

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
November 2016



Air, Community, and Environmental Research Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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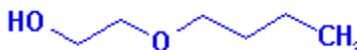
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Ethylene Glycol mono-n-Butyl Ether

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

CAS No. 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. The critical effects of EGBE in humans resulting from short- to long-term airborne 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 neurologic effects, but generally cause only minor to moderate hemolytic effects. Literature summarized and referenced in this document covers the relevant published literature for EGBE through Spring 2016.

38	1.1 EGBE Acute REL	
	<i>Reference exposure level</i>	4700 µg/m ³ (1000 parts per billion (ppb))
	<i>Critical effect(s)</i>	Ocular and nasal irritation (sensory irritation)
	<i>Hazard index target(s)</i>	Eyes and respiratory system
39		
40	1.2 EGBE 8-Hour REL	
	<i>Reference exposure level</i>	164 µg/m ³ (34 ppb)
	<i>Critical effect(s)</i>	Nasal hyaline degeneration of olfactory epithelium
	<i>Hazard index target(s)</i>	Respiratory system
41		
42	1.3 EGBE Chronic REL	
	<i>Reference exposure level</i>	82 µg/m ³ (17 ppb)
	<i>Critical effect(s)</i>	Nasal hyaline degeneration of olfactory epithelium
	<i>Hazard index target(s)</i>	Respiratory system
43		
44		

45 **List of Acronyms**

46

ADH	Alcohol Dehydrogenase	MCH	Mean Corpuscular Hemoglobin
AIC	Akaike Information Criterion	ME	2-methoxyethanol
AIDS	Acquired Immune Deficiency Syndrome	MV	Minute Volume
ALDH	Aldehyde Dehydrogenase	MV _A	Minute Volume for Animal
ARB	Air Resources Board	MV _H	Minute Volume for Human NOAEL
BAA	2-butoxyacetic Acid		No Observed Adverse Effect Level
BAL	Butoxyacetaldehyde	NTP	National Toxicology Program
BCH	Basal Cell Hyperplasia	NIOSH	National Institute for Occupational Safety and Health
2-BE	2-butoxyethanol	OECD	Organisation for Economic Co-operation and Development
BEG	Glucuronide conjugate of EGBE	OEHHA	Office of Environmental Health Hazard Assessment
BES	Sulfate conjugate of EGBE	PBPK	Physiologically Based Pharmacokinetic
BMCL ₀₅	the 95% lower confidence interval at the 5% response rate	PM	Particulate Matter
BMD	Benchmark Dose	POD	Point of Departure
BMDL ₀₅	BMD 95% lower confidence limit	ppb	Parts per billion
BMDS	Benchmark Dose Modelling Software	ppm	Parts per million
BPH	Benign Prostatic Hyperplasia	RBC	Red Blood Cell
BW	Bodyweight	RD50	Dose resulting in a 50% depression of respiratory rate
CE	Carboxylesterase	REL	Reference Exposure Level
CI	Confidence Interval	RGDR	Regional Gas Dose Ratio
CNS	Central Nervous System	RH	Relative Humidity
CTI	California Toxics Inventory	SA	Surface Area
CV	Coefficient of variation	SA _A	Surface Area for Animal
EE	2-ethoxyethanol	SA _H	Surface Area for Human
EG	Eosinophilic Globules	TOG	Total Organic Gas
EGBE	Ethylene Glycol mono-n-Butyl Ether	TSD	Technical Support Document
ER	Endoplasmic Reticulum	TWA	Time-weighted Average
EU	European Union	UF	Uncertainty factor
FLEC	Field and Laboratory Emission Cell	UF _{A-d}	Toxicodynamic portion of the interspecies uncertainty factor
GC-MS	Gas chromatography and mass spectrometry	UF _{A-k}	Toxicokinetic portion of the interspecies uncertainty factor
GD	Gestational Day	UF _{H-d}	Toxicodynamic portion of the intraspecies uncertainty factor
GSD	Geometric Standard Deviation	UF _{H-k}	Toxicokinetic portion of the intraspecies uncertainty factor
HEC	Human Equivalent Concentration	UF _L	LOAEL uncertainty factor
Hct	Hematocrit	VOC	Volatile Organic Compound
Hgb	Hemoglobin	US EPA	United States Environmental Protection Agency
Ig	Immunoglobulin		
IP	Intraperitoneal		
IV	Intravenous		
LC50	Lethal concentration required to kill 50% of the population		
LOAEL	Lowest Observed Adverse Effect Level		

47

48

49 **2. Physical & Chemical Properties (HSDB, 2005)**

<i>Description</i>	Colorless liquid
<i>Molecular formula</i>	C ₄ H ₉ -O-CH ₂ CH ₂ -OH (C ₆ H ₁₄ O ₂)
<i>Molecular weight</i>	118.2 g/mol
<i>Density</i>	0.90 g/cm ³ @ 20 °C
<i>Boiling point</i>	171 °C
<i>Melting point</i>	-70 °C
<i>Vapor pressure</i>	0.88 mm Hg @ 25°C
<i>Saturated Vapor Pressure</i>	5600 mg/m ³ (1,160 ppm) at room temp (Corley, 1996)
<i>Odor threshold in air</i>	0.48 mg/m ³ (0.10 ppm,; geometric mean) (AIHA, 1989) Sweet, ester-like, musty
<i>Water Solubility</i>	Miscible, but soluble in most organic solvents
<i>Log K_{ow}</i>	0.81
<i>Henry's law constant</i>	2.08 × 10 ⁻⁷ – 10 ⁻⁸ atm·m ³ /mole @ 25°C
<i>Flash point</i>	62°C (closed cup); 70°C (open cup)
<i>Conversion factor</i>	1 mg/m ³ = 0.207 ppm; 1 ppm = 4.83 mg/m ³ (at 298.26 K and 1 atm))

50

51 **3. Production, Major Uses, and Occurrence**

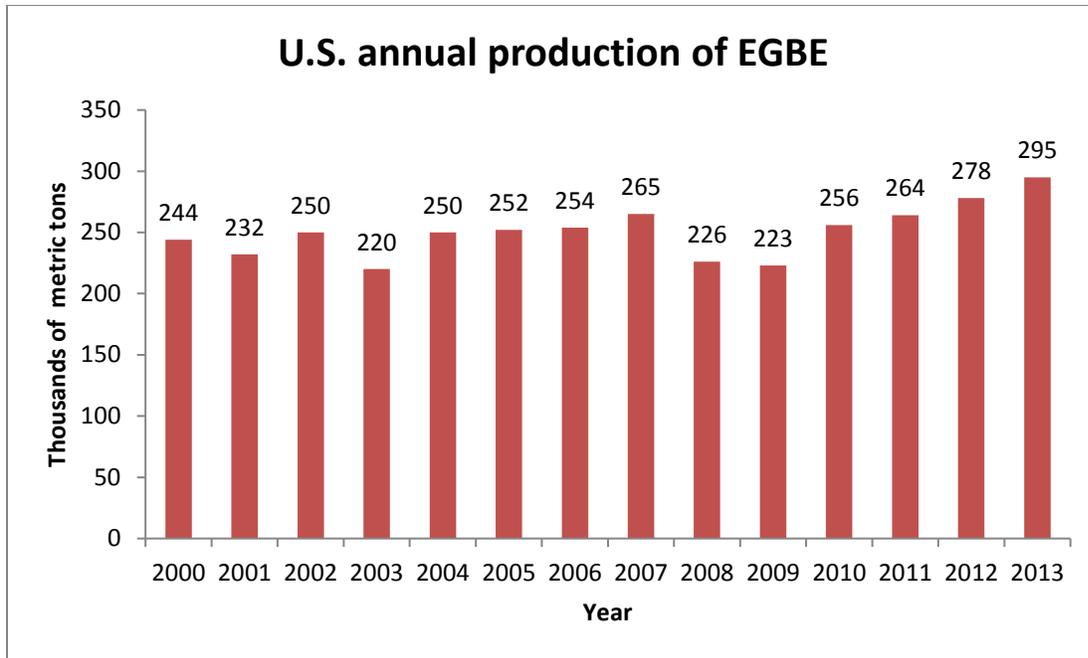
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53 **3.1 Production and Use**

54

55 Ethylene glycol mono-butyl ether (EGBE) is a solvent with the characteristics of both
56 alcohol and ether. As such, it is used for many applications, including as a coupling
57 agent to stabilize immiscible ingredients. Consequently, EGBE is a high production
58 volume chemical with estimated production at 295,000 tons in the United States in 2013
59 (Chinn *et al.*, 2014) (Figure 1), 161,000 tons in the European Union (EU) in 2003
60 (SCCP, 2007; SCHER, 2008; OECD, 2012), and up to 500,000 tons per year worldwide
61 in 2000. In the US, specifically, production of EGBE from 2013 to 2018 is expected to
62 increase at an average annual rate of 0.7% (Chinn *et al.*, 2014). For worldwide EGBE
63 production estimates, 60 - 75% is for paints and coatings (Rebsdatt and Mayer, 2001;
64 SCCP, 2007) and 18% is for metal cleaners and household cleaners (NLM, 2014). Of
65 this 18%, approximately 11% is used in detergents and cleaners, and about 0.5% is
66 used in cosmetics and personal care products (SCCP, 2007).

67



68
 69 **Figure 1.** US production of EGBE from 2000 to 2013 in thousands of metric tons
 70 (Chinn *et al.*, 2014).

71
 72 **3.2 Outdoor Emissions**

73
 74 The California Toxics Inventory (CTI) provides emissions estimates by stationary (point
 75 and aggregated point), area-wide, on-road mobile (gasoline and diesel), off-road mobile
 76 (gasoline, diesel, and other), and natural sources. The CTI estimates total organic gas
 77 (TOG) and particulate matter (PM) for area, mobile, and natural sources. Speciated
 78 emissions for each source category are then reconciled with reported stationary point
 79 source toxics data to establish a complete inventory. Stationary sources include point
 80 source emissions estimates provided by facility operators and/or districts pursuant to
 81 the Air Toxics “Hot Spots” Program ([AB 2588](#)), and aggregated point sources estimated
 82 by the Air Resources Board (ARB) and/or districts. Area-wide sources do not have
 83 specific locations but are spread out over large areas such as emissions from consumer
 84 products and unpaved roads. Mobile sources consist of both on-road and off-road
 85 transportation sources. Natural sources such as wildfires are also included. Estimated
 86 annual EGBE emissions in California increased from 3,881 tons in 2006 to 4,363 tons in
 87 2010 (Figure 2) (CARB, 2013).

88

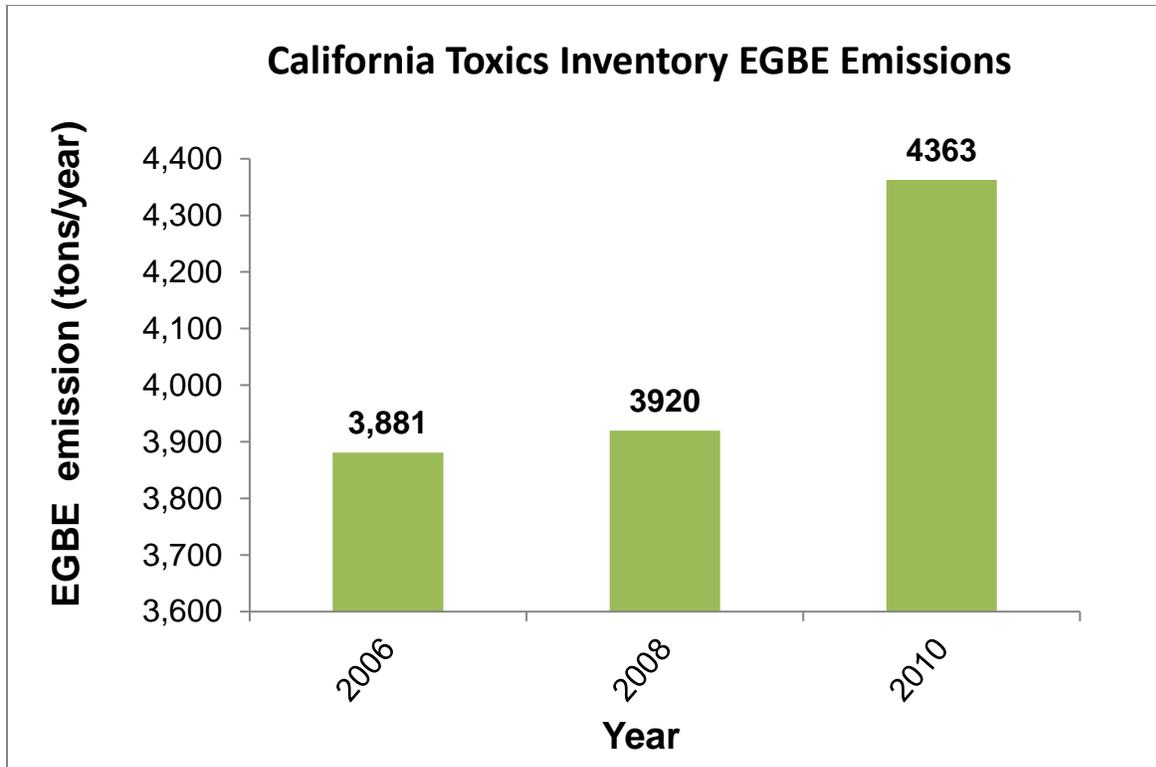


Figure 2. California Toxics Inventory EGBE emissions (tons/year)
 Source: (CARB, 2013).

3.3 Occurrence in Consumer Products and Modeled Indoor Exposures

Consumer products and building materials that may contain EGBE include liquid wax and wax strippers, varnish removers and lacquers, surface cleaners and coatings, caulking products and sealants, water-based paints, resilient floorings, nail enamel removers, and permanent hair colorants (Andersen, 1996; Fang *et al.*, 1999; Zhu *et al.*, 2001; IWMB, 2003; HSDB, 2005). Investigation of 1,242 industrial and commercial cleaning agent formulas by the National Research and Safety Institute for Occupational Accidents Prevention in France, showed that 10% of the products contained between 0.2 and 80% EGBE by volume (Vincent *et al.*, 1993). Approximately 50% of the formulas for window cleaning agents, specifically, contained between 1 and 30% EGBE by volume.

Analysis of 13 glycol ether-containing consumer products purchased from local stores in Canada revealed similar results (Zhu *et al.*, 2001). Gas chromatography and mass spectrometry (GC-MS) performed on headspace samples of the purchased products showed that seven of the 13 products contained detectable levels of volatile EGBE. Five of the seven products with detectable levels of EGBE were house-cleaning agents. The concentration of EGBE ranged from 7.9 to 90.7%, when calculated as the percentage of

112 the area of the individual peak in the total ion chromatogram for all VOCs in the
 113 headspace (Table 1).

114
 115 **Table 1. Description of consumer products containing volatilized EGBE in**
 116 **headspace samples.**

Product ID #	Product Type	EGBE Concentration in Headspace (% of total VOCs) ^a
1	All-purpose cleaner	90.70
2	Glass and surface cleaner (clear)	75.40
3	Glass and surface cleaner (blue)	13.00
4	Antibacterial glass and surface cleaner	9.20
5	Lemon-fresh antibacterial spray	7.90
6	Nail enamel remover	60.30
7	Permanent hair colorant	62.80

117 Table adapted from Zhu *et al.* (2001).

118 ^aThe value is the percentage of area of the individual peak in the total ion chromatogram.

119
 120 Subsequent GC-MS quantification of EGBE from the liquid fraction of the products
 121 showed that the EGBE concentrations ranged from 0.5 to 3.72% (Table 2). Field and
 122 laboratory emission cell (FLEC) testing data revealed emission rates from 145 to 938
 123 mg/m²/hour.

124
 125

126 **Table 2. Concentrations, masses, and emission rates of EGBE in house-cleaning**
 127 **products.**

Product ID #	EGBE Concentration (%) in Product ^a	Starting Product Mass (g) ^b	Ending Product Mass (g) ^b	Mean Emission Rate (mg/m ² /h) ^c	Emission Rate C.V. (%) ^c
1	3.72	6.06	0.21	938	12
1 ^d	0.744 ^e	6.10	0.05	176	14
2	0.87	5.76	0.01	223	13
3	0.50	6.03	0.03	145	14
4	0.83	6.06	0.03	169	11
5	1.280	6.20	0.11	426	12

128 Table adapted from Zhu *et al.* (2001).

129 Legend: Product numbers 1, 2, 3, 4, and 5 correspond to all-purpose cleaner, glass and surface cleaner
 130 (clear), glass and surface cleaner (blue), antibacterial glass and surface cleaner, and lemon-fresh
 131 antibacterial spray, respectively. C.V. – coefficient of variation.

132 ^a Values measured by gas chromatography and mass spectrometry unless otherwise indicated.

133 ^b Values measured at the start or end of field and laboratory emission cell testing as indicated.

134 ^c Values calculated using measured parameters.

135 ^d Product 1 diluted 5 times with water.

136 ^e Concentration = 3.72/5.

137
 138 EGBE air concentrations and inhalation exposures associated with cleaning activities
 139 using all-purpose and spray glass cleaners (Products 1, 2, 3, and 5) were estimated
 140 from these data. Air concentrations ranged from 2.8 to 62 mg/m³ (0.6 to 13 ppm), based
 141 on standard product use and standard room size (volume = 17.4 m³; air exchange rate
 142 = 0.5 air changes/hour). Exposures were conservatively estimated to range from 0.004
 143 to 0.211 mg/kg bodyweight (BW)/day (Table 3).

144

145 **Table 3. Estimated inhalation exposure to EGBE during cleaning activities using**
 146 **defined room conditions and product-use scenarios.**

Product ID #	Amount Applied per Surface Area ^a (mg/m ²)	Air Concentration ^b (mg/m ³)	Task ^c #	Daily Average Exposure by Task ^d (mg/kg BW/day)	Daily Average Exposure by Product ^e (mg/kg BW/day)
1	16,889	62	1	0.032	0.186 (0.211)
			2	0.063	
			3	0.043	
			4	0.048	
2	7,391	4.7	5	0.002	0.006 (0.008)
			6	0.004	
3	7,391	2.8	5	0.001	0.004 (0.004)
			6	0.003	
5	16,889	25	1	0.013	0.075 (0.084)
			2	0.025	
			3	0.017	
			4	0.019	

147 Table adapted from Zhu *et al.* (2001).

148 Legend: ^aFor Products #1 and #5 (all-purpose spray cleaners), the authors assumed a mass of 76,000
 149 mg product was applied to a surface area of 4.5 m² for each noted task (76,000 mg ÷ 4.5 m² ≈ 16,889
 150 mg/m²). For Products #2 and #3 (spray glass cleaners), it was assumed that a product mass of 17,000
 151 mg was applied to a surface area of 2.3 m² for each noted task (17,000 mg ÷ 2.3 m² ≈ 7,391 mg/m²).

152 ^bValues are 1-hour average EGBE concentrations in a “standard room” with a volume of 17.4 m³ and an
 153 air exchange rate of 0.5 air changes/hr.

154 ^cTask 1: Clean outside of cabinets; Task 2: clean counters; Task 3: clean bathroom or other tiled or
 155 ceramic walls; Task 4: clean outside of refrigerator and other appliances; Task 5: clean inside of windows;
 156 Task 6: clean other glass surfaces such as mirrors and tables.

