

The acute EGBE REL is based on three whole-body human exposure studies (small sample size) performed over an extended period. These studies identified a LOAEL of 98 ppm, based on subjective sensory irritation. The response at 98 ppm was reported to be nearly as great as that elicited at 195 ppm, which included immediate onset of nasal and throat irritation, followed by ocular irritation (Carpenter et al., 1956). Supporting studies that exposed volunteers to lower concentrations of 20 ppm (Swedish occupational exposure limit) and 49 ppm examined some physiological responses during exposure but did not find obvious health effects (Johanson et al., 1986; Johanson, 1986b; Jones et al., 2003b). However, these studies were primarily

toxicokinetic studies and not designed for a detailed analysis of acute sensory irritant effects or a dose-response assessment (i.e., both studies used a single dose exposure concentration).

There are several reasons why we decided not to use these studies for the point of departure (POD) for the acute REL derivation:

1. Examining only physiological factors (e.g., breathing rate, pulse rate, skin surface temperature and skin resistance), many of which may be less sensitive endpoints compared to subjective responses, may overestimate the NOAEL and miss the most sensitive endpoint (i.e., sensory irritation).

2. The toxicokinetic studies, mainly Jones et al (2003) and Johanson et al. (1986), used only one exposure concentration with no apparent adverse effects on the human subjects. As such, they are free-standing NOAELs. Our revised Noncancer REL TSD guidance (OEHHA, 2008) notes that, "*OEHHA may use a NOAEL without an associated LOAEL identified in the same study (a free-standing NOAEL), but only if there are no other suitable studies, and so long as the overall health hazard data (including any case reports or studies with shorter durations) for that substance are consistent with the NOAEL study.*" OEHHA guidance does not recommend using a NOAEL and a LOAEL from different studies, and that a free-standing NOAEL not be used as the basis of a REL if a more suitable study (e.g., a study with a LOAEL) exists. Thus, we base the proposed acute REL on the LOAEL of 98 ppm determined in the Carpenter et al. study, which OEHHA believes is a more suitable study.

3. Additionally, there are small sample sizes in studies that have free-standing NOAELs, particularly for Jones et al. study (n=4). As noted in the OEHHA Noncancer TSD (OEHHA, 2008 page 39), "*A NOAEL could be associated with a substantial (1-20%) but undetected incidence of adverse effects among the exposed population. This is so because only a subset of individuals from the population has been observed and because the experiment may not have been designed to observe all adverse effects associated with the substance.*" Therefore, OEHHA cannot conclude that the single-dose studies exposing only a few human subjects are not associated with any adverse effects.

For the acute REL derivation, the critical effects of trigeminal-mediated sensory irritation are usually a concentration-dependent response. Thus, no time adjustment from a 2-

hour to a 1-hour exposure was performed. Since these studies were conducted in humans, no interspecies UFs are required. However, a UF of 10 to account for extrapolation from a LOAEL to a NOAEL was applied.

The toxicokinetic component of the intraspecies UF_{H-k} is assigned a value = 1. Chemicals that result in eye and upper respiratory sensory irritation are not predicted to be substantially different in children compared to adults when dosimetric adjustments are made (OEHHA, 2008). An intraspecies toxicokinetic UF = 1 is used for acute sensory irritants if metabolic processes do not contribute to intraspecies variability. No systemic toxicity from metabolites (primarily BAA-related hemolysis) was observed during acute human exposures conducted by Carpenter et al., and *in vitro* studies have shown RBCs from children are resistant to BAA-induced hemolysis similar to RBCs from adults.

The toxicodynamic component of the intraspecies UF_{H-d} is assigned a value of 10 for potential exacerbation of asthma in sensitive subpopulations. In addition, the small sample size in the critical study (n= 3-4) warrants a larger intraspecies uncertainty factor. Epidemiological studies suggest cleaning products, including those products that utilize EGBE, increase the likelihood of an asthmatic episode in susceptible individuals. Although there is no direct evidence that EGBE by itself can exacerbate asthma, the respiratory irritation induced by inhaled EGBE may lead to an asthmatic reaction, particularly in children who may experience irritant-induced asthma; OEHHA views asthma as a more serious health problem in children versus adults (OEHHA, 2001). Thus, the cumulative UF is 100 for acute exposures and the acute REL is 1 ppm (4.7 mg/m^3).