157 ^dAssuming an inhalation rate of 1.3 m³/hr.

158 ^eAssuming an inhalation rate of 1.3 m³/hr. The values in parentheses are intake when the more
 159 conservative value of 0.18 air changes/hr air change rate in the “standard room” was assumed.

160
 161 Air concentration estimates from Zhu *et al.* (2001) overlapped with those from Singer *et al.*
 162 *et al.* (2006). To quantify emissions and concentrations of glycol ethers from cleaning
 163 products containing EGBE, experiments were conducted by Singer *et al.* (2006) in a 50-
 164 m³ chamber (ventilated at approximately 0.5 air changes/hr) designed to simulate a
 165 typical residential environment. Four cleaning products containing EGBE were applied
 166 full-strength (mass concentrations of 6 - 62 mg/ml) in countertop cleaning activities,
 167 while two of these products were diluted (53-153 g product diluted in 1 gal H₂O) for floor
 168 mopping activities. Countertop cleaning activities resulted in EGBE air concentrations in
 169 the first hour in the range of 0.27 to 2.3 mg/m³ (0.056 to 0.48 ppm). For floor mopping
 170 activities, EGBE air concentrations in the first hour were in the range of 0.38 to 1.3
 171 mg/m³ (0.079 to 0.27 ppm). During full-strength application including rinsing with a

172 sponge and wiping with towels, fractional emissions (mass volatilized/dispensed) of
173 EGBE were 50–100% with towels retained, and approximately 25–50% when towels
174 were removed after cleaning.

175

176 **3.4 Measured Indoor Concentrations of EGBE in Business and Residential** 177 **Settings**

178

179 Indoor air quality studies have measured numerous volatile organic compounds (VOCs)
180 that humans are exposed to, often as a result of complaints of poor indoor air quality
181 (Mendell, 1991; Daisey *et al.*, 1994; Nazaroff and Weschler, 2004). EGBE is often one
182 of the VOCs that is investigated in these indoor air quality studies due to its frequent
183 occurrence in cleaning products. Cleaning products that contain EGBE include all-
184 purpose cleaners, lemon-fresh antibacterial spray, and liquid wax (Knoppel and
185 Schauenburg, 1989; Zhu *et al.*, 2001). Use of cleaning products containing EGBE in
186 office buildings has linked the chemical as the cause of sensory irritation and
187 headaches in office workers (Rella *et al.*, 2012).

188

189 In a workplace air quality study of VOCs present in indoor air, an EGBE concentration
190 (geometric mean \pm geometric standard deviation (GSD)) of $0.0077 \pm 0.018 \text{ mg/m}^3$
191 ($0.0016 \pm 0.0037 \text{ ppm}$) was recorded in 12 northern California office buildings (Daisey
192 *et al.*, 1994). The concentration range for EGBE was $< 0.0019 - 0.13 \text{ mg/m}^3$ ($0.0004 -$
193 0.027 ppm). VOC concentrations were also collected outside the buildings and used in
194 indoor/outdoor ratios (I/O) for each VOC. For individual VOCs, the authors identified an
195 I/O ratio > 1.35 as predominantly from indoor sources, and an I/O ratio < 1.35 as
196 predominantly from outdoor sources. The I/O range for EGBE was $0.18 - 21$, which
197 suggested both indoor and outdoor sources of EGBE were present.

198

199 In a study of indoor air quality in buildings throughout the US, eight of 11 densely-
200 occupied administrative offices ($3-5 \text{ occupants}/1000 \text{ ft}^2$) emitted measurable levels of
201 EGBE (Shields *et al.*, 1996). The geometric mean \pm GSD EGBE concentration was
202 $0.001 \pm 0.0032 \text{ mg/m}^3$ ($0.0002 \pm 0.00067 \text{ ppm}$) with a maximum value of 0.032 mg/m^3
203 (0.0066 ppm). A much lower EGBE detection rate of 16 out of 59 was observed in 50
204 telecommunication offices and nine data centers, which was attributed to lower
205 occupancy density ($< 0.4 \text{ occupants}/1000 \text{ ft}^2$ for telco offices; $1-4 \text{ occupants}/1000 \text{ ft}^2$ for
206 data centers). The geometric means \pm GSD concentrations in telecommunication offices
207 and data centers were $0.0001 \pm 0.0007 \text{ mg/m}^3$ and $0.0002 \pm 0.0003 \text{ mg/m}^3$ ($0.00002 \pm$
208 0.00014 ppm and $0.00004 \pm 0.000068 \text{ ppm}$), respectively. Maximum values of 0.033
209 mg/m^3 (0.0068 ppm) and 0.016 mg/m^3 (0.0033 ppm) were recorded for
210 telecommunication offices and data centers, respectively. Suggested indoor sources of
211 EGBE were floor cleaners, wax strippers, varnish removers, and lacquers. Although

212 outdoor levels of all VOCs were also investigated near the buildings, no detectable
213 outdoor levels of EGBE were found.

214
215 In contrast to the large office and commercial buildings investigated by other
216 researchers, Wu *et al.* (2011) investigated the indoor air quality of 40 small- and
217 medium-sized commercial buildings in California. Small- (1,000 – 12,000 ft²) and
218 medium-sized (12,000 – 25,000 ft²) commercial buildings were defined as any low-rise
219 building (less than four stories) with roof-top heating, ventilation, and air-conditioning
220 units. EGBE was detected in 39 of the 40 buildings, with a geometric mean
221 concentration of 0.00421 mg/m³ (0.00087 ppm) and a range of 0.00002 to 0.356 mg/m³
222 (0.0000041 to 0.074 ppm) (Wu *et al.*, 2011). Dental offices/health care facilities (n=4
223 total) had the highest mean levels among the different types of small- to medium-sized
224 buildings examined, with a geometric mean \pm GSD of 0.0186 \pm 0.0105 mg/m³
225 (0.00385 \pm 0.00217 ppm) and a range of 0.0023 to 0.305 mg/m³ (0.00048 to 0.063
226 ppm).

227
228 EGBE is also a common component of VOCs in some newly constructed homes. For
229 example, Brown (2002) collected one or two indoor air samples each from the bedroom
230 and living room in a new home on days 2, 19, 72, and 246 post-construction to measure
231 levels of a number of VOCs, including EGBE. The EGBE concentration in the samples
232 collected during post-construction days 2 and 19 ranged from 0.081 to 0.011 mg/m³
233 (0.017 to 0.0023 ppm). On post-construction days 72 and 246, EGBE concentrations in
234 the samples collected were generally lower, ranging from 0.046 to 0.004 mg/m³ (0.0095
235 to 0.00083 ppm). EGBE in indoor air was thought to originate from water-based paints
236 or adhesives (Brown, 2002).

237
238 Finally, personal breathing zone monitoring by Vincent *et al.* (1993) observed
239 concentrations in the range of < 0.483 to 35.0 mg/m³ (0.10 to 7.25 ppm) (arithmetic
240 mean \pm SD: 11.25 \pm 11.79 mg/m³ (2.33 \pm 2.44 ppm) EGBE following daily use of EGBE-
241 containing surface cleaners by workers to clean cars.

242 **4. Toxicokinetics**

243 **4.1 Toxicokinetic Studies in Humans**

244
245 EGBE is well-absorbed and rapidly distributed in humans following inhalation, ingestion,
246 or dermal exposure. Inhalation studies in human volunteers found the respiratory uptake
247 of EGBE for two hours under light physical exercise (50 watts) averaged 57% of the
248 inspired amount and was fairly constant during the exposure period (Johanson *et al.*,
249 1986a). In four healthy male subjects who inhaled 121 mg/m³ (25 ppm) EGBE via a
250 mouthpiece at rest, the mean EGBE uptake was 80% in the last 5 minutes of the 10

251 minute respiration period (Kumagai *et al.*, 1999). The percentage of EGBE in the end-
252 exhaled air had reached a quasi-steady-state level within the first few minutes of
253 exposure.

254

255 Dermal studies in humans observed that airborne EGBE is also absorbed through the
256 skin. However, respiratory uptake has been shown to be quantitatively more important
257 than dermal uptake (Corley *et al.*, 1994; Corley *et al.*, 1997). Using a physiologically-
258 based pharmacokinetic (PBPK) model of a whole-body human exposure scenario,
259 Corley *et al.* (1994) calculated EGBE absorption through the skin (skin permeability
260 coefficient of 3 cm/hr) at about 21% of the total EGBE uptake.

261

262 The same investigators (Corley *et al.*, 1997) conducted a study in humans in which one
263 arm of each subject was exposed to 242 mg/m³ (50 ppm) ¹³C₂-EGBE for 2 hours. Blood
264 samples were collected from each subject by the finger-prick method from the exposed
265 arm and by intravenous (IV) catheter from the antecubital fossa of the non-exposed
266 arm. The concentrations of EGBE were nearly 1,500-fold higher in blood drawn from the
267 exposed arms than from the non-exposed arms. The authors concluded that the finger-
268 prick sampling technique overestimates systemic absorption of EGBE via the dermal
269 route. Using the finger-prick sampling technique, Johanson and Boman (1991) had
270 calculated a dermal EGBE uptake rate that was 2-3-fold higher than the inhalation
271 uptake rate, suggesting dermal uptake of EGBE accounted for 75% of the total EGBE
272 uptake from whole body exposure. Corley *et al.* (1997) concluded that even in a “worst-
273 case” scenario, in which respiratory rates are lowest, no clothing is worn (100% of the
274 body surface area is exposed), and temperatures and humidities are normal to
275 elevated, dermal uptake of EGBE vapor should account for a maximum of only 15 -
276 27% of the total (inhalation + skin) uptake.

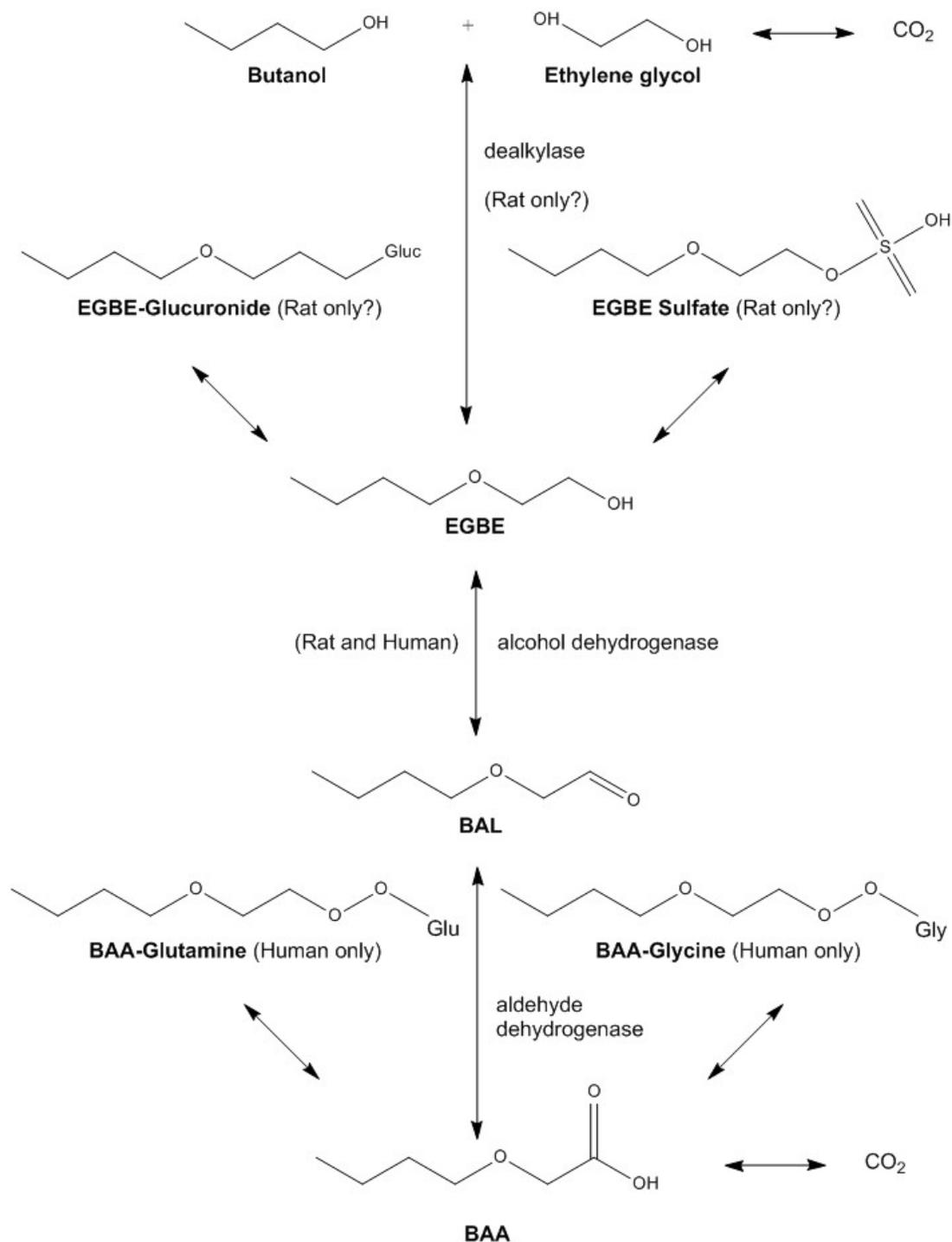
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278 Jones and Cocker (2003) and Jones *et al.* (2003b) found a slightly lower uptake than
279 Corley *et al.* (1997) under normal conditions of 25°C and 40% relative humidity (RH),
280 reporting approximately 11-12% dermal absorption after whole-body exposures of four
281 human volunteers to 242 mg/m³ (50 ppm) EGBE for two hours. Increasing the
282 temperature to 30°C or increasing RH to 65% resulted in little change in dermal
283 absorption compared to normal conditions (Jones *et al.*, 2003). Additionally, wearing
284 minimal clothing versus overalls under normal conditions did not affect the dermal
285 absorption rate. However, the combination of high temperature (33°C) and high RH
286 (71%) and wearing overalls increased the proportion of EGBE dermally absorbed to 37-
287 42%.

288

289 With respect to metabolism, EGBE is a substrate for alcohol dehydrogenase (ADH),
290 which catalyzes the conversion of the terminal alcohol to butoxyacetaldehyde (BAL) in

291 humans and rodent models. Aldehyde dehydrogenase (ALDH) then rapidly converts
292 BAL to 2-butoxyacetic acid (BAA), the predominant urinary metabolite responsible for
293 red blood cell hemolysis in rodents (Ghanayem *et al.*, 1987b; Medinsky *et al.*, 1990;
294 Corley *et al.*, 1997) (Figure 2). The metabolic conversion of EGBE to BAA is a saturable
295 process demonstrating Michaelis–Menten kinetics (Gualtieri *et al.*, 2003). Prolonged
296 EGBE elimination observed in overdose situations has been attributed to the saturable
297 metabolic pathways. Although elimination kinetics of EGBE (and BAA) have been
298 reported as independent of the route of exposure (Corley *et al.*, 1997), kinetics may vary
299 in repeated inhalation exposure scenarios, due to species, sex, age, time of exposure,
300 and/or exposure concentration (EPA, 2010).
301



302
 303 **Figure 3. EGBE Metabolism in Rats and Humans. Adapted from Medinsky *et al.***
 304 **(1990) and Corley *et al.* (1997).**
 305

306 PBPK modeling in workers continually exposed to EGBE suggests that its elimination
 307 from the most poorly perfused organs is rapid, and EGBE does not appear to
 308 accumulate in the body (Johanson, 1986). However, Sakai *et al.* (1994) found small

309 amounts of conjugated BAA in the urine of EGBE-exposed workers in the morning after
310 a work shift, indicating slight accumulation or relatively slower elimination of the EGBE
311 metabolites in the body.

312
313 In seven male human volunteers exposed to EGBE 97 mg/m³ (20 ppm) for two hours
314 under light physical exercise (50 watts), EGBE was removed from the blood with an
315 average elimination half-life of approximately 40 minutes (Johanson *et al.*, 1986a).
316 EGBE could no longer be detected in their blood 2-4 hours after the end of exposure.
317 The major metabolite, BAA, was rapidly excreted in urine of human volunteers with a
318 half-life of approximately 3-6 hours. Although not specifically described by the authors,
319 the urinary BAA half-life was likely estimated based on quantitation of BAA in urine
320 collected immediately after EGBE exposure, and from sampling at 2 hour intervals for 6
321 hours. Urinary excretion of EGBE was low (<0.03%) and difficult to quantify. The
322 absorbed dose of EGBE eliminated as BAA was lower than expected, suggesting to the
323 authors the formation of other metabolites. Following acid hydrolysis of urine samples,
324 the amount of total uptake excreted as BAA in urine was 17 to 55%. However, the
325 concentration of BAA in urine varied more than 10-fold among the subjects.

326
327 In six workers exposed to EGBE, Sakai *et al.* (1994) determined free and total BAA
328 before (free BAA) and after (total BAA) acid hydrolysis of urine samples. The
329 percentages of conjugated BAA vs. total BAA varied from 44.4% to 92.2%, with a mean
330 of 71.1%. The concentration of total BAA in urine was linearly correlated with the worker
331 air exposure levels of EGBE, thought to be due to use of gloves that prevented dermal
332 absorption of EGBE.

333
334 Based on the Johanson *et al.* (1986a) findings, Rettenmeier *et al.* (1993) collected end
335 of work-shift urine samples from six lacquerers to quantify levels of free BAA and its
336 suspected conjugate, BAA-glutamine. EGBE was a key constituent in the lacquers used
337 by the workers. Using high-performance liquid chromatography for analysis, a
338 considerable fraction of total BAA, ranging from 16 to 64% (mean value 48%), was
339 excreted in the form of BAA-glutamine. Only trace levels of these metabolites were
340 found in pre-shift urine samples of the workers. In addition to BAA-glutamine, it has
341 been suggested that a small percentage of the amino acid conjugate (<10%) excreted in
342 urine may be in the form of BAA-glycine (Corley *et al.*, 1997).

343
344 The elimination of BAA, largely in the form of the glutamine conjugate, was confirmed in
345 a dermal exposure study. Corley *et al.* (1997) exposed an arm of volunteers to 242
346 mg/m³ (50 ppm) ¹³C₂-EGBE vapor for two hours to study the elimination kinetics of
347 EGBE. Consistent with previous studies, metabolism and elimination of EGBE and BAA
348 were independent of exposure route. Dermally-absorbed EGBE was primarily

349 eliminated as the BAA metabolite in the urine during the first 12-hour collection interval.
350 About 67% of the total BAA excreted in the urine was in the form of the acid-labile
351 glutamine conjugate. The remainder of the total BAA eliminated was free BAA. Unlike
352 rodent species, no conjugates of ethylene glycol (free or acid-labile) or glycolic acid
353 were detected in the urine.

354
355 EGBE itself has been deemed a sub-optimal marker of EGBE exposure due to its rapid
356 metabolism and removal from venous blood (Corley *et al.*, 1997). Use of EGBE as a
357 marker of EGBE exposure is particularly problematic in cases when a study employs 1)
358 dermal exposures, which could create high local EGBE blood concentrations in exposed
359 areas of the body (Corley *et al.*, 1997); or 2) measures of EGBE in breath, which may
360 suffer from poor detection sensitivity (Jones and Cocker, 2003).

361
362 The metabolite BAA may be a practical marker for EGBE exposure. The study by Sakai
363 *et al.* (1994) was the first to demonstrate a significant linear relationship between
364 occupational EGBE exposure levels and conjugated or total BAA (including free BAA
365 and conjugated BAA metabolites after acid hydrolysis) concentrations in urine. For
366 example, based on time-weighted average (TWA) EGBE vapor concentrations in the
367 breathing zone of six workers exposed to EGBE and their subsequent total BAA levels
368 in urine, a total BAA concentration of 6 mg/g creatinine roughly translated to an EGBE
369 air concentration of 1.9 mg/m³ (0.4 ppm). A poorer correlation was found for EGBE
370 exposure and the urinary concentration of free BAA. In this study, direct skin contact
371 with liquid EGBE was considered minimal due to use of gloves by the workers.

372
373 Accordingly, Jones and Cocker (2003) proposed that total urine BAA be used as the
374 biomarker of choice for monitoring EGBE exposure due to high variability of BAA
375 conjugate among workers. Their research with urine from 48 occupationally-exposed
376 workers and four chamber-exposed volunteers showed that 1) the extent of BAA
377 conjugation in urine post EGBE exposure varied from 0 – 100% within and between
378 individuals; 2) this variability was not related to time of day, urinary BAA concentration,
379 or urinary pH; and 3) similar to the finding of Sakai *et al.* (1994), use of total BAA in
380 urine as a biomarker of EGBE exposure decreased this inter-individual variability.

381
382 Emissions of EGBE from facilities that may impact surrounding communities will likely
383 be in the gaseous or aerosol form resulting in the inhalation route as the primary route
384 of exposure. Unlike occupational exposure situations, dermal contact with liquid EGBE
385 is not expected to occur in exposure scenarios involving releases from industrial
386 facilities. Nevertheless, exposure to liquid EGBE from consumer products may occur
387 concurrently with airborne exposure from a facility source, resulting in cumulative
388 exposure to EGBE via multiple exposure sources and routes. Therefore, additional

389 information on dermal absorption of EGBE in aqueous solution is included below for
390 reference.

391
392 Unlike the occupational study by Sakai *et al.* (1994), poor correlations were found
393 between airborne EGBE levels and urinary BAA excretion in other occupational studies
394 due to significant skin contact with aqueous EGBE solutions. For example, Hung *et al.*
395 (2011) investigated EGBE inhalation and dermal exposure of 80 workers. The workers
396 were divided into three groups based on EGBE exposure: decal transfer workers (high
397 exposure, n=31), self-adhesive decal workers (moderate exposure, n=25) and assembly
398 workers (little or no exposure, n=24). Personal air sampling (8-hour TWA) was
399 performed to determine EGBE air exposure, and pre- and post-shift urine samples were
400 collected for determination of total BAA. Results showed that the decal transfer workers
401 whose hands were in direct contact with a dilute aqueous EGBE solution were exposed
402 to an average concentration of 8.1 mg/m³ (1.7 ppm) EGBE in air. A poor correlation was
403 observed between air levels of EGBE and post-shift total BAA levels in urine ($R^2 =$
404 0.0435 for Monday; $R^2 = 0.0559$ on Friday), which indicated to the authors that
405 significant dermal uptake had occurred. Post-shift total BAA levels in urine on Monday
406 and Friday (446.8 and 619.4 mg/g creatinine, respectively) were around 223% and
407 310% of the ACGIH proposed Biological Exposure Index (BEI; 200 mg/g creatinine),
408 respectively. Employing a PBPK model that only estimates the urinary BAA
409 concentration via whole-body exposure to airborne EGBE, only 3.7% of the increase in
410 urinary BAA could be explained by the airborne exposure route. The authors noted that
411 the mean pre-shift BAA level on Friday was significantly higher than that on Monday,
412 implying accumulation of EGBE metabolites over the workweek.

413
414 Hung *et al.* (2011) also investigated exposure of 25 self-adhesive decal workers, who
415 provided occasional assistance to the decal transfer workers, and 24 assembly workers,
416 who acted as controls. Personal air exposure to EGBE was below the detection limit for
417 most of the self-adhesive decal workers, so no correlation of urinary BAA level to EGBE
418 air concentration was attempted by the authors. However, end-shift total BAA levels
419 were found to be about 10-fold less than that of the decal transfer worker group. In the
420 assembly workers, personal air exposure to EGBE was not detected, and no BAA was
421 found in the urine.

422
423 Studies of dermal absorption and metabolism kinetics of EGBE were carried out in four
424 male volunteers (Korinth *et al.*, 2007). Percutaneously penetrated EGBE was sampled
425 and measured before it entered systemic circulation using micro-dialysis capillaries
426 embedded under the subjects' skin. Volunteers were dermally exposed twice to 90%
427 and 50% aqueous solutions (v/v) of EGBE for 4.5 hours. The dialysate samples were
428 collected at 30-minute intervals during exposure. The systemic absorption of EGBE was

429 estimated from the concentration of free BAA in urine. A pseudo steady-state dermal
430 absorption was reached after approximately 2 hours of exposure. The maximum dermal
431 flux of the 50% EGBE solution was higher than that of the 90% EGBE solution ($2.8 \pm$
432 0.4 and 1.9 ± 0.6 mg/ cm²-hr, respectively). The more diluted EGBE solution exhibited a
433 shorter lag time for dermal absorption: 25 versus 39 minutes. Micro-dialysis indicates
434 that the dermal metabolism of EGBE was low; with BAA accounting for 0.03% to 1.9%
435 of the EGBE in the same dialysate. This study demonstrated that dermal absorption of
436 EGBE is dependent on the EGBE concentration in solution.

437
438 In another controlled human exposure study, Kezic *et al.* (2004) exposed male
439 volunteers to EGBE via dermal and inhalation routes to compare the kinetics of urinary
440 elimination of free and total BAA. Dermally-exposed volunteers (n=6) had a 50%
441 aqueous solution of EGBE applied to the volar forearm for four hours. Six other male
442 volunteers were exposed by inhalation (mouth-only) to 93 mg/m³ (19 ppm) EGBE for 30
443 minutes. The absorbed amount of EGBE after inhalation exposure was 20.9 ± 5.0 mg,
444 with $55 \pm 21\%$ of the total urinary excretion of BAA in the form of the conjugate. The
445 absorbed amount of EGBE after dermal exposure was higher (567 mg), but with nearly
446 the same proportion of BAA conjugate ($58 \pm 14\%$) excreted in urine. The urinary half-life
447 of free and total BAA via inhalation was 3.1 and 3.4 hours, respectively. The urinary
448 half-life of the free and total BAA following dermal exposure was 3.8 and 5.1 hours,
449 respectively. The urinary elimination half-life of BAA was obtained from the slope of the
450 curve of the log-linear excretion rate versus time data, if data from at least three time
451 points were available. The authors observed that the extent of urinary BAA conjugation
452 was highly variable between individuals, and that total BAA was a better biomarker of
453 exposure due to reduced variation. The proportion of BAA conjugate increased in urine
454 with time, which was consistent with the longer half-life of the conjugate compared to
455 free BAA in urine.

456

457 **4.2 Toxicokinetic Studies in Animals**

458

459 ¹⁴C-labelled EGBE administered by gavage to rats was rapidly distributed to all tissues
460 via the blood stream, with the highest levels of radioactivity found in the forestomach,
461 followed by the liver, kidneys, spleen and glandular stomach (Ghanayem *et al.*, 1987b).
462 Following subcutaneous administration, ¹⁴C-labelled EGBE in rats was also distributed
463 widely to all tissues, but with the greatest level of radioactivity in the spleen and thymus,
464 followed by the liver (Bartnik *et al.*, 1987).

465

466 In groups of rats inhaling 97 or 483 mg/m³ (20 or 100 ppm) EGBE continuously for up to
467 12 days, EGBE and its metabolite BAA increased rapidly in blood during the first 1-3
468 days, then began to level off over the remaining days (Johanson, 1994). EGBE and
469 BAA concentrations displayed linear kinetics, with the EGBE concentration

470 approximately five times higher in the 483 mg/m³ (100 ppm) group compared to the 97
471 mg/m³ (20 ppm) group. The observed urinary excretion of BAA corresponded to 64% of
472 the calculated respiratory uptake.

473

474 In groups of rats inhaling ¹⁴C-labelled EGBE at concentrations of 20.8, 237, and 2115
475 mg/m³ (4.3, 49, and 438 ppm), an average of 69% of the ¹⁴C-label was eliminated in
476 urine during the 66-hour post exposure period (Sabourin *et al.*, 1992a). About 7% was
477 metabolized and exhaled in the form of ¹⁴CO₂, and another 10-20% of the label
478 remained in the carcass, suggesting possible binding of EGBE metabolites to tissue
479 macromolecules. BAA was the major metabolite in urine at all exposure concentrations;
480 although the proportion of metabolite in urine as BAA decreased with increasing dose
481 from 43.2 to 36.6%. A minor urinary metabolite, ethylene glycol, also decreased with
482 increasing concentration from 16.1 to 7.9%. These data indicated that metabolism of
483 EGBE by pathways leading to ethylene glycol and BAA appears to be easily saturated.
484 The EGBE-glucuronide conjugate (BEG) was also excreted in urine, increasing
485 proportionally with increasing concentration from 3.4 to 10.4%. BEG elimination was
486 also favored early during the exposures. This finding suggested to the authors that
487 formation of BEG is favored at higher substrate concentrations (high K_m), but shifts to
488 more ethylene glycol and BAA elimination as the internal EGBE concentration declines
489 after exposure. Lesser amounts of two unknown metabolites were also detected in urine
490 (≤10.5% of ¹⁴C-label eliminated in urine).

491

492 The elimination kinetics of EGBE and BAA in rats appear to be independent of exposure
493 route. In a drinking water study, rats exposed to 28 to 140 mg/kg BW/day of ¹⁴C-labeled
494 EGBE in drinking water eliminated 50-60% of the label in urine as BAA (Medinsky *et al.*,
495 1990). Another 10% of the label was eliminated in urine as ethylene glycol and
496 approximately 7% was eliminated as BEG. About 8-10% of the label was removed as
497 ¹⁴CO₂ in exhaled breath.

498

499 In rats orally administered ¹⁴C-labelled EGBE (125 mg/kg body weight), five metabolites
500 were observed in urine in the first eight hours after treatment (Ghanayem *et al.*, 1987a).
501 BAA and BEG were the major urinary metabolites. BAA accounted for more than 75%
502 of the radioactivity excreted in urine, whereas BEG accounted for <20% of the
503 radioactivity excreted in urine. A small percentage of the radioactivity in urine was the
504 sulfate conjugate (BES), while the other minor metabolite was unidentified.

505

506 The elimination kinetics of ¹⁴C-labelled EGBE have also been investigated in dermally-
507 exposed rats (Sabourin *et al.*, 1992b). EGBE was applied to a shaved area on the back
508 of rats in metabolism cages for 72 hours. As with other exposure routes, BAA was the
509 main metabolite found in urine (68% of total urine metabolites). BEG accounted for 14%

510 of total urine metabolites, and ethylene glycol accounted for another 5% of total urine
511 metabolites. Approximately 4.5% of the radiolabel was exhaled as $^{14}\text{CO}_2$.

512

513 A few studies have examined the toxicokinetics of EGBE in mice. Poet *et al.* (2003)
514 administered EGBE to mice via intraperitoneal injection (IP; 53.2 and 261 mg/kg) and
515 oral gavage (265.2 mg/kg). BAA was the major metabolite eliminated in urine, 50.8% of
516 the dose via IP and 37.5% of the dose via gavage. An unidentified conjugate of BAA
517 represented 0-1.7% of the dose via IP, and about 7% of the dose via oral gavage. Very
518 little unconjugated EGBE (<0.2%) was detected in urine. Following acid hydrolysis,
519 0.7-2.8% of the total dose via IP and 3.3% of the total dose via oral gavage were
520 recovered as an EGBE conjugate presumed by the authors to be BEG.

521

522 **4.3 Species Differences in Metabolism and Elimination of EGBE**

523

524 Physiologically-based pharmacokinetic modeling of EGBE and BAA showed that even
525 though rats metabolize EGBE and eliminate BAA faster per kilogram body weight than
526 humans, the balance of these two processes in addition to physiological differences
527 between species resulted in higher predicted peak blood levels as well as higher total
528 areas under the blood concentration time curves for BAA in rats compared to humans
529 (Corley *et al.*, 1994; Corley *et al.*, 2005). For example, the PBPK model predicted peak
530 blood levels of BAA in male rats to be roughly twice that of humans over a range of
531 EGBE air concentrations from 531 to 1208 mg/m³ (110 to 250 ppm), and suggested that
532 the blood concentration of BAA in humans cannot attain a level at which hemolysis can
533 occur. In mice and female rats, the PBPK model showed peak BAA blood
534 concentrations for air concentrations from 725 to 1208 mg/m³ (150 to 250 ppm) EGBE
535 was even greater (2-4x) compared to humans. Mice, on the other hand, eliminated both
536 EGBE and BAA from blood faster than rats when chronically exposed to EGBE (Dill *et*
537 *al.*, 1998).

538

539 In summary, while Phase I metabolism of EGBE to BAA is similar between humans and
540 rodents, there are major differences in Phase II metabolism between the species (Table
541 4). Humans extensively conjugate BAA via the amino acid glutamine and probably
542 glycine, while rats excrete mostly free BAA and a small amount as BEG. Similar to rats,
543 mice excrete mainly free BAA in urine and a small amount (<10%) as an EGBE
544 conjugate, possibly BEG. Ethylene glycol or glycolic acid urinary metabolites are also
545 excreted by rats (and probably mice), but have not been found in humans.

546

547 **Table 4. Comparisons of human, rat and mouse urinary EGBE metabolites, and**
 548 **¹⁴C-labelled EGBE exhaled as ¹⁴CO₂.**

Study, Species, Exposure Route	% BAA	%Gln	%BEG	%EG	%other	%CO ₂
Johanson <i>et al.</i> (1986) Human, inhalation	17-55 ^a	NR	NR	NR	NR	NR
Sakai <i>et al.</i> (1994) Human, inhalation	NR	44-92 ^b	NR	NR	NR	NR
Rettenmeier <i>et al.</i> (1993) Human, inhalation	NR	16-64 ^c	NR	NR	NR	NR
Corley <i>et al.</i> (1997) Human, dermal	33 ^d	67 ^c	NR	NF	^e	NR
Kezic <i>et al.</i> (2004) Human, inhalation Human, dermal	45 ^d 42 ^d	55 ^b 58 ^b	NR	NR	NR	NR
Sabourin <i>et al.</i> (1992a) Rat, inhalation	43-37 ^f	NR	3-10	8-16	≤10.5 ^g	7
Medinsky <i>et al.</i> (1990) Rat, drinking water	50-60 ^f	NR	7	10	NR	8-10
Ghanayem <i>et al.</i> (1987) Rat, oral gavage	75 ^f	NR	<20	NR	^h	NR
Sabourin <i>et al.</i> (1992b) Rat, dermal	68 ^f	NR	14	5	NR	4.5
Poet <i>et al.</i> (2003) Mouse, oral gavage Mouse, IP	37.5 ⁱ 50.8 ⁱ	NR	3.3 ^j 0.7-2.8 ^j	NR	7 ^k 0-1.7 ^k	NR

549 Legend: Gln, BAA-glutamine conjugate; BEG, EGBE-glucuronide conjugate; EG, ethylene glycol; NF -
 550 Not found; NR – Not reported.

551 ^a Amount of total EGBE uptake excreted as total BAA (Free BAA + conjugated BAA)

552 ^b Percent of total BAA eliminated as BAA-conjugate, presumed to be BAA-glutamine

553 ^c Percent of total BAA eliminated as glutamine-conjugate. Corley *et al.* (1997) suggested a portion of this
 554 amino acid conjugate (<10%) is the glycine conjugate

555 ^d Percent of total BAA eliminated as free BAA

556 ^e Fraction just above detection limit eliminated as unidentified EGBE-conjugate

557 ^f Percent of total urinary metabolites excreted as free BAA

558 ^g Unidentified metabolite(s)

559 ^h Small, unspecified percentage eliminated as the sulfate conjugate

560 ⁱ Percent of dose excreted in urine as free BAA

561 ^j Percent of dose excreted in urine; EGBE conjugate presumed to be BEG

562 ^k Percent of dose excreted in urine; unidentified BAA-conjugate

563 4.4 Age- and Sex-Related Differences in Rodents

564

565 Age-related differences in the metabolism and clearance of EGBE have been observed
566 in rodents. Compared to older rats (9-13 weeks old), young rats (4-5 weeks old)
567 eliminated a larger proportion of gavage-administered EGBE as CO₂ in exhaled breath
568 and excreted more EGBE metabolites (BAA, BEG, and/or BES) in the urine, resulting in
569 lower plasma concentrations of EGBE and BAA (Ghanayem *et al.*, 1990a). Urinary
570 excretion of BAA appeared to be impaired in older rats resulting in a larger area under
571 the BAA time–concentration blood curve (AUC) compared to younger rats. This finding
572 suggests older rats have a greater susceptibility to hemolysis (Ghanayem *et al.*, 1990a).

573

574 As part of a National Toxicology Program (NTP) chronic exposure study, sex and age-
575 related differences in the toxicokinetics of EGBE were examined in rats and mice over
576 their lifespan (Dill *et al.*, 1998). Urine and blood samples were collected periodically
577 from the rodents during an 18-month exposure (6 hrs/day, 5 days/wk) to EGBE. A
578 separate group of mice was exposed to EGBE only for 3 weeks when they were 19
579 months old. In 19-month-old mice, EGBE was rapidly cleared from the systemic
580 circulation, exhibiting clearance profiles similar to young mice 6-7 weeks old. However,
581 old mice eliminated the BAA metabolite from blood over 10 times more slowly than
582 young mice after a 1-day exposure. This delayed elimination of BAA in old mice was
583 less obvious after 3 weeks of exposure. This finding indicated that there might be other
584 factors in addition to the age of animals, such as acute renal dysfunction due to
585 exposure followed by rapid compensation, that could be the cause of BAA kinetic
586 differences between young and old mice.

587

588 In rats, a sex-related difference in BAA elimination was observed, as females were
589 about half as efficient in clearing BAA from the blood as males (Dill *et al.*, 1998). The
590 authors suggested that the differences in renal excretion of BAA in rats were most likely
591 responsible for the sex-dependent difference in BAA blood levels.

592

593 Overall, mice eliminated both EGBE and BAA from blood faster than rats (Dill *et al.*,
594 1998). However, in both species, the rates of elimination of EGBE and BAA decreased
595 with continued exposure resulting in longer residence times in blood. The authors
596 concluded that the elimination kinetics of EGBE and BAA following long-term exposure
597 appear to be dependent on sex and age of the animal, but can also vary depending on
598 the species, time of exposure, and exposure concentration.