In contrast, the LOAEL and NOAEL for hematological effects in a subacute EGBE inhalation rat study (9 days total exposure; 5 days, two days of no exposure, then 4 days, 6 hr/day) (Dodd et al., 1983) were 86 ppm and 20 ppm, respectively. That data set was not used to develop an acute REL, because the use of human toxicity data to develop a REL is preferred when possible over animal data (OEHHA, 2008), and as discussed above, humans tend to be resistant to EGBE hematological effects. Further, the multi-day exposure study design is not particularly amenable to estimating an acute REL, which is meant for infrequent 1 hour exposures.

8.2 EGBE 8-Hour Reference Exposure Level

The 8-hour REL is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures (see Section 6 of the Noncancer REL TSD (OEHHA, 2008).

Study	(NTP, 2000)
Study population	Rats (50 animals/group/gender)
Exposure method	Discontinuous whole-body inhalation exposure to 0, 31.2, 62.5, 125 ppm
Critical effects	Nasal hyaline degeneration of olfactory epithelium
LOAEL	31.2 ppm
NOAEL	Not observed
$BMCL_{05}$	7.6 ppm (Logistic model from female rats)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Time-adjusted exposure	2.714 ppm (7.6 ppm x 6/24 x 5/7 x 20/10)
Human Equivalent Concentration	0.950 ppm (gas with extrathoracic respiratory effects, RGDR = 0.35)
LOAEL uncertainty factor	1 (with use of a $BMCL_{05}$)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1
Toxicodynamic (UF_{A-d})	√10
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	30
Reference Exposure Level	0.15 mg/m^3 (0.032 ppm)

Note: Time-adjusted Exposure: The POD is first adjusted to a 24-hour continuous exposure (6/24 hours x 5/7 days per week), then multiplied by 2 (20m^3/10m^3) to represent an active worker breathing half the volume of air that they would breathe in a 24-hour period during an 8-hour work day. HEC = Time-adjusted Exposure × the Regional Gas Dose Ratio (RGDR). RGDR = (MV_A/MV_H) / (SA_A/SA_H); MV is Minute Volume = inhaled volume × respiratory rate, and SA is surface area for the lung region of concern ($_A$ and $_H$ represent animal and human respectively). Gas with extrathoracic respiratory effects, RGDR = $0.35MV_A$ = 0.38 m^3/day, MV_H = 14.48 m^3/day, SA_A = 15 cm^2, SA_H = 200 cm^2 (OEHHA, 2008).

In the key study (NTP, 2000), rats and mice subjected to a whole-body inhalation exposure of 0, 31.2, 62.5, or 125 ppm for two years displayed nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, and forestomach epithelial hyperplasia and ulcers in both species. This study was chosen because it used a lifetime inhalation exposure, and provided the most sensitive toxicity endpoint not dependent on hemolytic anemia (humans tend to be resistant to EGBE hematological effects).

Exposure doses and related toxicity endpoints are listed in Table 1. Benchmark dose analysis was performed using Benchmark Dose Modeling Software (BMDS) version 2.6 (EPA, 2015). The calculated $BMCL_{05}$ values, and corresponding NOAEL and LOAEL values are listed in Table 2. We are using the $BMCL_{05}$ values as the POD for REL derivation. For each endpoint, the $BMCL_{05}$ is derived from the models that provided the best visual and statistical fit to the data, particularly in the low dose region of the dose-response curve where the $BMCL_{05}$ resides. Following U.S. EPA guidelines, the model with the lowest Akaike Information Criterion (AIC) was chosen in instances where various model fits to the data were similar.