599

600 5. Acute Toxicity of EGBE

601 5.1 Acute Toxicity to Adult Humans

602 5.1.1 Inhalation Exposure

603

604 **Acute Accidental, and Incidental EGBE Inhalation Exposures**

605

606 EGBE is an irritant of the eyes and upper respiratory tract in humans. Use of cleaning
607 products containing EGBE in office buildings specifically implicated EGBE as the cause
608 of sensory irritation and headaches in office workers (Rella *et al.*, 2012). Although the
609 air levels of 0.013 to 0.032 mg/m³ (0.0027 to 0.0066 ppm) in the study by Rella *et al.*
610 were well below occupational limit values, and other potential sensory irritants were
611 present (*e.g.*, limonene, dimethylstyrene and hexanal), elimination of the cleaning
612 products resulted in improvement of air quality and reduction of symptoms.

613

614 Accidental exposures of humans to high levels of EGBE vapors originating from misuse
615 of concentrated EGBE cleaning products have resulted in immediate, intense eye and
616 respiratory irritation, marked dyspnea, nausea, and faintness (Raymond *et al.*, 1998).
617 Respiratory irritation due to EGBE exposure could trigger asthmatic episodes in people
618 with asthma and also pose risks for people with chronic obstructive pulmonary disease,
619 emphysema, and/or other respiratory diseases and conditions (Bello *et al.*, 2009; Burns,
620 2010). Epidemiological investigations have shown an association between exposure to
621 cleaning products and respiratory dysfunction, including exacerbation of asthma (Zock
622 *et al.*, 2007; Siracusa *et al.*, 2013; Folletti *et al.*, 2014). Although EGBE has been
623 implicated as a potential irritant in cleaning products that leads to respiratory problems,
624 the presence of other VOC irritants in cleaning products and lack of quantitative
625 assessments of exposure during cleaning activities often make it difficult to characterize
626 the specific role of EGBE as a respiratory irritant in these products (Bello *et al.*, 2009;
627 Bello *et al.*, 2013; Fromme *et al.*, 2013; Gerster *et al.*, 2014).

628

629 Measured EGBE concentrations ranging from 62.8 to 816 mg/m³ (13 to 169 ppm) near
630 silk screening equipment have resulted in complaints of odor and sensory irritation
631 during use (Kullman, 1987). Raymond *et al.* (1998) reported that long-term effects of
632 high acute accidental EGBE exposures (approximately 41.4 – 62.1 mg/m³; 200 – 300
633 ppm) included recurrent eye and respiratory irritation, dry cough, and headache eight
634 months post-exposure, and new cherry angiomas 4 – 60 months post exposure. The
635 appearance of cherry angiomas was reported in 6 of 7 workers (mean age: 36 yrs) four
636 months following the high acute EGBE exposure. Cherry angiomas can appear
637 spontaneously, usually after age 50, but have been observed in workers following
638 exposure to other irritating gases (*e.g.*, mustard gas). The authors suggested cherry

639 angiomas may represent, in some persons, a nonspecific response of exposure to
640 noxious agents.

641

642 ***Acute EGBE Inhalation Chamber Studies***

643

644 In a chamber study conducted to investigate the toxicokinetics of EGBE, seven healthy
645 male adults were exposed to 97 mg/m³ (20 ppm) EGBE for 2 hours during light exercise
646 on a bicycle ergometer (Johanson *et al.*, 1986a). There were reportedly no complaints
647 or any other adverse effects from exposure. No changes in pulmonary ventilation,
648 respiratory frequency or heart rate were seen, but the study was not designed to collect
649 detailed information on potential sensory irritant effects. In another toxicokinetic study,
650 whole body 2-hour exposure of four volunteers to 237 mg/m³ (49 ppm) EGBE did not
651 result in physiological changes in breathing rate, pulse rate, skin surface temperature or
652 skin resistance (Jones and Cocker, 2003; Jones *et al.*, 2003b). Although an odor was
653 noted upon entering the chamber, and some volunteers found it initially unpleasant,
654 perception of the smell diminished over time during exposure (electronic communication
655 from K. Jones, 2005).

656

657 In whole-body chamber studies conducted by Carpenter *et al.* (1956), human volunteers
658 were exposed to 473 mg/m³ (98 ppm; two men and one woman) or 942 mg/m³ (195
659 ppm; two men and two women) EGBE for a total of 8 hours. Even at the lower exposure
660 level, eye, nose, and throat irritation, taste disturbances, headache, and nausea were
661 reported by the human volunteers. Two men exposed to 546 mg/m³ (113 ppm) EGBE
662 for 4 hours reported similar effects. RBC osmotic fragility and urinalysis were normal in
663 the human subjects during and after exposure.

664 ***5.1.2 High-dose Oral, Intentional Exposure***

665 In separate case reports, two women who ingested large amounts of window cleaner
666 (containing about 12% EGBE; dose range 391 – 933 mg/kg) showed severe respiratory
667 effects including pulmonary edema and increased respiration rate (20 breaths/minute
668 versus adults normal range: 12 – 18 breaths/minute) that required a ventilator
669 (Rambourg-Schepens *et al.*, 1988; Gijzenbergh *et al.*, 1989). After exposure to
670 approximately 45 g EGBE, one 50-year-old woman experienced moderate
671 hemoglobinuria on the third day post-exposure, which lasted until the sixth day, inducing
672 progressive erythropenia (RBC 3 x10¹²/L, hematocrit (Hct) 28.6%, hemoglobin (Hgb) 9.7
673 g/L on the 10th day) (Rambourg-Schepens *et al.*, 1988). Another 23-year-old woman,
674 who had ingested approximately 25 – 30 g EGBE, experienced a fall in Hgb from 11.9
675 g/dL on admission to 8.9 g/dL on the second day, together with the appearance of
676 hematuria (Gijzenbergh *et al.*, 1989). Both patients recovered and were discharged in
677 good condition after 8 to 10 days.

678

679 One 53-year-old patient was admitted to the intensive care unit after attempting suicide
680 with ingestion of 500 ml of a house cleaning fluid (Bauer *et al.*, 1992). The cleaning
681 fluid's composition included 2.5% ethanol, 9.1% (45.5 g) EGBE, and traces of
682 diethylene glycol monoethyl ether, which was determined by gas-chromatography. The
683 patient was comatose (Glasgow Coma Score 5/15) with metabolic acidosis, shock
684 (blood pressure 60/30 mmHg), and non-cardiogenic pulmonary edema confirmed by a
685 hemodynamic study. Physical and laboratory exams found crackling sounds in both
686 lungs and a transient polyuria (2500 ml urine in 2 hours), respectively. No blood ethanol
687 could be detected, but the serum EGBE concentration was 0.00528 mg/L. No EGBE
688 was found in gastric lavage juice or urine. This patient was an alcohol abuser, exhibited
689 neurosis, and had a history of trichloroethylene ingestion (14 and 4 weeks before that
690 event). The patient had undergone vascular surgery in the past. This patient's outcome
691 was marked by a dramatic improvement of respiratory function within five days. Acidosis
692 and hypoxemia were corrected in 4 hours; shock was stabilized in 12 hours. By 36
693 hours after admission, biologic data showed a non-hemolytic hypochromic anemia (Hct:
694 25% with thrombopenia (platelet count: 85 000)). The patient was discharged and had
695 fully recovered after 15 days. The author concluded that acute poisoning by EGBE
696 could cause not only hematologic, neurologic, renal, and metabolic disturbances, but
697 also severe acute and transient respiratory failure, the mechanism of which is unknown
698 (Bauer *et al.*, 1992).

699

700 A case report by Gualtieri *et al.* (2003) described an 18-year-old male who ingested
701 360–480ml of a glass cleaner which contained 22% EGBE and then again ingested
702 approximately 480 ml of the same cleaner 10 days later. Approximately 10 hours after
703 the first ingestion, the patient developed severe central nervous system (CNS)
704 depression, metabolic acidosis, hematuria, and mild elevation of hepatic enzymes. He
705 was treated initially with ethanol therapy but continued to deteriorate and was started on
706 hemodialysis. The highest BAA and EGBE serum concentrations noted after the first
707 ingestion were 4.86 and 0.00038 mmol/L, respectively, from a sample collected
708 approximately 16 hours post-ingestion and 7 hours prior to hemodialysis. Within four
709 hours after the second ingestion, the patient again received ethanol and hemodialysis
710 treatments. During his second hospitalization, the patient did not develop severe CNS
711 depression or profound metabolic acidosis. The highest BAA and EGBE serum
712 concentrations noted after his second ingestion were 2.07 and 0.108 mmol/L,
713 respectively, collected approximately 22 hours post-ingestion and 2 hours after the start
714 of hemodialysis. Neither episode produced clinically significant hemolytic anemia,
715 oxaluria, ethylene glycol production, or renal failure.

716

717 Lastly, Hung *et al.* (2010). reported that a 53-year old worker co-ingested an unknown
 718 quantity of ethanol and 150–250 mL of 99% EGBE, which resulted in rapid obtundation
 719 (altered level of consciousness), severe airway edema, hypotension, and prolonged
 720 acidosis despite the co-ingestion of ethanol and the administration of a loading dose of
 721 fomepizole, an alcohol dehydrogenase inhibitor. Following hemodialysis, the patient
 722 recovered without apparent sequelae. The authors concluded that alcohol
 723 dehydrogenase inhibitors may not be adequate to prevent acidosis for significant EGBE
 724 ingestions and hemodialysis treatment may be necessary. A summary of EGBE
 725 poisoning cases is presented in Table 5 below.

726 **Table 5: Synopsis of EGBE poisoning cases.**

	Rambourg-Schepens <i>et al.</i> , 1988*	Gijsenbergh <i>et al.</i> , 1989*	Bauer <i>et al.</i> , 1992*	Gualtieri <i>et al.</i> (2003)	Hung <i>et al.</i> , 2010
Sex	Female	Female	Male	Male	Unknown
Age (years)	50	23	53	18	53
Ingested Dose (g)	45	25 - 30	45	80 - 100	135-225
CNS depression	Yes	Yes	Yes	Yes	Yes
Lung injury	No	No	Yes	No	Yes
Liver injury	No	No	Yes	Yes	
Renal injury	Yes	No	No	Yes	
pH	7.23	7.08	7.05	7.34	7.16
HCO ₃ ⁻ (mmol/L)	5	2.4	5.6	19.5	21
Hematocrit (%)	28.6 (10 th Day)	Unknown	25 (2 nd Day)	Unknown	Unknown
Hemoglobin (g/dL)	9.7 (10 th Day)	8.9 (2 nd Day)	9.1 (2 nd Day)	Unknown	10.7 (2 nd Day)
Outcome	Discharged	Discharged	Discharged	Discharged	Discharged

727 * Adapted from Bauer *et al.* (1992) to include data from Gualtieri *et al.* (2003) and Hung *et al.* (2010).
 728

729 **5.2 Acute Toxicity to Infants and Children**

730
 731 No studies of children exposed to airborne EGBE were located. However, acute
 732 ingestions of EGBE in cleaning solutions by 24 children (aged from 7 months to 9 years)
 733 from a regional poison control center have been reviewed (Dean and Krenzelok, 1992).
 734 These reports included the ingestion of 5-300 ml of liquid glass cleaning products
 735 containing 0.5 to 9.9% EGBE. All ingestions were reported within 5 minutes of ingestion,

736 and all 24 children, including two children who ingested more than 15 ml of EGBE-
737 containing glass/window cleaners, were hospitalized for 24 hours following gastric
738 emptying and gastric lavage. The children were asymptomatic both at the time the
739 ingestions were reported and 24 hours later. The five-month retrospective review of the
740 two hospitalized children who ingested >15 m EGBE failed to find symptoms consistent
741 with hemolysis, nervous system depression, acidosis, or renal compromise.

742 **5.3 Acute and Subacute Toxicity to Experimental Animals**

743 **5.3.1 Acute and Subacute Studies**

744 Kane *et al.* (1980) exposed male Swiss Webster (outbred) mice (n = 4/group; age and
745 weight not stated) to EGBE vapor for 10 minutes over a concentration range of
746 approximately 676 – 6762 mg/m³ (140 – 1400 ppm). They estimated an RD50 (an
747 airborne concentration of a chemical that produces a 50% decrease in respiratory rate)
748 of 7,995 mg/m³ (2825 ppm). The RD50 bioassay measures decreases in respiratory
749 frequency in mice as a result of stimulation of the trigeminal or laryngeal nerve endings.
750 This RD50 needed to be extrapolated because the authors were unable to generate
751 EGBE concentrations that were adequately high to directly determine the RD50.
752 Although not specified by the authors, this could be a result of the exposures reaching
753 the saturated vapor pressure, about 2,830 to 4,528 mg/m³ (1,000 to 1,600 ppm)
754 depending on the temperature and humidity, prior to reaching the RD50. EGBE was
755 categorized as a weak sensory irritant by Kane *et al.* (1980) when compared to the
756 RD50 of potent sensory irritants such as chlorine, acrolein, formaldehyde and toluene
757 diisocyanate.

758
759 In range finding inhalation studies conducted by Carpenter *et al.* (1956) as a guide for
760 subsequent 30-day exposure trials (discussed in Section 6.3), an unspecified strain of
761 rats were exposed to a range of EGBE concentrations for 4 to 8 hrs/day, for up to 6
762 days. Mortality and hemoglobinuria were the endpoints assessed. Hemoglobinuria was
763 used as the basis of the NOAEL and LOAEL (604 and 1208 mg/m³, 125 and 250 ppm
764 EGBE, respectively) when it was observed in young female rats (n = 6/group; 5 –
765 6 weeks of age; 88 – 104 g) exposed 8 hrs/day for 6 days. In older female rats (age not
766 specified) weighing 140-160 gms, 8-hour exposures to 1208 mg/m³ (250 ppm) EGBE
767 for four days resulted in hemoglobinuria and mortality (n = 1 of 5). In rats about 1 yr old,
768 one 7-hour exposure to 1811 mg/m³ (375 ppm) EGBE resulted in hemoglobinuria and
769 mortality in all 23 exposed female rats (250-330 g), and in 11 of 13 exposed male rats
770 (380-500 g). At higher EGBE concentrations of 2,415 mg/m³ and 3,864 mg/m³ (500 and
771 800 ppm), 6 week-old female rats weighing 100-130 g exhibited hemoglobinuria, but
772 were more resistant to the lethal effects of EGBE compared to the 1-yr olds. Exposure
773 to 2,415 mg/m³ (500 ppm) for 4 or 8 hours (n = 6/group) resulted in only one death.

774 Exposure to 3,864 mg/m³ (800 ppm) resulted in no mortality with 4 hours exposure, and
775 50% mortality (n = 3 of 6) with 8 hours exposure.

776

777 Dodd *et al.* (1983) performed a comprehensive study on the effects of EGBE vapor
778 inhalation in 6 – 7-week old Fischer 344 (inbred) rats. Acute, 9-day, and 90-day
779 (discussed in Section 6.3) exposure experiments were performed in a 3,800-liter
780 chamber for 4 hours on one day, 6 hrs/day for 9 days, and 6 hrs/day, 5 days/wk for 13
781 weeks, respectively. Biological endpoints including RBC Hgb, mean corpuscular
782 hemoglobin (MCH) concentration and numbers of nucleated RBCs, reticulocytes, and
783 lymphocytes were assessed.

784

785 In acute experiments, male and female rats (n = 6/sex/group) were exposed by
786 inhalation to EGBE for 4 hours at concentrations of 976, 2,526, or 4,188 mg/m³ (202,
787 523, or 867 ppm, respectively). There was no control group. All EGBE exposed rats
788 exhibited loss of coordination, rapid shallow breathing, and red discharge from the
789 urogenital region. All of the rats in the 4,188 mg/m³ (867 ppm) group died within 24
790 hours of exposure. The estimated LC₅₀ was 2,348 mg/m³ (486 ppm) for males and
791 2,174 mg/m³ (450 ppm) for females (Dodd *et al.*, 1983).

792

793 In 9-day (6 hrs/day, 5 days/wk) experiments, rats (n = 8/sex/group) were exposed to
794 EGBE concentrations of 0, 97, 415, or 1,183 mg/m³ (0, 20, 86 or 245 ppm,
795 respectively). An additional 8 rats/sex/group were assigned to the control and highest
796 EGBE exposure groups and allowed a 14-day recovery following the ninth exposure
797 day. The authors found EGBE exposure significantly ($p \leq 0.05$) affected hematological
798 parameters and body/organ weights. Male and female rats from the 1,183 mg/m³ (245
799 ppm) group had reduced RBC counts, Hgb and MCH concentrations, and BW gains,
800 and increased nucleated RBCs, reticulocytes, lymphocytes, and liver weights relative to
801 control when necropsied immediately after the 9-day exposure. A 14-day post-exposure
802 recovery resulted in substantial reversal of the affected blood parameters. Similar
803 hematologic effects were observed in the 415 mg/m³ (86 ppm) group, but not in the
804 97 mg/m³ (20 ppm) group. The authors reported a No Observed Adverse Effect Level
805 (NOAEL) and a Lowest Observed Adverse Effect Level (LOAEL) of 97 and 415 mg/m³
806 (20 and 86 ppm), respectively, based on an anemia endpoint (Dodd *et al.*, 1983).

807

808 Whole body inhalation exposure of 400 – 500 g, 5-week old Hartley albino guinea pigs
809 for 1 hour to EGBE at 3,057 mg/m³ (633 ppm; 5 males) and 3,338 mg/m³ (691 ppm; 5
810 females) resulted in no mortality or clinical signs of toxicity immediately or up to 14 days
811 following exposure (Gingell *et al.*, 1998). Eight-hour exposures of male guinea pigs to
812 3,212 mg/m³ (665 ppm) EGBE by a different group did not result in increased osmotic

813 fragility or hemoglobinuria (Carpenter *et al.*, 1956). No information was provided
814 regarding the guinea pig strain, age, or BW for the 8-hour study.
815

816 **5.3.2 Species Differences**

817 Substantial species differences exist among experimental animals in their acute/sub-
818 acute responses to EGBE. In sensitive mammalian species, hemolytic anemia and
819 increased RBC osmotic fragility are primary toxic endpoints of EGBE exposure.
820

821 According to the study by Carpenter *et al.*(1956), hemolytic responses were observed in
822 highly susceptible species including rats, mice and rabbits, but not humans, monkeys,
823 dogs and guinea pigs. Some of the responses reported by Carpenter *et al.* (1956) have
824 been observed in at least one other *in vivo* study (Ghanayem and Sullivan, 1993) and
825 two *in vitro* studies (Corley *et al.*, 1994; Udden, 2002). In their comparison of
826 hematological parameters in rats and guinea pigs, Ghanayem and Sullivan noted that a
827 single gavage administration of EGBE to rats at 250 mg/kg caused an early increase (1
828 hour post-treatment) in mean corpuscular volume and Hct, which declined over a 24
829 hour period. This was associated with hemolysis and a decline in Hgb and RBC
830 numbers. However, the same treatment in guinea pigs had no similar effect (Ghanayem
831 and Sullivan, 1993).
832

833 Species comparisons by Carpenter *et al.* (1956) were primarily made using results of
834 separate exposures for each tested species. However, simultaneous chamber
835 exposures of six rats and two men to EGBE (546 mg/m³, 113 ppm) for four hours
836 showed humans to be insensitive to hemolytic endpoints at this dose level when
837 compared to rats (Carpenter *et al.*, 1956). No differences in pre- and post-exposure
838 RBC fragility were observed in the men, but according to the authors, RBC fragility in
839 rats “rose appreciably.” These rat responses were not quantified in the text.
840

841 In 30-day exposures in C3H mice (7 hrs/day/ 5 days/wk), hemoglobinuria was observed
842 after the first 7-hour exposure to 966 mg/m³ (200 ppm) (n= 9 of 60) and 1,932 mg/m³
843 (400 ppm) (n = 26 of 60) EGBE (Carpenter *et al.*, 1956). This effect was not apparent
844 after the third 7-hour exposure. No hemoglobinuria was observed in mice exposed to
845 483 mg/m³ (100 ppm) for 7 hours. However, RBC osmotic fragility was noted at all three
846 concentrations after the first 7-hour exposure.
847

848 Rabbits exposed to 604 or 952 mg/m³ (125 or 197 ppm) EGBE for 7 hours were
849 reported to have significantly increased RBC osmotic fragility at 604 mg/m³ (125 ppm)
850 but no hemoglobinuria at concentrations up to 952 mg/m³ (197 ppm) (Carpenter *et al.*,

851 1956). (Animal numbers were not stated, the *p*-value was not defined, and it was
852 unclear from the text that a control group was included.)

853
854 Experiments in dogs suggested that concentrations up to 966 mg/m³ (200 ppm) may
855 have no adverse effects in the short term, while those at 1860 mg/m³ (385 ppm) and
856 above may be lethal. Dogs (n = 1/sex) exposed to 966 mg/m³ (200 ppm) EGBE
857 intermittently for 7 hrs/day showed no apparent toxic manifestations during the first two
858 weeks of exposure. Toxic manifestations were observed during the first week of
859 exposure in dogs (n = 1/sex) breathing 1860 mg/m³ (385 ppm) EGBE 7 hrs/day.
860 Responses included emesis, generalized weakness, increased RBC osmotic fragility,
861 and in the male only, significantly decreased RBC count and Hgb levels. (It is unknown
862 whether statistical tests were done for RBC fragility, and for the last two endpoints, no
863 *p*-values were given.) The female dog died after the 8th day. Daily 7-hour exposures of
864 2702 mg/m³ (617 ppm) EGBE in one female dog resulted in emesis and extreme
865 weakness during the first two days, with death occurring near the end of the second day
866 (Carpenter *et al.*, 1956).

867
868 Monkeys(n = 1/sex; strain not identified) exposed to 966 mg/m³ (200 ppm) EGBE for 7
869 hours did not result in increased osmotic RBC fragility or hemoglobinuria. However, a
870 rhesus monkey (sex unstated) exposed to 1014 mg/m³ (210 ppm) EGBE for 30 days (7
871 hrs/day, 5 days/wk) exhibited transient RBC osmotic fragility after the fourth exposure.

872
873 Table 6 presents a summary of the *in vivo* findings from acute and subacute studies
874 with animals.

875

876 **Table 6. Summary of acute and subacute EGBE inhalation exposure studies in**
 877 **animals.**

Reference	Species	Exposure	Results
Kane <i>et al.</i> (1980)	Mice (n = 4/group) Age not indicated	676 – 6762 mg/m ³ (140 – 1400 ppm) for 10 min	RD50 (50% depression in respiratory rate) at 7995 mg/m ³ (2825 ppm).
Dodd <i>et al.</i> (1983)	Rats (n = 6/sex/group) 6-7 wks old	976, 2526, or 4188 mg/m ³ (202, 523, or 867 ppm) for 4 hrs	LC50: 2347 mg/m ³ (486 ppm) for males and 2174 mg/m ³ (450 ppm) for females. Other findings include ↓ coordination, ↑ rate of shallow breathing, and red urogenital discharge in all rats. Death at highest concentration.
	Rats n = 8/sex/group 6-7 wks old	0, 97, 415, or 1183 mg/m ³ (0, 20, 86 or 245 ppm), for 9 days (6 hrs/day, 5 days/wk)	Transiently ↓ RBCs, Hgb, MCH and BWGs, and ↑ reticulocytes, lymphocytes, NRBCs, and liver weights at the two highest exposure concentrations.)
Gingell <i>et al.</i> (1998)	Guinea pigs n = 5/sex/group 5 wks old	3057 mg/m ³ (633 ppm; males) or 3338 mg/m ³ (691 ppm; females) for 1 hr	LC50: > 3057 mg/m ³ (633 ppm) for males and > 3338 mg/m ³ (691 ppm) for females. No mortality or clinical signs of toxicity.

878 Legend: BWG – Body weight gain; Hgb – Hemoglobin; MCH – Mean corpuscular Hgb;
 879 NRBC – Nucleated red blood cell; RBC – Red blood cell; LC50: lethal concentration required to kill 50%
 880 of the population.
 881

882 **Table 6. Summary of acute and subacute EGBE inhalation exposure studies in**
 883 **animals (continued).**
 884

Reference	Species	Exposure	Results
Carpenter <i>et al.</i> (1956)	Mice n = 15/sex/group age not stated	0, 483, 966, or 1932 mg/m ³ (0, 100, 200, or 400 ppm) for 7 hrs	Hemoglobinuria at 966 and 1932 mg/m ³ (200 and 400 ppm) ↑ RBC osmotic fragility at all EGBE exposures
	Rats n= 5 – 6/group ages variable	604, 1208, 1811, 2415 or 3864 mg/m ³ (125, 250, 375, 500 or 800 ppm) for 4 to 8 hrs	Hemoglobinuria in all groups. Death at >250 ppm (1208 mg/m ³) in 5-6-week old rats and >125 ppm (604 mg/m ³) in “older rats”: 5-6 week-old rats: NOAEL 604 mg/m ³ (125 ppm) LOAEL 1208 mg/m ³ (250 ppm)
	Guinea pigs n = 2 per group age not stated	3212 mg/m ³ (665 ppm) for 8 hrs	No effect on RBC osmotic fragility or hemoglobinuria
	Rabbits n = 2-4/group age not stated	604 or 952 mg/m ³ (125 or 197 ppm) for 7 hrs	↑ RBC osmotic fragility at 604 mg/m ³ (125 ppm), but no hemoglobinuria up to 952 mg/m ³ (197 ppm)
	Dogs n = 1 - 2/group age not stated	966, 1860 or 2980 mg/m ³ (200, 385 or 617 ppm) for for 1 to 5 days (7 hrs/day)	966 mg/m ³ (200 ppm) - No effect. 1860 mg/m ³ (385 ppm) - Emesis, weakness, ↑ RBC osmotic fragility, ↓ RBC count and Hgb. 2980 mg/m ³ (617 ppm) - Emesis, extreme weakness, death at end of day 2.
	Monkeys n = 1 - 2/group age not stated	966 mg/m ³ (200 ppm) for 7 hrs or 1014 mg/m ³ (210 ppm) for 7 hrs/day, 5 days/wk	No ↑ RBC osmotic fragility or hemoglobinuria for 7 hours exposure. On 4 th day of exposure to 1014 mg/m ³ (210 ppm) - ↑ osmotic fragility

885 Legend: Hgb – Hemoglobin;RBC – Red blood cell
 886

887 **5.3.3 *In Vitro* Studies**

888

889 *In vitro* studies have shown considerably less risk of hemolysis in human RBCs
890 compared to rat RBCs when blood is incubated with BAA (Corley *et al.*, 1994; Udden,
891 2002). After comparing *in vivo* and *in vitro* studies for several species, including
892 monkeys, Carpenter *et al.* (1956) stated “the *in vivo* response of erythrocytes [RBCs] to
893 butyl Cellosolve [EGBE] is more closely correlated to the *in vitro* response to sodium
894 butoxyacetate [BAA] than to the *in vitro* response to butyl Cellosolve. This suggests that
895 [BAA] is more directly responsible for *in vivo* RBC fragility or hemolysis than is [EGBE].”
896

897 PBPK modeling for exposures to saturated atmospheres of EGBE showed that the
898 maximum blood concentration (up to 195 μM) of BAA is below that needed to produce
899 hemolysis in humans. An *in vitro* no effect level of 2 mM BAA was observed by Corley
900 *et al.* (1997) when BAA was incubated for 4 hours with “normal” human blood and blood
901 from humans susceptible to hemolysis. These *in vitro* studies with human blood
902 suggested that pre-hemolytic changes (*i.e.* increased osmotic fragility) are not reached
903 until concentrations are well above 5 mM in 4-hour incubations (Udden, Corley’s
904 personal communication). The resistance of RBCs in healthy adults to the hemolytic
905 effects of BAA *in vitro* extends to RBCs from elderly individuals, children, and
906 individuals with sickle cell disease or hereditary spherocytosis (Udden and Patton,
907 1994; Udden, 2002). Given these cumulative findings by Corley, Udden, and their
908 respective colleagues, human inhalation exposure to EGBE is unlikely to reach a
909 concentration that will cause hemolysis. At the same time, human RBC resistance to
910 hemolysis may be overwhelmed by high oral exposures in individuals who ingest high
911 amounts of EGBE, as previous studies have shown it to have some hematotoxicity with
912 intakes ranging from 25 – 225 g (Carpenter *et al.*, 1956; Gijzenbergh *et al.*, 1989;
913 Raymond *et al.*, 1998), with at least one case of hemoglobinuria (Gijzenbergh *et al.*,
914 1989).

915

916 Some chemicals have a protective effect, known as heteroprotection, against the
917 hemolytic effects of EGBE exposure. For example, research by Palkar *et al.* (2007)
918 showed that a priming dose of phenylhydrazine may protect rats from the hemolytic and
919 lethal effects of BAA. The authors stated that this heteroprotection may be due to
920 phenylhydrazine-treated rats having lower renal and hepatic BAA levels and
921 approximately 3-fold higher urinary excretion of BAA compared to control rats. However,
922 hepatic ADH and ALDH activities were unaltered, indicating that bioactivation of EGBE
923 to BAA was unaffected by phenylhydrazine. Instead, higher erythropoietin levels,
924 reticulocyte count, and resiliency of RBCs in phenylhydrazine-primed rats indicated that
925 newly formed RBCs were resistant to the hemolytic action of BAA (Palkar *et al.*, 2007).

926 Young rodent RBCs have been found to be less sensitive to BAA than older RBCs
927 (Ghanayem *et al.*, 1992).

928

929 **6. Chronic Toxicity of EGBE**

930 **6.1 Chronic Toxicity to Adult Humans**

931 **6.1.1 Occupational Inhalation Exposure**

932

933 Occupations in the US that lead to personal exposures to EGBE above the NIOSH REL
934 of 24 mg/m³ (5 ppm) have been reported by ATSDR (1998). These include silk
935 screening and printing press operations, furniture production and asbestos/mastic
936 removal. Other sources of exposure include spray painting operations, specialty
937 chemical production, and paint formulating. The occupational studies summarized
938 below investigated the effects of EGBE, primarily on erythroid endpoints.

939

940 One cross-sectional study (Haufroid *et al.*, 1997) reported significant effects in some of
941 the measured erythroid parameters. The study included 31 male workers (22 - 45 years
942 old) who had been employed for 1 to 6 years in a beverage packing plant. These
943 workers were exposed at a mean concentration (\pm SD) of 2.91 \pm 1.30 mg/m³
944 (0.59 \pm 0.27 ppm) EGBE in varnish or during external décor production. (It was not
945 stated whether the mean and SD were geometric or arithmetic.) Co-exposure to methyl
946 ethyl ketone was also reported. The control group was comprised of 21 workers who
947 were working in a shop or administrative section of the plant and not occupationally
948 exposed to EGBE. There was a reasonably good correlation between the EGBE
949 concentration in air and post-shift BAA in urine (average 10.4 mg/g creatinine; $r = 0.55$;
950 $p = 0.0012$), which was thought to be related to prevention of dermal absorption through
951 use of gloves. Slight but significant effects on Hct (a 3.3% decrease, $p = 0.03$) and MCH
952 concentrations (a 2.1% increase, $p = 0.02$) relative to controls suggested RBC
953 membrane damage in exposed workers, but no significant effects were found for other
954 erythroid parameters (*e.g.*, RBC number, Hgb, mean corpuscular volume, MCH,
955 haptoglobin, and reticulocytes). The US Environmental Protection Agency (US EPA)
956 (2010) noted that Hct and MCH concentrations in exposed workers reported by Haufroid
957 *et al.* (1997) were still within normal clinical ranges.

958

959 In another occupational study, investigators evaluated the hematological status of nine
960 parquet floorers exposed to a mean 8-hour concentration of 24.6 mg/m³ (5.1 ppm)
961 EGBE (max: 350 mg/m³ (72 ppm) by personal air sampling) (Denkhaus *et al.*, 1986).
962 The control group consisted of nine healthy age-matched volunteers (age 25 – 56
963 years, average 37.9) from non-EGBE-exposed occupations. No other details about the
964 controls were available. An active "personal air" sampling technique was applied (pump:
965 Compur 4900; UL SKC, USA), using NIOSH charcoal tubes (100 + 50 mg), which were

966 changed every hour during an 8-hour working period. The workers (age range = 25 – 58
967 years) had all been occupationally exposed to mixtures of organic solvents for an
968 average of 18.9 years. Detected organic solvents in the air and in the blood samples
969 included 1-butanol, iso-butanol, EGBE, 2-ethoxyethanol, 2-methoxyethanol, toluene, m-
970 xylene, 2-butanone, and 2-hexanone. The workers' RBC counts showed a slight but
971 non-significant ($p > 0.05$) decrease, and their Hgb concentrations were unaffected.

972
973 Hung *et al.* (2011) analyzed the Hgb concentration in the blood of 80 bicycle factory
974 workers. These workers were divided into three groups based on EGBE exposure:
975 decal transfer workers (high exposure, $n=31$), self-adhesive decal workers (moderate
976 exposure, $n=25$) and assembly workers (little or no exposure, $n=24$). Based on personal
977 air sampling (8-hour TWA), the decal transfer workers were exposed to an average
978 concentration of 8.1 mg/m^3 (1.7 ppm) EGBE in air. A poor correlation was observed
979 between air levels of EGBE and post-shift total BAA levels in urine due to considerable
980 dermal absorption via direct contact on their hands with a dilute aqueous solution of
981 EGBE. Only 3.7% of the increase in urinary BAA could be explained by airborne EGBE
982 exposure. In the self-adhesive workers with only occasional inhalation and dermal
983 EGBE exposure, end-shift total BAA levels were found to be about 10-fold less than that
984 of the decal transfer worker group. In the assembly workers, personal air exposure to
985 EGBE was not detected, and no BAA was found in the urine. Hgb test results showed
986 assembly workers (24 females, no males) had a slightly higher mean Hgb concentration
987 ($8.02 \pm 0.16 \text{ mmol/l}$) compared to decal transfer workers ($7.72 \pm 0.19 \text{ mmol/l}$; 30
988 females, one male) and the self-adhesive decal workers ($7.80 \pm 0.19 \text{ mmol/l}$; 24 females,
989 one male). However, no statistical difference was found between the assembly workers
990 and the decal transfer workers (Mann Whitney U test, $p = 0.2731$). Normal levels of Hgb
991 for females and males were regarded as 7.4-9.9 mmol/L and 8.3-10.9 mmol/L,
992 respectively. The percentage of below-normal Hgb levels in the decal transfer group
993 (29%, 9 of 31) appeared higher than the self-adhesive decal workers (28%, 7 of 25) and
994 the assembly workers (21%, 5 of 24). However, the difference was not statistically
995 significant (X^2 test, $p = 0.4319$).

996
997 These studies showing slight changes in some hematological parameters with exposure
998 to EGBE were not considered suitable by OEHHA to develop RELs because the
999 changes were either non-significant or values were within normal ranges.

1000
1001

1002 **6.1.2 Exposure and Asthma Risk**

1003 As noted in Section 3 of this document, EGBE is used in a variety of industrial and
1004 consumer products, including cleaning products. Exposure to substances in the
1005 workplace has been estimated to cause about 10% of all cases of adult-onset asthma
1006 (Blanc and Toren, 1999). A prospective study of 6,837 participants from 13 countries in
1007 the EU found the population-attributable risk for adult asthma due to occupational
1008 exposures ranged from 10% to 25%, equivalent to an incidence of new-onset
1009 occupational asthma of 250–300 cases per million people per year. Asthma risk was
1010 also reported to be increased in participants who reported an acute symptomatic
1011 inhalation event such as fire smoke exposure, mixing cleaning products, or chemical
1012 spills (RR = 3.3, 95% CI 1.0–11.1, p = 0.051) (Kogevinas *et al.*, 2007). Cleaning
1013 workers have been described as an exposure group at high risk of developing
1014 occupational asthma and asthma-like symptoms (Kogevinas *et al.*, 2007). However, the
1015 determination of which health hazards are associated with exposure to cleaning agents
1016 is a complex issue, and the contribution of sensitization to specific agents or exposure
1017 to irritants in the pathogenesis of respiratory symptoms associated with cleaning is
1018 unclear (Quirce and Barranco, 2010). A European Academy of Allergy and Clinical
1019 Immunology task force consensus statement indicated cleaning sprays, bleach,
1020 ammonia, disinfectants, mixing products, and specific job tasks have been identified as
1021 specific causes and/or triggers of asthma (Siracusa *et al.*, 2013). Siracusa *et al.* (2013)
1022 did not indicate that cleaning products containing glycol ethers (including EGBE) were
1023 specifically included as asthmagens in their assessment.

1024

1025 **6.2 Chronic Toxicity to Infants and Children**

1026

1027 Choi *et al.* (2010) conducted a case-control study of exposure to common household
1028 chemicals and the resulting prevalence of allergic airway disease in Swedish pre-school
1029 age children. Cases (n = 198) were defined, through a baseline questionnaire or a
1030 follow-up questionnaire (done 1.5-years after the baseline questionnaire), as children 3-
1031 8 years of age who were reported to have at least two symptoms of wheezing, rhinitis,
1032 or eczema without a cold during the preceding 12 months. Controls (n = 202) were
1033 randomly identified from 1,100 symptom-free children from local primary care clinics.
1034 Air and dust samples were collected from the bedrooms of the houses where the cases
1035 and controls lived and analyzed for several classes of VOCs, including glycols and
1036 glycol ethers.

1037

1038 Of the original population of cases and controls, 18 cases and 9 controls were found to
1039 have EGBE indoor air concentrations greater than the EGBE functional detection limit
1040 (not specified). No significant differences in the geometric mean EGBE indoor air
1041 concentrations were noted between the controls (3×10^{-3} mg/m³; 6.21×10^{-4} ppm; 95%

1042 confidence interval (CI) $3 \times 10^{-4} - 2.96 \times 10^{-2} \text{ mg/m}^3$, $6.21 \times 10^{-5} - 6.13 \times 10^{-3} \text{ ppm}$) and
1043 the cases ($3.11 \text{ } \mu\text{g/m}^3$, 0.64 ppm ; 95% CI $0.76\text{-}12.67 \text{ } \mu\text{g/m}^3$, $0.16\text{-}2.62 \text{ ppm}$).