Table 2: $BMCL_{05}$, NOAEL and LOAEL values for nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, and forestomach ulcers in rats and mice, and epithelial hyperplasia in mice exposed to EGBE by inhalation for two years (NTP, 2000)

Endpoints	$BMCL_{05}$	NOAEL	LOAEL
Nasal Olfactory Epithelial Hyaline Degeneration			
Male rats	8.0 (Probit)	31.2	62.5
Female rats	**7.6 (Logistic)**	31.2	62.5
Male and female rats combined	8.2 (Probit)	---------	31.2
Male mice	NA	NE	62.5
Female mice	34.3 (LogLogistic)	NE	62.5
Male and female rats combined	74.2 (LogLogistic)	---------	*62.5*
Liver Kupffer Cell Pigmentation			
Male rats	5.7 (Logistic)	31.2	62.5
Female rats	11.6 (LogLogistic)	31.2	62.5
Male and female rats combined	5.5 (Logistic)	*31.2*	*62.5*
Male mice	97.9 (Dichotomous-Hill)	62.5	125
Female Mice	37.5 (LogProbit)	NE	62.5
Male and female mice combined	49.9 (LogProbit)	---------	*62.5*
Forestomach Epithelial Hyperplasia			
Male Mice	16.2 (Weibull)	NE	62.5
Female Mice	9.7 (LogProbit)	NE	62.5
Male and female mice combined	11.4 (Dichotomous-Hill)	---------	*62.5*
Forestomach Ulcer			
Male mice	64.5 (Dichotomous-Hill)	62.5	125
Female Mice	17.5 (Quantal-linear)	NE	62.5
Male and female rats combined	**26.3 (LogLogistic)**	---------	*62.5*

Note: $BMCL_{05}$ is based on dichotomous models (model shown in parenthesis) with best visual and statistical fit (EPA, 2015); NE, Not established; NA, Not applicable (a poor dose-response curve for BMC determination).

Of the chronic effects noted in rats and mice in Table 2, hyaline degeneration of the olfactory epithelium is more analogous to what would occur with human exposure to EGBE than the other lesions. The primary cause of the nasal lesions is likely to be direct EGBE irritation through the inhalation route (NTP, 2000). We are focusing on the

regional (nose and upper respiratory tract) responses/changes, which is the most sensitive endpoint, and is more consistent with the acute inhalation effect of EGBE in humans (Carpenter et al., 1956).

While the use of nasal hyaline degeneration of the olfactory epithelium in female rats by OEHHA is inconsistent with other expert hazard assessments (EPA, 1999; NTP, 2000; EU, 2006; EPA, 2010), new information undocumented in the reviews by NTP, US EPA, and the EU supports our interpretation that this lesion is indicative of an adverse response to toxicant exposures. This new information suggests that hyaline degeneration, also known as formation of eosinophilic globules (EG), represents stages of cell injury and death related to condensation of cellular constituents, blebbing, auto- and hetero-phagocytosis, and intracellular accumulation of plasma proteins.

Previous research in F-344 rats and B6C3F$_1$ mice by Buckley et al. (1985) showed increased incidence of EG in combination with other adverse pathologies such as destruction of the naso-and maxilloturbinates after exposure to dimethylamine. Monticello et al. (1990) stated that cells with EG often “exhibit massively dilated cisternae of the rough endoplasmic reticulum [ER]”. Similar swelling of the smooth ER in cells of the nasal mucosa was noted by Lewis and colleagues (1994), who observed increased numbers of globules and decreased P-450 enzymes in CDF(F344)/CrlBR rats exposed to cigarette smoke for 32 weeks versus those exposed for 4 weeks. According to Schönthal (2012), lumenal dilation of the ER appears to be a coping mechanism for increased crowding of proteinaceous constituents resulting from accumulation of un- or mis-folded proteins. ER stress can result in either adaptation and neutralization of stress or activation of pro-apoptotic pathways and eventual cell death.

Papadimitriou et al. (2000) stated that the role of the ER in apoptosis is related to proteolysis and solubilization of cytoskeletal proteins, and they observed EG often in or around the ER of dying cells. Their research on 80 tumor cases (24 tumor types) containing EG led them to hypothesize that all EG reflect stages of cell injury related to apoptosis.