1044

1045 **6.3 Chronic Toxicity to Experimental Animals**

1046

1047 The principal toxic effect of exposure to EGBE in sensitive species is reversible
1048 hemolytic anemia. In rodents, the primary effect on the hematologic system was anemia
1049 characterized as macrocytic (rat), normocytic (mouse), normochromic, and regenerative
1050 in exposed rats and mice (NTP, 2000). More generally, EGBE also causes irritation and
1051 damage to epithelial tissues at portal of entry sites (*i.e.*, eyes and respiratory airways).

1052

1053 In a series of experiments by Carpenter *et al.* (Carpenter *et al.*, 1956), both rodent
1054 (mice, rats, and guinea pigs) and non-rodent (rabbits, dogs, and monkeys) species were
1055 exposed to EGBE via inhalation for 7 hrs/day, 5 days/wk for up to 90 days. The authors
1056 did not indicate which statistical methods were used, and in many cases, it was unclear
1057 whether the reported biological responses were statistically significant.

1058

1059 Groups of male mice ($n = 10 - 15$ /group) exposed to 0, 541, 966, or 1,932 mg/m^3 (0,
1060 112, 200, or 400 ppm) EGBE for 30, 60, or 90 days exhibited RBC fragility at all
1061 concentrations. Fragility appeared to be as great after the first exposure as it was after
1062 89th exposure, and, in all instances, was normal after a 17-hour rest. At 1,932 mg/m^3
1063 (400 ppm), liver weights normalized to BW were significantly ($p < 0.05$) decreased
1064 relative to controls after 30 exposure days and significantly increased after 60 or 90
1065 exposure days. Normalized liver weights of mice exposed at this concentration for 90
1066 days and allowed a 42-day rest period prior to necropsy were not significantly different
1067 from controls. Transient hemoglobinuria was also observed at the highest
1068 concentration. However, no mortality occurred, and no gross pathology of organs was
1069 observed 42 days after cessation of exposure (Carpenter *et al.*, 1956).

1070

1071 Male and female Sherman rats ($n = 15/\text{sex}/\text{group}$; 140 – 190 g) were exposed to
1072 EGBE at concentrations ranging from 0 – 2,087 mg/m^3 (0 – 432 ppm) for 30 days (6
1073 weeks). A dose-dependent increase in RBC osmotic fragility was observed at all
1074 exposure levels. At 517 and 980 mg/m^3 (107 and 203 ppm), “significant [$p < 0.05$]
1075 increases” in liver weights (normalized to BW) were observed in male and female rats
1076 compared to controls. Normalized kidney weights were significantly ($p < 0.05$) increased
1077 relative to controls at the 517 mg/m^3 (107 ppm) exposure concentration, and
1078 hemoglobinuria was evident at concentrations $\geq 980 \text{ mg/m}^3$ (203 ppm). Liver and kidney
1079 weight data were not provided for groups exposed at $\geq 1,517$ and $\geq 980 \text{ mg/m}^3$ (≥ 314 and
1080 $\geq 203 \text{ ppm}$), respectively. However, at concentrations $\geq 1,517 \text{ mg/m}^3$ ($\geq 314 \text{ ppm}$), cloudy
1081 swelling of the liver was noted upon histological examination. Gross pathological

1082 findings at the same concentrations included hemorrhage of the lungs and congestion
1083 of the lungs and abdominal viscera. Deaths also occurred at $\geq 1,517$ mg/m³ (≥ 314 ppm),
1084 but at these concentrations, females appeared more susceptible to the effects of EGBE,
1085 with 100% mortality at 1,517 and 2,087 mg/m³ (314 and 432 ppm) in contrast to 0% and
1086 80% mortality in males, respectively (Carpenter *et al.*, 1956).

1087
1088 Male guinea pigs (n = 10/group; 435 – 580 g; age and strain not stated) exposed to
1089 EGBE at 0, 261, 517, 980, 1,517, or 2,386 mg/m³ (0, 54, 107, 203, 376, or 494 ppm,
1090 respectively) for 30 days did not show evidence of RBC hemolysis at any concentration.
1091 BW-normalized kidney weights were significantly ($p < 0.05$) increased relative to
1092 controls at (≥ 517 mg/m³) (≥ 107 ppm), but no significant effects were observed with
1093 respect to liver weights. Lung congestion and kidney swelling were the only findings
1094 among the three animals that died at 1,517 mg/m³ (376 ppm) or higher (Carpenter *et*
1095 *al.*, 1956).

1096
1097 Several experiments in dogs were performed by Carpenter *et al.* (Carpenter *et al.*,
1098 1956). In one experiment, Basenji dogs from the same litter (n = 1/sex/group; age not
1099 stated) were exposed to EGBE at 0 or 966 mg/m³ (0 or 200 ppm) for 31 days. RBC
1100 osmotic fragility, compared to similar control dogs, increased slightly (not statistically
1101 significant) in the EGBE-exposed male and female.

1102
1103 A separate inhalation experiment by the same authors, exposed male and female wire-
1104 haired terrier littermates (n = 1/sex; age = 8 months) to EGBE at 483 mg/m³ (100 ppm)
1105 for 90 days. Hematological parameters were tested before exposure, for use as the
1106 baseline control, and after 90 days of exposure. Midway through the 90-day exposure,
1107 transient doubling of the leucocyte count was observed in both dogs. By the end of the
1108 exposure period, the leucocyte count in the female returned to baseline, while that in the
1109 male remained 50% higher than the pre-exposure level. Hct values in males decreased
1110 from 43% packed RBC volume before the first exposure to 34.5% after 90-days
1111 exposure.

1112
1113 In high-exposure, short-term, repeated inhalation experiments, two Basenji hybrid dogs
1114 (n = 1/sex) were exposed to EGBE at 1,860 mg/m³ (385 ppm) for 27 – 28 exposures.
1115 No controls were used. Both dogs exhibited nasal and ocular infection, generalized
1116 weakness, apathy, anorexia, emesis and death following the 8th (female) and 28th
1117 (male) exposures. It was of note that in an RBC osmotic fragility test using varying
1118 degrees of saline concentration, the fragility value of the male dog RBCs reached a
1119 maximum of 0.54-0.42% saline (saline concentrations eliciting initial and complete
1120 hemolysis, respectively) in 7 days and fell to 0.32-0.20% saline after 27 days. The
1121 authors stated this demonstrated that “all susceptible RBCs had been removed from

1122 this animal's blood stream" (Carpenter *et al.*, 1956). Although RBC fragility was not
1123 discussed for the female, it was reported that she exhibited severe hemorrhage of the
1124 lung, and congestion of the lung, kidneys and liver.

1125
1126 Two monkeys (n = 1/sex; age and strain not stated) were also exposed to 483 mg/m³
1127 (100 ppm) EGBE for 90 days. Transient RBC osmotic fragility was observed in both
1128 monkeys, with a greater response in females versus males. However, by the end of the
1129 exposure period, RBCs returned to "normal." The authors did not mention controls.
1130 Pulmonary tuberculosis was also found in both monkeys at autopsy, at a level that may
1131 have obscured EGBE-related effects. Tuberculosis has been shown to contribute to
1132 decreased RBC osmotic resistance (Marks *et al.*, 2002; Reddy *et al.*, 2012). However,
1133 no other noteworthy histopathological findings were reported. A separate study with one
1134 rhesus monkey (age not stated) exposed to 1,014 mg/m³ (210 ppm) EGBE for 30 days
1135 resulted in transiently increased RBC fragility (RBCs returned to baseline overnight.), a
1136 quadrupled level of plasma fibrinogen, and a 50% decreased RBC count and Hgb level
1137 after the 4th, 14th, and 30th exposure, respectively. Emesis was observed four times
1138 during the latter part of the exposure period, and a suggestion of pulmonary tuberculosis
1139 was reported at autopsy. In this study, pre-exposure hematological values served as
1140 controls (Carpenter *et al.*, 1956).

1141
1142 In a 90-day inhalation experiment by Dodd *et al.* (1983), Fischer 344 rats (16 rats/sex/
1143 group; 6 – 7 weeks old) were exposed for 13 weeks (6 hrs/day, 5 days/wk) to EGBE at
1144 target concentrations of 0, 24, 121, or 372 mg/m³ (0, 5, 25, or 77 ppm, respectively). A
1145 subset of six rats/sex/group was killed after 6 weeks of exposure for hematologic
1146 evaluation only. Significantly decreased RBC (13% below control, $p < 0.01$) and slightly
1147 decreased Hgb (4.5% below control, not statistically significant) concentrations were
1148 reported, accompanied by increased MCH (11% above control) in 372 mg/m³- (77 ppm)
1149 exposed females after 6 weeks. At the end of the exposure period, RBC and MCH
1150 levels in these females were still significantly different from control (7% lower; $p < 0.01$,
1151 and 4% higher; $p < 0.001$, respectively). The only significant hematological finding in
1152 males was a 5% decrease in MCH relative to controls, which occurred in the 372 mg/m³
1153 (77 ppm) exposed group. The severity of RBC depression in this study was not
1154 increased compared to the 9-day study (discussed in Section 5.3.2). There were no
1155 significant biological effects in rats exposed subchronically at the 24 mg/m³ (5 ppm)
1156 EGBE concentration. Therefore, NOAEL and LOAEL values of 121 and 372 mg/m³ (25
1157 and 77 ppm), respectively, are appropriate for anemia in male and female rats from this
1158 study.

1159
1160 Chronic/subchronic EGBE toxicity studies by Carpenter *et al.* (1956) and Dodd *et al.*
1161 (1983) are summarized in Table 7.

1162 **Table 7. Summary of chronic/subchronic EGBE inhalation studies by Carpenter et**
 1163 **al. (1956) and Dodd et al. (1983).**

Reference	Species	Exposure	Results
Carpenter <i>et al.</i> (1956) ^a	Male mice n = 10-15/group	0, 541, 966, or 1932 mg/m ³ (0, 112, 200, or 400 ppm) for 30 –90 days	Transient RBC osmotic fragility in all EGBE-exposed groups. Transient hemoglobinuria and liver weight changes at 1932 mg/m ³ (400 ppm).
	Rats n= 15/sex/group	0, 261, 517, 981, 1517, or 2087 mg/m ³ (0, 54, 107, 203, 314, or 432 ppm) for 30 days	RBC osmotic fragility in all EGBE-exposed groups. At 517 mg/m ³ (107 ppm), ↑ kidney and liver weights. At ≥980 mg/m ³ (203 ppm), hemoglobinuria, ↑ liver weights. Deaths at ≥1517 mg/m ³ (314 ppm).
	Male guinea pigs n = 10/group	0, 261, 517, 981, 1517, or 2386 mg/m ³ (0, 54, 107, 203, 376, or 494 ppm) for 30 days	No effect on RBC hemolysis. ↑ kidney weights at ≥517 mg/m ³ (≥107 ppm). Lung congestion and kidney swelling in 3 animals that died at ≥1,517 mg/m ³ (≥376 ppm).

1164 Legend: Hct – Hematocrit; RBC – Red blood cell; WBC – White blood cell (leukocyte).
 1165 ^aAnimals were exposed 7 hrs/day, 5 days/wk for up to 90 days.

1166

1167 **Table 7. Summary of chronic/subchronic EGBE inhalation studies by Carpenter et**
 1168 **al. (1956) and Dodd et al. (1983) (continued).**

Carpenter et al. (1956) ^a	Dogs n = 1/sex/group	0 or 966 mg/m ³ (0 or 200 ppm) for 31 days	RBC osmotic fragility (not statistically significant)
	Dogs n = 1/sex	483 mg/m ³ (100 ppm) for 90 days	↑ WBCs in both dogs midway through the exposure period, with the female's returning to baseline and the male's remaining ~50% higher at the end of exposure. In males, ↓ Hct after 90-days.
	Dogs n = 1/sex	1859.55 mg/m ³ (385 ppm) for 27 – 28 days	In both dogs, nasal and ocular infection, generalized weakness, apathy, anorexia, emesis and death. Temporally variable RBC osmotic fragility in the male.
	Monkeys n = 1/sex	483 mg/m ³ (100 ppm) for 90 days	Transiently ↑ RBC osmotic fragility. Pulmonary tuberculosis.
	Monkey n = 1	1014.3 mg/m ³ (210 ppm) EGBE for 30 days	Emesis, ↑ plasma fibrinogen, ↓ RBCs, ↓ Hgb, and transient RBC fragility at various timepoints. Suggestion of pulmonary tuberculosis
Dodd et al. (1983)	Rats n=16/sex/group	0, 24, 121, or 372 mg/m ³ (0, 5, 25, or 77 ppm) for 13 weeks (6 hrs/day, 5 days/wk)	↓ RBCs and Hgb, and ↑ MCH in 372 mg/m ³ - (77 ppm-) exposed females after 6 weeks. RBC and MCH responses remained until the end of the exposure period, but decreased in magnitude. In males, ↓ MCH at the highest exposure concentration.

1169 Legend: Hgb – Hemoglobin; MCH – Mean corpuscular hemoglobin; RBC – Red blood cell;

1170 ^aAnimals were exposed 7 hrs/day, 5 days/wk for up to 90 days.

1171
 1172 Subsequently, NTP (2000) conducted a 14-week whole-body EGBE inhalation exposure
 1173 study in Fischer 344 rats and B6C3F₁ mice. Exposure (6 hrs/day, 5 days/wk) to 150,
 1174 302, 604, 1208, or 2415 mg/m³ (31, 62.5, 125, 250, or 500 ppm) EGBE resulted in
 1175 clinical findings that included abnormal breathing, pallor, red urine stains, nasal and eye
 1176 discharge, lethargy, and increased salivation and/or lacrimation primarily at the three
 1177 highest concentrations in rats, and at the highest concentration in mice. The most

1178 pronounced effect was concentration-related hemolytic anemia in male rats and mice
1179 exposed to 604 mg/m³ (125 ppm) or above and, to a greater extent, in all exposed
1180 groups of female rats and mice. Exposure-related increases in the incidences of
1181 forestomach inflammation and epithelial hyperplasia, bone marrow hyperplasia (rats
1182 only), Kupffer cell pigmentation of the liver, splenic hematopoietic cell proliferation, and
1183 renal tubule pigmentation were observed in male and/or female rats and mice surviving
1184 to the end of the study. The latter three effects were secondary to red cell hemolysis
1185 and regenerative anemia, with female rats showing the greatest sensitivity. Statistically
1186 significant increases in Kupffer cell pigmentation and bone marrow hyperplasia were
1187 apparent in female rats at concentrations as low as 302 mg/m³ (62.5 ppm).

1188
1189 In the following NTP 2-year study, Fischer 344 rats and B6C3F₁ mice were exposed to
1190 0, 151 (rats only), 302, 604, or 1,208 (mice only) mg/m³ (0, 31.2, 62.5, 125, and 250
1191 ppm) EGBE via inhalation for 6-hrs/day, 5 days/wk. In rats, anemia occurred in females
1192 starting at 151 mg/m³ (31.2 ppm), and in males starting at 302 mg/m³ (62.5 ppm). The
1193 anemia was considered mild and persisted with no apparent progression or amelioration
1194 of severity from 3 months to 12 months (final blood collection). Incidences of hyaline
1195 degeneration of the olfactory epithelium were increased in 302 or 604 mg/m³ (62.5 or
1196 125 ppm) groups of both sexes, although the severity of this lesion was minimal
1197 (incidence presented in Table 8).

1198
1199 In mice, survival of males was reduced at 604 and 1,208 mg/m³ (125 and 250 ppm)
1200 concentrations (NTP, 2000). Anemia was observed following 3, 6, or 12 months of
1201 exposure at 604 or 1,208 mg/m³ (125 or 250 ppm) in both male and female mice.
1202 Incidences of forestomach ulcer and hyperplasia, and nasal hyaline degeneration of
1203 olfactory and respiratory epithelia were increased in all exposed female mice. In male
1204 mice, there was an increased incidence of forestomach ulcer at 604 mg/m³ (125 ppm).
1205 All groups of exposed males showed increased incidence of forestomach hyperplasia. A
1206 mouse urologic infection syndrome was apparent in males, and appeared to be
1207 exacerbated by EGBE exposure at the 604 and 1,208 mg/m³ (125 and 250 ppm)
1208 concentrations. Effects secondary to hemolysis were also observed including splenic
1209 congestion and hemosiderin deposition in Kupffer cells of the liver in both rats and mice
1210 (incidence presented in Table 8). The principal non-cancer toxic endpoints not linked to
1211 RBC hemolysis were nasal olfactory epithelial lesions (hyaline degeneration),
1212 forestomach epithelial hyperplasia, and forestomach ulcers (incidences presented in
1213 Table 8).

1214

1215 **Table 8. Incidence of nasal olfactory epithelial hyaline degeneration, liver Kupffer**
 1216 **cell pigmentation, forestomach epithelial hyperplasia and ulcer in rats and mice**
 1217 **following 2-year EGBE inhalation study (NTP, 2000)**

Endpoints	Exposure Doses mg/m ³ (ppm)					Trend test p-value
	0	151 (31.2)	302 (62.5)	604 (125)	1208 (250)	
Nasal Olfactory Epithelial Hyaline Degeneration						
Male Rats	13/48	21/49	23/49*	40/50***	-----	<0.0001
Female Rats	13/50	18/48	28/50**	40/49***	-----	<0.0001
<i>Total Rats</i>	<i>26/98</i>	<i>39/97*</i>	<i>51/99***</i>	<i>80/99***</i>	-----	<i><0.0001</i>
Male Mice	1/50	-----	2/50	3/48	1/48	0.5074
Female Mice	6/50	-----	14/50*	11/49	12/50	0.1532
<i>Total Mice</i>	<i>7/100</i>	-----	<i>16/100*</i>	<i>14/97</i>	<i>13/98</i>	<i>0.1743</i>
Liver Kupffer Cell Pigmentation						
Male Rats	23/50	30/50	34/50*	42/50***	-----	<0.0001
Female Rats	15/50	19/50	36/50***	47/50***	-----	<0.0001
<i>Total Rats</i>	<i>38/100</i>	<i>49/100</i>	<i>70/100***</i>	<i>89/100***</i>	-----	<i><0.0001</i>
Male Mice	0/50	-----	0/50	8/49**	30/49***	<0.0001
Female Mice	0/50	-----	5/50*	25/49***	44/50***	<0.0001
<i>Total Mice</i>	<i>0/100</i>	-----	<i>5/100*</i>	<i>33/98***</i>	<i>74/99***</i>	<i><0.0001</i>
Forestomach Epithelial Hyperplasia						
Male Mice	1/50	-----	7/50*	16/49***	21/48***	<0.0001
Female Mice	6/50	-----	27/50***	42/49***	44/50***	<0.0001
<i>Total Mice</i>	<i>7/100</i>	-----	<i>34/100***</i>	<i>58/98***</i>	<i>65/98***</i>	<i><0.0001</i>
Forestomach Ulcer						
Male Mice	1/50	-----	2/50	9/49**	3/48	0.1324
Female Mice	1/50	-----	7/50*	13/49***	22/50***	<0.0001
<i>Total Mice</i>	<i>2/100</i>	-----	<i>9/100*</i>	<i>22/98***</i>	<i>25/98***</i>	<i><0.0001</i>

1218 Note: Statistically significant differences compared to the control group were measured with the Fisher
 1219 exact test. *p < 0.05, **p < 0.01, ***p < 0.001 (statistical analysis performed by OEHHHA). Trend test
 1220 incorporated in BMDS software (version 2.6) (EPA, 2015).