Microscopic observations revealed that EG: 1) occurred almost exclusively in areas of apoptosis and sometimes contained pyknotic nuclear fragments; 2) exhibited the same ultrastructural features irrespective of tumor type or location; 3) occurred in cells exhibiting intense blebbing; and 4) stained positively for plasma proteins and occurred in cells with increased membrane permeability. Intracellular globules were linked to dense networks of fibrin fibrils which crossed through the cells and into the extracellular

matrix. Extracellular EG were also shown to be linked to the extracellular matrix by fibrils suggesting a process of remodeling. Given their findings, Papadimitriou et al. (2000) hypothesized that the globules are not specific to any tumor type but represent a degenerative process leading to apoptosis, which is common to all cell types. The authors also recognized that although the concept of apoptosis does not generally allow for outward leakage of intracellular constituents, condensation of the cell with the observed cross-linking of the cytoskeleton maintains internal contents *in situ* preventing the random release of contents that leads to inflammation in necrosis. Influx and accumulation of plasma proteins with anti-protease activity would also inhibit inflammatory responses that can occur with organelle and lysosomal enzyme release. Linking of the intracellular globules to the extracellular matrix allows for their incorporation into the matrix, which accounts for the final disposal of apoptotic cell remnants.

Dikov et al. (2007) studied quantitative and qualitative differences between normal and pathologic gastrointestinal (GI) epithelia from a series of 2,230 biopsies. Eosinophilic globules were rarely found in normal tissues (1.1% incidence). In comparison, EG frequency was higher in tissues with non-ischemic inflammation (gastritis, duodenitis, and colitis; $p = 0.007$), circulatory disorders/ischemic injury (acute edema and congestion, pericarcinomatous mucosa, ischemic colitis; $p < 0.0001$), and ulcerous edges ($p < 0.0001$). Their incidence in benign regenerative cell proliferation lesions (e.g. hyperplastic polyps, or focal foveolar hyperplasia), adenomatous polyps, and adenocarcinomas was also higher than in normal tissues ($p < 0.05$).

Since 1) EG formation is likely related to a continuum of changes known to represent an established adverse effect, and 2) some female rats (n = 3/49) in the 2-year NTP EGBE study (2000), which as a group appear to be more sensitive to EGBE than exposed males of the genus, exhibited increased EG severity at the 125 ppm concentration, OEHHA believes that olfactory hyaline degeneration as hallmarked by EG formation is an appropriate choice as the critical endpoint for REL development.

Although liver Kupffer cell pigmentation in rats would provide a little lower $BMCL_{05}$, this effect is secondary to hemolytic anemia, which is not considered by OEHHA to be relevant for EGBE REL derivation in humans. Regarding the forestomach effects in mice, humans do not have a similar organ, but it is conceivable that EGBE could irritate the lining of the esophagus or stomach in humans. However, this endpoint was not as sensitive as hyaline degeneration of the olfactory epithelium (Table 2), and there is

evidence that humans would not be as sensitive as mice for upper gastrointestinal effects.

Little difference was observed in the incidence of nasal lesions between male and female rats, compared to the gender differences for incidences observed for the other endpoints presented in Table 1. Therefore, combining male and female rats for $BMCL_{05}$ estimation is potentially applicable for the nasal endpoint in Table 2. However, the $BMCL_{05}$ results (7.6 ppm) in female rats were chosen as the POD for REL derivation because the $BMCL_{05}$ was slightly lower with this set of data. Table 3 lists the Benchmark Dose (BMD), BMD 95% lower confidence limit ($BMDL_{05}$), AIC and goodness-of-fit P-values for the several dichotomous models fit to the female rat incidences of nasal olfactory epithelial hyaline degeration. Figure 2 provides a graphic display of the dichotomous logistic model fit to the female rat nasal olfactory epithelium lesion incidence data.

Table 3. BMDS dichotomous models fit to incidence of hyaline degeneration of the olfactory epithelium in female rats after inhalation exposure to EGBE for 2 years (NTP, 2000)

Model Name	BMD	$BMDL_{05}$	Goodness-of-fit p-value	AIC	Scaled residual
Multistage	5.2374	3.9823	0.4685	241.690	0.463
Gamma	15.1739	4.3513	0.9612	242.149	0.008
Logistic	**9.1707**	**7.5634**	**0.9581**	**240.233**	**0.121**
LogLogistic	17.8418	5.8485	0.8758	242.171	0.100
LogProbit	19.8745	7.3567	0.8306	242.192	0.129
Probit	8.9602	7.5020	0.9493	240.251	0.109
Weibull	13.1786	4.3451	0.8851	242.168	0.029
Quantal-Linear	5.2374	3.9822	0.4685	241.690	0.463

Note: Results are from benchmark dose analysis using BMDS version 2.6 (EPA, 2015). We selected the best available model based on a smaller AIC and larger goodness-of-fit P-value among the different models. In this case, the Logistic model (bold) was the most appropriate model. AIC = Akaike Information Criterion. Scaled residual is for the dose group nearest the BMD.

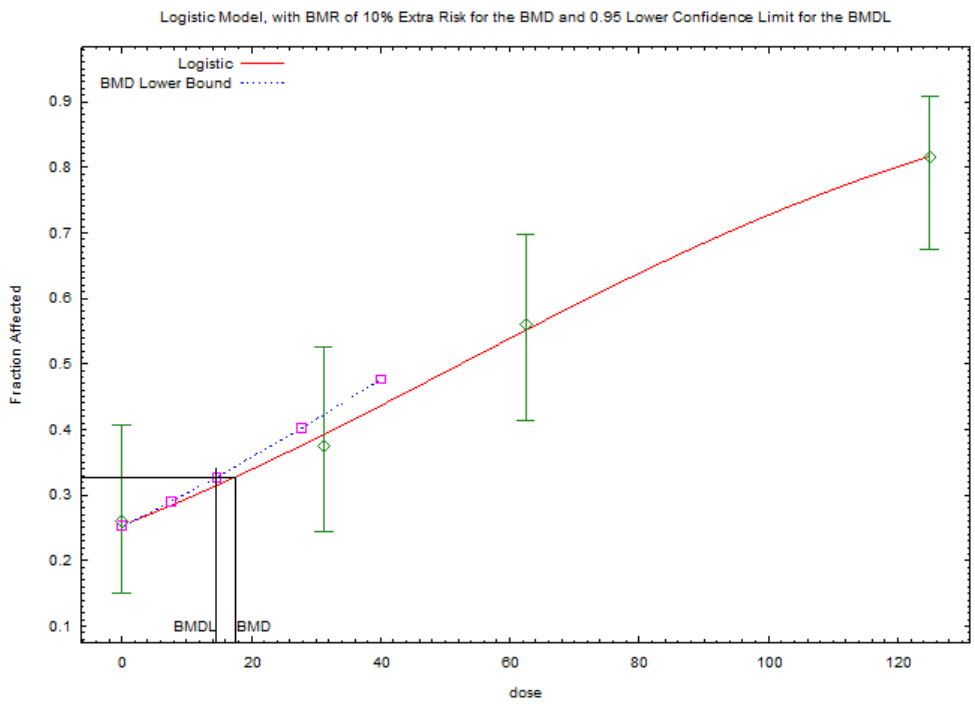


Figure 2. Dichotomous Logistic model fit to nasal olfactory epithelium incidences in female rats after inhalation exposure to EGBE for 2 years (NTP, 2000)

The average experimental exposure was adjusted for 8-hour exposures, seven days/week. The assumption is that the rats show both mixed active and inactive periods during exposure, and a time adjustment is made to simulate an active 8-hour working period during which the off-site worker is exposed. The concentration is first adjusted down to 24-hour continuous exposure (6/24 hours x 5/7 days per week), then multiplied by 2 ($20m^3/10m^3$) to represent an active individual breathing half the air breathed in a day during an active working 8-hour period when exposure occurs, compared to what a resident would breathe over a 24-hour period.