1221 Chronic contact irritation by EGBE, and in particular the EGBE metabolites BAA and 2-
 1222 butoxyacetaldehyde, has been implicated in the damage to the forestomach in mice
 1223 (Green *et al.*, 2002; Poet *et al.*, 2003). Metabolism of EGBE by ADH to BAA in the

1224 rodent forestomach is thought to play a role in the development of epithelial hyperplasia
1225 and ulcers. A similar mechanism of action in rat and mouse nasal olfactory epithelium
1226 also likely occurs (Gift, 2005). Intravenous, oral, and inhalation studies have shown
1227 accumulation of EGBE and BAA in the mouse forestomach (Boatman *et al.*, 2004).
1228 Thus, systemic blood circulation, grooming of contaminated fur, and clearance of mucus
1229 from the respiratory tract are all factors in the accumulation of EGBE in the forestomach
1230 (NTP, 2000). For the development of the chronic REL, we focus on the respiratory
1231 endpoints (upper respiratory tract irritation and nasal hyaline degeneration of the
1232 olfactory epithelium) due to their greater relevance for human exposure. Details for
1233 selecting the endpoint to derive the 8-hour and chronic RELs for EGBE are provided in
1234 Section 8.2.

1235

1236 7. Developmental and Reproductive Effects

1237

1238 EGBE is not listed as a developmental or reproductive toxicant under California
1239 Proposition 65 (OEHHA, 2016). Unlike some structurally-similar glycol ethers listed
1240 under Proposition 65, EGBE exposure did not cause significant effects in the male
1241 reproductive organs, including testes (Dodd *et al.*, 1983; NTP, 2000). Quantitative
1242 Structure Toxicity Relationship (QSTR) models have also predicted that EGBE has no
1243 developmental toxicity (Ruiz *et al.*, 2011).

1244

1245 The following studies in animals have been conducted to investigate the effects of
1246 EGBE on the female reproductive system and the embryo.

1247

1248 In an inhalation study, EGBE was vaporized at doses of 0, 725, 966 mg/m³ (0, 150, 200
1249 ppm) and administered to approximately 15 pregnant SD rats in each exposure group
1250 (except control; n = 34) for 7 hrs/day on gestational days (GD) 7 – 15. Dams were
1251 sacrificed on GD 20, and data were analyzed on a litter basis. Some hematuria was
1252 observed on the first day of exposure in the group exposed to 966 mg/m³ (200 ppm)
1253 EGBE, but no increase in congenital defects was observed at that concentration. No
1254 other adverse effects were observed in the dams or the pups in either treatment group.
1255 The number of resorptions and fetal weights, and the incidence of malformations did not
1256 differ from the controls (Nelson *et al.*, 1984).

1257

1258 In another inhalation study of developmental toxicity, female Fisher 344 rats (n =
1259 36/group) and female New Zealand White rabbits (n = 24/group) were exposed to
1260 EGBE vapors at 0, 121, 242, 483, or 966 mg/m³ (0, 25, 50, 100, or 200 ppm,
1261 respectively) for 6 hrs/day on GD 6-15 for rats and GD 6-18 for rabbits (Tyl *et al.*, 1984).
1262 In rats, maternal toxicity included evidence of anemia, and significantly ($p < 0.05$)
1263 decreased BW gain and food consumption relative to controls in the 483 and 966 mg/m³

1264 (100 and 200 ppm) groups. Embryotoxicity included, at the highest concentration (966
1265 mg/m³; 200 ppm), significantly decreased numbers of viable implantations and percent
1266 live fetuses per litter, and significantly increased numbers of totally resorbed litters. At
1267 483 and 966 mg/m³ (100 and 200 ppm), significantly delayed skeletal ossification in
1268 offspring was observed. In rabbits, toxicity included maternal deaths, spontaneous
1269 abortions and significantly decreased BW at 966 mg/m³ (200 ppm) relative to control,
1270 while hematological parameters were normal. Embryotoxicity was indicated by
1271 significantly reduced gravid uterine weight and a significant concomitant reduction in
1272 total and viable implantations at 966 mg/m³ (200 ppm).

1273
1274 In a two-generation reproductive toxicity study, performed in accordance with NTP's
1275 Continuous Breeding Protocol, 11-week old outbred Swiss CD-1 mice of both sexes (n=
1276 13-20/sex/group) were exposed to EGBE in drinking water available *ad libitum* at
1277 concentrations of 0 (distilled water), 0.5, 1, or 2% (weight/vol) (Heindel *et al.*, 1989;
1278 Heindel *et al.*, 1990; EPA, 2010). Using average fluid consumption and mean BW data
1279 from adult male mice, the authors estimated that at these concentrations, animals
1280 received 0, 700, 1300, or 2100 mg EGBE/kg BW-day, respectively. However, these
1281 data were not shown, and neither were corresponding data for adult females or weaned
1282 but sexually immature offspring, so it was unclear to OEHHA that the dose estimates
1283 were accurate for all animals. The study consisted of four separate, step-wise
1284 experiments including a dose-setting phase (not discussed here), a continuous breeding
1285 phase, a crossover breeding phase in which exposures were halted, and an offspring
1286 assessment phase, as prescribed in the NTP protocol. Results showed that EGBE
1287 exposure produced significant ($p < 0.05$) changes in BWs and organ weights relative to
1288 control. Decreased BWs and increased kidney and/or liver weights were observed in
1289 parental mice and their offspring at non-lethal doses (nominal 700 mg/kg BW-day). At
1290 the same time, this reproductive study had several issues which ultimately undermined
1291 the ability of the authors to make solid conclusions regarding the reproductive and
1292 developmental toxicity of EGBE. These included, but were not limited to:

- 1293
- 1294 1) two out of three EGBE exposure doses that resulted in excessive maternal
1295 toxicity;
 - 1296 2) no reported gross, histopathological, or weight analysis of female reproductive
1297 organs despite signs that they appeared more sensitive than males (which was
1298 confirmed in the crossover breeding phase); and
 - 1299 3) limited assessment of biological endpoints from offspring that died before birth or
1300 lived through the end of the offspring reproductive assessment phase.

1301 Deaths in mid- and high-dose parental (filial generation 0; F₀) females in the continuous
1302 breeding phase equated to mortality of 30% (6/20) and 65% (13/20), respectively. In the
1303 crossover breeding phase, 7/20 females previously exposed at 1,300 mg/kg BW-day

1304 appeared to have died prematurely. This represents a 35% mortality in the group,
1305 similar to that noted in the continuous breeding experiment. In contrast, no deaths were
1306 reported in F₀ males. These results suggested that the nominal 1,300 and 2,100 mg/kg
1307 BW/day doses may have been too high for assessing reproductive/developmental
1308 toxicity of EGBE in F₀ mice and their offspring. According to US EPA guidelines for
1309 developmental toxicity assessments (1991), the high dose should produce no more than
1310 10% mortality in dams; otherwise, resulting responses [in dams and/or offspring] may
1311 be difficult to interpret and of limited value.

1312
1313 In an oral gavage study (Wier *et al.*, 1987), random-bred, virus-antibody-free CD- 1
1314 pregnant mice were exposed to EGBE at doses of 0, 350, 650, 1,000, 1,500, and 2,000
1315 mg/kg-day (6 animals per group) during GD 8-14 and sacrificed at GD18. Hemolytic
1316 effects in the dams were observed starting at 650 mg/kg-day. At 1,500 mg/kg-day and
1317 2,000 mg/kg-day, the maternal mortality rate was 3/6 and 6/6 (50% and 100%),
1318 respectively. Increased resorption rates ($p \leq 0.05$, compared to the control) and a
1319 reduced number of viable fetuses were observed at exposures of 1,000 and 1,500
1320 mg/kg-day. Four (all in the same litter) of 43 fetuses (9%) at 1,000 mg/kg-day and one
1321 of 25 fetuses (4%) at 1,500 mg/kg-day had cleft palates. For this study, the NOAEL for
1322 maternal toxicity was 350 mg/kg-day and the NOAEL for developmental toxicity was
1323 650 mg/kg-day (Wier *et al.*, 1987; SCCP, 2007). Since only some of the offspring of
1324 pregnant mice exposed to very large doses of EGBE by gavage had cleft palates, it was
1325 concluded by EPA (2010) and ATSDR (1998) that EGBE was not significantly toxic to
1326 the reproductive organs of adult males or females, or to the developing fetuses of
1327 laboratory animals.
1328

1329 **8. Derivation of Reference Exposure Levels**

1330

1331 **8.1 EGBE Acute Reference Exposure Level**

1332

	<i>Study</i>	Carpenter <i>et al.</i> , 1956
	<i>Study population</i>	2 to 4 human subjects per study
	<i>Exposure method</i>	Whole body exposure, 474, 546 and 942 mg/m ³ (98, 113 and 195 ppm)
	<i>Exposure duration</i>	8 hours, 474 and 942 mg/m ³ (98 and 195 ppm) in chamber or 4 hours, 546 mg/m ³ (113 ppm) in room
	<i>Critical effects</i>	Subjective ocular and respiratory irritation
	<i>LOAEL</i>	473 mg/m ³ (98 ppm)
	<i>NOAEL</i>	None
	<i>Time- adjusted exposure</i>	None
	<i>Human equivalent concentration (HEC)</i>	None
	<i>LOAEL uncertainty factor (UF_L)</i>	10
	<i>Subchronic uncertainty factor (UF_S)</i>	N/A
	<u><i>Interspecies uncertainty factor</i></u>	
	<i>Toxicokinetic (UF_{A-k})</i>	1
	<i>Toxicodynamic (UF_{A-d})</i>	1
	<u><i>Intraspecies uncertainty factor</i></u>	
	<i>Toxicokinetic (UF_{H-k})</i>	1 (site of action; no systemic effects)
	<i>Toxicodynamic (UF_{H-d})</i>	10 (potential asthma exacerbation in children; small sample size)
	<i>Cumulative uncertainty factor</i>	100
	<i>Reference Exposure Level</i>	4700 µg/m ³ (1000 parts per billion (ppb))

1333

1334 RELs are based on the most sensitive and relevant health effects reported in the
 1335 medical and toxicological literature. Acute RELs are levels at which infrequent one-hour
 1336 exposures are not expected to result in adverse health effects (OEHHA, 2008). The
 1337 acute EGBE REL is based on three whole-body human exposure studies of small
 1338 sample size (n=2 to 4) (Carpenter *et al.*, 1956). These studies identified a LOAEL of
 1339 473 mg/m³ (98 ppm), based on subjective sensory irritation. The response at 473 mg/m³
 1340 (98 ppm) was reported to be nearly as great as that elicited at 942 mg/m³ (195 ppm),
 1341 which included immediate onset of nasal and throat irritation, followed by ocular
 1342 irritation. Supporting studies (Johanson, 1986; Johanson *et al.*, 1986a; Jones *et al.*,
 1343 2003b) in which volunteers were exposed to lower concentrations of 97 mg/m³ (20 ppm)
 1344 and 237 mg/m³ (49 ppm) examined some physiological responses during exposure but
 1345 did not find obvious health effects. However, these studies were primarily toxicokinetic

1346 studies that were not designed for a detailed analysis of acute sensory irritant effects or
1347 for a dose-response assessment (*i.e.*, both studies used a single dose exposure
1348 concentration).

1349
1350 For the acute REL derivation, the critical effects of trigeminal-mediated sensory irritation
1351 are usually a concentration-dependent response. Thus, no time-adjustment to the
1352 exposure was applied. Since these studies were conducted in humans, no interspecies
1353 UFs are required. However, a UF_L of 10 to account for extrapolation from a LOAEL to a
1354 NOAEL was applied.

1355
1356 The toxicokinetic component of the intraspecies UF_{H-k} is assigned a value of one.
1357 Chemicals that result in eye and upper respiratory sensory irritation are not predicted to
1358 be substantially different in children compared to adults when dosimetric adjustments
1359 are made (OEHHA, 2008). An intraspecies toxicokinetic of one ($UF_{H-k} = 1$) is applied to
1360 acute sensory irritants if metabolic processes do not contribute to intraspecies
1361 variability. No systemic toxicity from metabolites (primarily BAA-related hemolysis) was
1362 observed during acute human exposures conducted by Carpenter *et al.*. *In vitro* studies
1363 have shown RBCs from children are similarly resistant to BAA-induced hemolysis as
1364 RBCs from adults.

1365
1366 The toxicodynamic component of the intraspecies UF_{H-d} is assigned a value of 10 for
1367 potential exacerbation of asthma in sensitive subpopulations. In addition, the small
1368 sample size in the critical study ($n = 3 - 4$) warrants a larger intraspecies uncertainty
1369 factor. Epidemiological studies suggest cleaning products, including those products that
1370 utilize EGBE, increase the likelihood of an asthmatic episode in susceptible individuals
1371 (Bello *et al.*, 2009; Bello *et al.*, 2013; Fromme *et al.*, 2013; Gerster *et al.*, 2014).
1372 Although there is no direct evidence that EGBE by itself can exacerbate asthma, the
1373 respiratory irritation induced by inhaled EGBE may lead to an asthmatic reaction,
1374 particularly in children who may experience irritant-induced asthma; OEHHA views
1375 asthma as a more serious health problem in children than in adults (OEHHA, 2001).
1376 Thus, the cumulative UF is 100 and the acute REL is 4.7 mg/m^3 (1 ppm).

1377
1378 An acute animal exposure study was not chosen for the derivation of the acute REL.
1379 The LOAEL and NOAEL for the most sensitive endpoint, RBC hemolysis, in a subacute
1380 EGBE inhalation rat study (9 days total exposure; 5 days, two days of no exposure, then
1381 4 days, 6 hrs/day) were 415 and 97 mg/m^3 (86 ppm and 20 ppm), respectively (Dodd *et al.*,
1382 1983). This data set was not used to develop an acute REL because humans tend
1383 to be resistant to the hematological effects of EGBE and, as discussed above, the use
1384 of human toxicity data to develop a REL is preferred when possible over animal data

1385 (OEHHA, 2008). Further, the multi-day exposure study design is not particularly
1386 amenable to estimating an acute REL, which is meant for infrequent 1-hour exposures.
1387

1388 More recent human exposure studies (primarily Jones *et al.* (2003) and Johanson *et al.*
1389 (1986a)) were also not used for derivation of the acute REL. There are several reasons
1390 why OEHHA staff decided not to use these studies as the point of departure (POD) for
1391 the acute REL derivation:
1392

- 1393 1. Physiological factors (e.g., breathing rate, pulse rate, skin surface temperature
1394 and skin resistance) may be less sensitive endpoints compared to subjective
1395 responses. These may overestimate the NOAEL and miss the most sensitive
1396 endpoint (*i.e.*, sensory irritation).
1397
- 1398 2. The toxicokinetic studies, mainly Jones *et al.* (2003) and Johanson *et al.* (1986a),
1399 used only one exposure concentration and produced no apparent adverse effects
1400 on the human subjects. As such, they are free-standing NOAELs. Our revised
1401 Noncancer REL TSD guidance (OEHHA, 2008) notes that, “*OEHHA may use a*
1402 *NOAEL without an associated LOAEL identified in the same study (a free-*
1403 *standing NOAEL), but only if there are no other suitable studies, and so long as*
1404 *the overall health hazard data (including any case reports or studies with shorter*
1405 *durations) for that substance are consistent with the NOAEL study.”* In other
1406 words, OEHHA guidance does not recommend using a NOAEL and a LOAEL
1407 from different studies, or a free-standing NOAEL as the basis of a REL if a more
1408 suitable study (*e.g.*, a study with a LOAEL) exists. Thus, we base the proposed
1409 acute REL on the LOAEL of 473 mg/m³ (98 ppm) determined in the Carpenter *et*
1410 *al.* (1956) study.
1411
- 1412 3. The studies that have free-standing NOAELs have small sample sizes,
1413 particularly the Jones *et al.* study (n=4). As noted in the OEHHA Noncancer TSD
1414 ((OEHHA, 2008), page 39), “*A NOAEL could be associated with a substantial (1-*
1415 *20%) but undetected incidence of adverse effects among the exposed*
1416 *population. This is so because only a subset of individuals from the population*
1417 *has been observed and because the experiment may not have been designed to*
1418 *observe all adverse effects associated with the substance.”* Therefore, single-
1419 dose studies exposing only a few human subjects may easily miss adverse
1420 effects that would be apparent in larger groups of exposed individuals.

1421
1422 The Carpenter *et al.* (1956) study, upon which the acute REL is based, does have
1423 several limitations compared to the more recent toxicological studies that were
1424 considered. These limitations include 1) unknown purity of the EGBE used to generate

1425 the exposure atmosphere; 2) potential presence of other irritant gases in the exposure
1426 chamber; 3) use of a gas interferometer to estimate EGBE exposure concentrations;
1427 and 4) unknown variability in the EGBE exposure concentrations over time.

1428

1429 The purity of the EGBE used in the human and animal exposures was not stated by
1430 Carpenter *et al.* (1956), so the quantity and types of impurities in the EGBE solution are
1431 unknown. Toxicological and pharmacokinetic studies conducted since the 1980s
1432 generally used EGBE with a purity of >99%. Impurities in purified EGBE may include 2-
1433 butoxyethoxyethanol ($\leq 0.3\%$ w/w), 1,2-ethanediol ($\leq 0.3\text{-}0.5\%$ w/w), 1-butanol ($\leq 0.1\text{-}$
1434 0.2% w/w) and water ($< 0.1\text{-}0.2\%$ w/w) (EU, 2006). Some of these impurities may also
1435 be sensory irritants. Current EGBE preparations frequently include an additive (0.008-
1436 0.012% w/w 2,6-bis(1,1-dimethylethyl)-4-methylphenol) to prevent the formation of
1437 peroxides. If no additive was in the formulation used by Carpenter *et al.*, some level of
1438 peroxides may have been present in the test substance.

1439

1440 Although EGBE exposure can result in eye and respiratory tract irritation, the
1441 contribution of other potentially irritant gases in the Carpenter *et al.* (1956) study is
1442 possible. Unfortunately, case reports of EGBE sensory irritation resulting from
1443 occupational exposure (Kullman, 1987; Raymond *et al.*, 1998) are complicated by
1444 unknown exposure concentrations and potential co-exposure to other irritating gases.
1445 There are currently no other controlled human studies that estimated air concentrations
1446 of EGBE that resulted in sensory irritation. In rodent studies in which the purity of the
1447 EGBE used was stated (reagent quality or >99% purity), sensory irritation was apparent
1448 in the form of abnormal breathing, eye and nasal discharge (NTP, 2000) and respiratory
1449 depression (Kane *et al.*, 1980).