Adjustments for differences in MV and for relative areas of human and rat extrathoracic regions of the respiratory tract resulted in a human equivalent concentration of 0.95 ppm (OEHHA, 2008). We used an interspecies UF = √10. This was composed of a toxicokinetic UF of 1 because we utilized the HEC dosimetric adjustment and the toxicological endpoint is a port of entry effect. We retained a UF of √10 to account for interspecies tissue sensitivity differences. The intraspecies toxicokinetic and toxicodynamic UFs were both assigned √10. No additional adjustment was made for early life exposures, since the effect of concern is at the portal of entry and thus age-

related differences in toxicokinetics do not likely influence response. The cumulative UF was 30 which results in an 8-hour REL of 0.032 ppm (0.15 mg/m^3) and this value is just slightly higher than EGBE's odor threshold (0.10 ppm).

8.3 EGBE Chronic Reference Exposure Level

Study	(NTP, 2000)
Study population	Rats (50 animals/group/gender)
Exposure method	Discontinuous whole-body inhalation exposure of 0, 31.2, 62.5, 125 ppm
Critical effects	Nasal hyaline degeneration of olfactory epithelium
LOAEL	31.2 ppm
NOAEL	Not observed
BMC_{05}	7.6 ppm (Logistic model from female rats)
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	2 years
Time-adjusted exposure	1.357 ppm (7.6 ppm x 6/24 x 5/7)
Human Equivalent Concentration	0.475 ppm (gas with extrathoracic respiratory effects, RGDR = 0.35)
LOAEL uncertainty factor	NA
Subchronic uncertainty factor	1
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1
Toxicodynamic (UF_{A-d})	√10
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	√10
Toxicodynamic (UF_{H-d})	√10
Cumulative uncertainty factor	30
Reference Exposure Level	0.077 mg/m^3 (0.016 ppm)

The chronic REL is based on the same study as the 8-hour REL (NTP, 2000) and uses the same benchmark dose analysis with a POD of 7.6 ppm. In this instance the time adjusted exposure reflects conversion of an intermittent to a continuous exposure. The same uncertainty factors apply to give a cumulative UF of 30 and a chronic REL of 0.016 ppm (0.077 mg/m^3).

NIOSH based an 8-hour TWA Recommended Exposure Limit of 5 ppm (24 mg/m^3) on tissue irritation, CNS depression, and adverse effects on the blood and hematopoietic systems. Both the Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH) have a TWA of 25 ppm (120 mg/m^3), based on the risk of hematologic and other systemic effects associated with exposure to EGBE. These values were established more than 20 years ago (NIOSH, 1992).

9. Evidence for Differential Sensitivity of Children

No human inhalation studies were found that addressed differential sensitivity of children relative to adult exposed to EGBE, in terms of eye and upper respiratory irritation. In experimental animals, no evidence was found for differential sensitivity in developmental studies, as both maternal toxicity and fetotoxicity occurred at similar exposure concentrations. Regarding the hemolytic action of EGBE, an animal oral gavage study found that adult (9-13 weeks) male rats were significantly more sensitive to the hemolytic effects of EGBE than young (4-5 weeks) male rats (Ghanayem et al., 1987). In humans, *in vitro* studies in erythrocytes from children and healthy adults showed no difference in their resistance to the hemolytic effects of BAA (Udden, 1994; Udden, 2002). Due to the sensory irritant action of EGBE exposure, asthmatics including children may be more sensitive to EGBE exposure compared to the general population. However, there is currently insufficient evidence to consider EGBE a chemical for which children are more sensitive compared to the general population.

Several epidemiological studies indicated that indoor factors might cause asthma in childhood. The most consistent finding for an induction of asthma in childhood is related to exposure to environmental tobacco smoke, to living in homes close to busy roads, and in damp homes with visible molds. However, more research is needed to clarify the potential risk for exposure to volatile and semi-volatile organics due to renovation activities or cleaning (Heinrich, 2011). Further study is needed to identify whether EGBE contributes to increased childhood asthma in the home environment.

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