1450

1451 Another potential limitation of the Carpenter *et al.* (1956) study is the method of
1452 analysis, a gas interferometer, used to estimate the EGBE concentration in exposure
1453 chambers. Interferometers have a number of different applications, but in gas
1454 interferometry the instrument can measure the difference in refractivity between a
1455 standard gas of known refractivity and a mixture of some contaminating gas or vapor
1456 (Patty, 1939). With knowledge of the refractivities of both the standard gas (*i.e.*, usually
1457 air without airborne contaminants) and the contaminating vapor (*i.e.*, EGBE, in this
1458 case), the concentration of a contaminant gas can be estimated. Drawbacks with this
1459 instrumentation include high price, difficulties of calibration, and necessity for gas
1460 concentrations to be greater than the expected measurement error for a particular gas.
1461 Advantages for the use of gas interferometers include quick analysis of gas
1462 concentrations and accuracy (once calibration of the instrument has been mastered by
1463 the recorder). More recently, other forms of analysis (infrared spectrophotometry; flame
1464 ionization detector; gas chromatography) are used for measurement of EGBE in

1465 exposure chambers. Gas interferometry has some current use in the form of Fourier
1466 transform infrared spectroscopy for the measurement of toxic gases and vapors in the
1467 environment and in the workplace (Xiao and Levine, 1993; Schafer *et al.*, 1994).

1468
1469 Even if it is assumed that the Carpenter *et al.* (1956) study was not hindered by the use
1470 of a noise-limited and difficult-to-calibrate analytical device, the study is still limited by
1471 unknown variability of EGBE chamber concentrations. The EGBE concentrations were
1472 analyzed four times during each exposure, but standard curves and the chamber
1473 measurement variability were not presented in the report.

1474
1475 Given the limitations of the Carpenter *et al.* (1956) study, we compared the inhalation
1476 toxicity of the EGBE used by Carpenter *et al.* against other toxicity studies in which
1477 better analysis of gas concentrations and EGBE purity (*i.e.*, >99%) are presented.
1478 Comparisons are presented below in Table 9.

1479
1480 In the Carpenter *et al.* (1956) study, the critical hematological endpoint examined was
1481 hemoglobinuria. The NOAEL and LOAEL for this endpoint in both rats and mice were
1482 about 483 and 966 mg/m³ (100 and 200 ppm), respectively, with 7-hour acute exposure
1483 to EGBE (Table 9). Similar values were obtained with repeated exposures (7 hrs/day, 5
1484 days/wk) for up to 30 days. However, the test for osmotic fragility of RBCs with a range
1485 of saline solution concentrations following the acute exposures resulted in a lower
1486 NOAEL and LOAEL of 155 and 299 mg/m³ (32 and 62 ppm), respectively.

1487
1488 In the rodent studies by Tyl *et al.* (1984), NTP (2000) and Dodd *et al.* (1983) the critical
1489 endpoint was primarily hemolytic anemia, a hematological endpoint determined in blood
1490 samples. Repeated exposure protocols yielded NOAELs and LOAELs for this endpoint
1491 in the range of 121 – 302 mg/m³ (25 - 62.5 ppm) and 372 – 604 mg/m³ (77 - 125 ppm),
1492 respectively. In these studies, a number of blood parameters were usually affected,
1493 including reduced RBC counts and reduced Hct.

1494

1495 **Table 9. Comparison of NOAELs and LOAELs for hematological endpoints in**
 1496 **rodent EGBE exposure studies**

Study	Species EGBE Exposure Duration	Hematological Endpoint	NOAEL mg/m ³ (ppm)	LOAEL mg/m ³ (ppm)
Carpenter <i>et al.</i> (1956)	Rats/mice 7 hrs	Hemoglobinuria	483 – 517 (100 -107)	966 – 980 (200 -203)
	Rats 7 hrs/day x 5 days/wk x 30 times	Hemoglobinuria	517 (107)	980 (203)
	Mice 7 hrs/day x 5 days/wk x 30 times	Hemoglobinuria	541 (112)	966 (200)
	Rats 4 hrs	RBC osmotic fragility	155 (32)	299 (62)
Tyl <i>et al.</i> (1984)	Rats 6 hrs/day on days 6-15 of gestation	Hemolytic anemia	242 (50)	483 (100)
		Hemoglobinuria	242 (50)	483 (100)
		RBC osmotic fragility	966 (200)	nd
NTP (2000)	Rats/mice 6 hrs/day, 5 days/wk for 14 wks	Hemolytic anemia	302 (62.5)	604 (125)
Dodd <i>et al.</i> (1983)	Rats 6 hrs/day, 5 days/wk for 9 days	Hemolytic anemia	97 (20)	415 (86)
		Hemolytic anemia	121 (25)	372 (77)
	Rats 6 hrs/day, 5 days/wk for 90 days	RBC osmotic fragility	121 (25)	372 (77)

1497

1498 The 2-fold higher NOAELs and LOAELs mostly observed in the Carpenter *et al.* (1956)
 1499 study compared to the more recent studies may, in part, be a result of increased
 1500 sensitivity in measuring hematological endpoints in the later studies. However, lower
 1501 purity of EGBE and/or lower sensitivity of measurement instrumentation could also be
 1502 reasons for the higher NOAEL and LOAEL values of the study by Carpenter *et al.*
 1503 (1956). The relevance of the hematological endpoints for human sensory irritation is

1504 unclear; although one might assume that the LOAEL (and NOAEL) for sensory irritation
1505 may actually occur at lower concentrations using the better methodology applied in later
1506 studies. This discrepancy is addressed using a full 10-fold LOAEL-to-NOAEL
1507 uncertainty factor, although uncertainty factors in general are meant to address these
1508 types of methodological uncertainties.

1509

1510 Basing a REL on a free-standing NOAEL of a different human chamber exposure study
1511 using analytical grade EGBE did not result in an appreciably different value, as
1512 presented below:

1513

1514 For a comparison acute REL, the free-standing NOAEL of 97 mg/m³ (20 ppm) based on
1515 subjective remarks made by volunteers in the Johanson *et al.* (1986a) toxicokinetic
1516 study is used as a POD. This study is better supported than the Jones *et al.* (2003b)
1517 study in which a free-standing NOAEL of 242 mg/m³ (50 ppm) was observed. Unlike the
1518 Jones *et al.* (2003b) study, Johanson *et al.* (1986a) had reported that “none of the
1519 subjects complained of or showed any signs of adverse effects that could be related to
1520 the exposure to 2-butoxyethanol”; although the odor of EGBE should have been
1521 apparent to the subjects (but was not described). Also, Johanson *et al.* (1986a) had a
1522 greater number of subjects participating in their study (n=7) compared to the Jones *et al.*
1523 *et al.* (2003b) study (n=4). No time extrapolation from the 2-hour exposures to 1 hour was
1524 applied since sensory irritation is usually a concentration-dependent response. Applying
1525 the same intraspecies UF = 10 (10 for toxicokinetic UF_{H-k} and 1 for toxicodynamic UF_{H-d})
1526 to the POD as that used for the acute REL derivation results in an acute REL of 9.7
1527 mg/m³ (2 ppm), which is approximately twice the REL value of 4.8 mg/m³ (1 ppm) based
1528 on the Carpenter *et al.* (1956) study. Given that the human studies with a single
1529 exposure and small sample size could easily miss an adverse effect, the more health
1530 protective acute REL resulting from the Carpenter *et al.* study was selected.

1531

1532 **8.2 EGBE 8-Hour Reference Exposure Level**

1533 The 8-hour REL is a concentration at or below which adverse noncancer health effects
 1534 would not be anticipated for repeated 8-hour exposures (see Section 6 of the
 1535 Noncancer REL TSD (OEHHA, 2008).

	<i>Study</i>	NTP, 2000
	<i>Study population</i>	Rats (50 animals/group/gender)
	<i>Exposure method</i>	Discontinuous whole-body inhalation exposure to 0, 151, 302, or 604 mg/m ³ (0, 31.2, 62.5, or 125 ppm)
	<i>Critical effects</i>	Nasal hyaline degeneration of olfactory epithelium
	<i>LOAEL</i>	151 mg/m ³ (31.2 ppm)
	<i>NOAEL</i>	Not observed
	<i>BMCL₀₅</i>	39.4 mg/m ³ (8.16 ppm),; Probit model from male and female rats
	<i>Exposure continuity</i>	6 hrs/day, 5 days/wk
	<i>Exposure duration</i>	2 years
	<i>Time-adjusted exposure</i>	14.1 mg/m ³ (2.91 ppm) (= 8.16 ppm x 6/24 x 5/7 x 20/10)
	<i>Human Equivalent Concentration (HEC)</i>	4.93 mg/m ³ (1.02 ppm) (gas with extra-thoracic respiratory effects, RGDR = 0.35)
	<i>LOAEL uncertainty factor</i>	1 (with use of a BMCL ₀₅)
	<i>Subchronic uncertainty factor</i>	1
	<u><i>Interspecies uncertainty factor</i></u>	
	<i>Toxicokinetic (UF_{A-k})</i>	1
	<i>Toxicodynamic (UF_{A-d})</i>	√10
	<u><i>Intraspecies uncertainty factor</i></u>	
	<i>Toxicokinetic (UF_{H-k})</i>	√10
	<i>Toxicodynamic (UF_{H-d})</i>	√10
	<i>Cumulative uncertainty factor</i>	30
	<i>Reference Exposure Level</i>	164 µg/m ³ (34 ppb)

1536 Note: Time-adjusted Exposure: The POD is first adjusted to a 24-hour continuous exposure
 1537 (6/24 hours x 5/7 days per week), then multiplied by 2 (20m³/10m³) to represent an active
 1538 worker breathing half the volume of air breathed in a 24-hour period during an 8-hour work day.
 1539 HEC = Time-adjusted Exposure x the Regional Gas Dose Ratio (RGDR). RGDR = (MV_A/MV_H) /
 1540 (SA_A/SA_H); MV is Minute Volume = inhaled volume x respiratory rate, and SA is surface area for
 1541 the lung region of concern (A and H represent animal and human respectively). Gas with extra-
 1542 thoracic respiratory effects, RGDR = 0.35, MV_A = 0.38 m³/day, MV_H = 14.48 m³/day,
 1543 SA_A = 15 cm², SA_H = 200 cm² (OEHHA, 2008).

1544 In the key study (NTP, 2000), rats and mice subjected to a whole-body inhalation
1545 exposure of 0, 151, 302, or 604 mg/m³ (0, 31.2, 62.5, or 125 ppm) for two years
1546 displayed nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation,
1547 and forestomach epithelial hyperplasia and ulcers in both species. This study was
1548 chosen because it used a lifetime inhalation exposure, and provided the most sensitive
1549 toxicity endpoint not dependent upon hemolytic anemia (Humans are more resistant to
1550 the hematological effects of EGBE compared to rodents).

1551
1552 Exposure doses and related toxicity endpoints are listed in Table 8 of Section 6.3.
1553 Benchmark dose analysis was performed using Benchmark Dose Modeling Software
1554 (BMDS) version 2.6 (EPA, 2015). The calculated BMCL₀₅ values, and corresponding
1555 NOAEL and LOAEL values are listed in Table 10. Because dose-responses were not
1556 noted for nasal hyaline degeneration in male or female mice, or for forestomach ulcers
1557 in male mice, specifically (Table 8), associated BMCL data were excluded from Table
1558 10. We are using the BMCL₀₅ values as the POD for REL derivation. For each endpoint,
1559 the BMCL₀₅ is derived from the models that provided the best visual and statistical fit to
1560 the data, particularly in the low dose region of the dose-response curve where the
1561 BMCL₀₅ resides. Following US EPA guidelines, the model with the lowest Akaike
1562 Information Criterion (AIC) was chosen in instances where various model fits to the data
1563 were similar.

1564 **Table 10: BMCL₀₅, NOAEL and LOAEL values for nasal olfactory epithelial hyaline**
 1565 **degeneration, liver Kupffer cell pigmentation, and forestomach ulcers in rats and**
 1566 **mice, and epithelial hyperplasia in mice exposed to EGBE by inhalation for two**
 1567 **years (NTP, 2000)**

Endpoints	BMCL₀₅ mg/m³ (ppm) (BMD model)	NOAEL mg/m³ (ppm)	LOAEL mg/m³ (ppm)
Nasal Olfactory Epithelial Hyaline Degeneration			
Male rats	39 (8.0) (Probit)	151 (31.2)	302 (62.5)
Female rats	37 (7.6) (Logistic)	151 (31.2)	302 (62.5)
<i>Male and female rats combined</i>	40 (8.2) (Probit)	NE	151 (31.2)
Liver Kupffer Cell Pigmentation			
Male rats	28 (5.7) (Logistic)	151 (31.2)	302 (62.5)
Female rats	56 (11.6) (LogLogistic)	151 (31.2)	302 (62.5)
<i>Male and female rats combined</i>	27 (5.5) (Logistic)	151 (31.2)	302 (62.5)
Male mice	354 (73.2) (LogProbit)	302 (62.5)	604 (125)
Female Mice	181 (37.5) (LogProbit)	NE	302 (62.5)
<i>Male and female mice combined</i>	241 (49.9) (LogProbit)	NE	302 (62.5)
Forestomach Epithelial Hyperplasia			
Male Mice	78 (16.2) (Weibull)	NE	302 (62.5)
Female Mice	47 (9.7) (LogProbit)	NE	302 (62.5)
<i>Male and female mice combined</i>	55 11.4 (Dichotomous-Hill)	NE	302 (62.5)
Forestomach Ulcer			
Female Mice	85 (17.5) (Quantal-linear)	NE	302 (62.5)
<i>Male and female mice combined</i>	127 (26.3) (LogLogistic)	NE	302 (62.5)

1568 Note: BMCL₀₅ is based on dichotomous models (model shown in parenthesis) with best visual and
 1569 statistical fit (EPA, 2015); NE, Not established.

1570

1571 Of the chronic effects noted in rats and mice in Table 10, hyaline degeneration of the
1572 olfactory epithelium is more analogous to what would occur with human exposure to
1573 EGBE than the other lesions. The primary cause of the nasal lesions is likely to be
1574 direct EGBE irritation through the inhalation route (NTP, 2000). We are focusing on the
1575 regional responses/changes in the nose and upper respiratory tract, which is the most
1576 sensitive endpoint, and is more consistent with the acute inhalation effect of EGBE in
1577 humans (Carpenter *et al.*, 1956).

1578
1579 Hyaline degeneration of the olfactory epithelium often appears at increased rates in
1580 aging rats and mice. Other entities establishing health values have based their hazard
1581 assessments on hematological endpoints rather than nasal hyaline degeneration of the
1582 olfactory epithelium in rats (ATSDR, 1998; EPA, 1999; EU, 2006; EPA, 2010). However,
1583 OEHHA here considers information not discussed in the reviews by others that supports
1584 our interpretation that this lesion is indicative of an adverse response to toxicant
1585 exposures. This additional information suggests that hyaline degeneration, also known
1586 as formation of eosinophilic globules (EG), represents stages of cell injury and death
1587 related to condensation of cellular constituents, blebbing, auto- and hetero-
1588 phagocytosis, and intracellular accumulation of plasma proteins.

1589
1590 Perturbations in the frequency of apoptotic events result in disease, suggesting EG
1591 formation is a degenerative change. Previous research in F-344 rats and B6C3F₁ mice
1592 by Buckley *et al.* (1985) showed increased incidence of EG in combination with other
1593 adverse pathologies such as destruction of the naso- and maxillo-turbinates after
1594 exposure to dimethylamine. Monticello *et al.* (1990) stated that cells with EG often
1595 “exhibit massively dilated cisternae of the rough endoplasmic reticulum [ER]”. Similar
1596 swelling of the smooth ER in cells of the nasal mucosa was noted by Lewis and
1597 colleagues (1994), who observed increased numbers of globules and decreased P-450
1598 enzymes in CDF(F344)/CrIBR rats exposed to cigarette smoke for 32 weeks versus
1599 those exposed for 4 weeks. According to Schönthal (2012), luminal dilation of the ER
1600 appears to be a coping mechanism for increased crowding of proteinaceous
1601 constituents resulting from accumulation of un- or mis-folded proteins. ER stress can
1602 result in either adaptation and neutralization of stress or activation of pro-apoptotic
1603 pathways and eventual cell death.

1604
1605 Papadimitriou *et al.* (2000) stated that the role of the ER in apoptosis is related to
1606 proteolysis and solubilization of cytoskeletal proteins, and they observed EG often in or
1607 around the ER of dying cells. Their research on 80 tumor cases (24 tumor types)
1608 containing EG led them to hypothesize that all EG reflect stages of cell injury related to
1609 apoptosis.

1610

1611 Microscopic observations revealed that EG: 1) occurred almost exclusively in areas of
1612 apoptosis and sometimes contained pyknotic nuclear fragments; 2) exhibited the same
1613 ultrastructural features irrespective of tumor type or location; 3) occurred in cells
1614 exhibiting intense blebbing; and 4) stained positively for plasma proteins and occurred
1615 in cells with increased membrane permeability. Intracellular globules were linked to
1616 dense networks of fibrin fibrils which crossed through the cells and into the extracellular
1617 matrix. Extracellular EG were also shown to be linked to the extracellular matrix by
1618 fibrils suggesting a process of remodeling. No research was found by OEHHA that
1619 linked EG and fibrosis (e.g., by imaging, laboratory or lung function tests, and/or
1620 histology). Given their findings, Papadimitriou *et al.* (2000) hypothesized that the
1621 globules are not specific to any tumor type but represent a degenerative process
1622 leading to apoptosis, which is common to all cell types. The authors also recognized
1623 that although the concept of apoptosis does not generally allow for outward leakage of
1624 intracellular constituents, condensation of the cell with the observed cross-linking of the
1625 cytoskeleton maintains internal contents *in situ* preventing the random release of
1626 contents that leads to inflammation and necrosis. Influx and accumulation of plasma
1627 proteins with anti-protease activity would also inhibit inflammatory responses that can
1628 occur with organelle and lysosomal enzyme release. Linking of the intracellular globules
1629 to the extracellular matrix allows for their incorporation into the matrix, which accounts
1630 for the final disposal of apoptotic cell remnants.

1631
1632 Dikov *et al.* (2007) studied quantitative and qualitative differences between normal and
1633 pathologic gastrointestinal (GI) epithelia from a series of 2,230 biopsies. Eosinophilic
1634 globules were rarely found in normal tissues (1.1% incidence). In comparison, EG
1635 frequency was higher in tissues with non-ischemic inflammation (gastritis, duodenitis,
1636 and colitis; $p = 0.007$), circulatory disorders/ischemic injury (acute edema and
1637 congestion, pericarcinomatous mucosa, ischemic colitis; $p < 0.0001$), and ulcerous
1638 edges ($p < 0.0001$). Their incidence in benign regenerative cell proliferation lesions (e.g.
1639 hyperplastic polyps, or focal foveolar hyperplasia), adenomatous polyps, and
1640 adenocarcinomas was also higher than in normal tissues ($p < 0.05$).

1641
1642 Since EG formation is a marker of stress/injury that could lead to apoptosis and is likely
1643 related to a continuum of changes known to represent an established adverse effect,
1644 OEHHA believes that olfactory hyaline degeneration hallmarked by EG formation is an
1645 appropriate choice as the critical endpoint for REL development.

1646
1647 Although liver Kupffer cell pigmentation in rats would provide a slightly lower BMCL₀₅,
1648 this effect is secondary to RBC hemolysis, which is not considered by OEHHA to be
1649 relevant for EGBE REL derivation in humans. Regarding the forestomach effects in
1650 mice, humans do not have a similar organ, but it is conceivable that EGBE could irritate

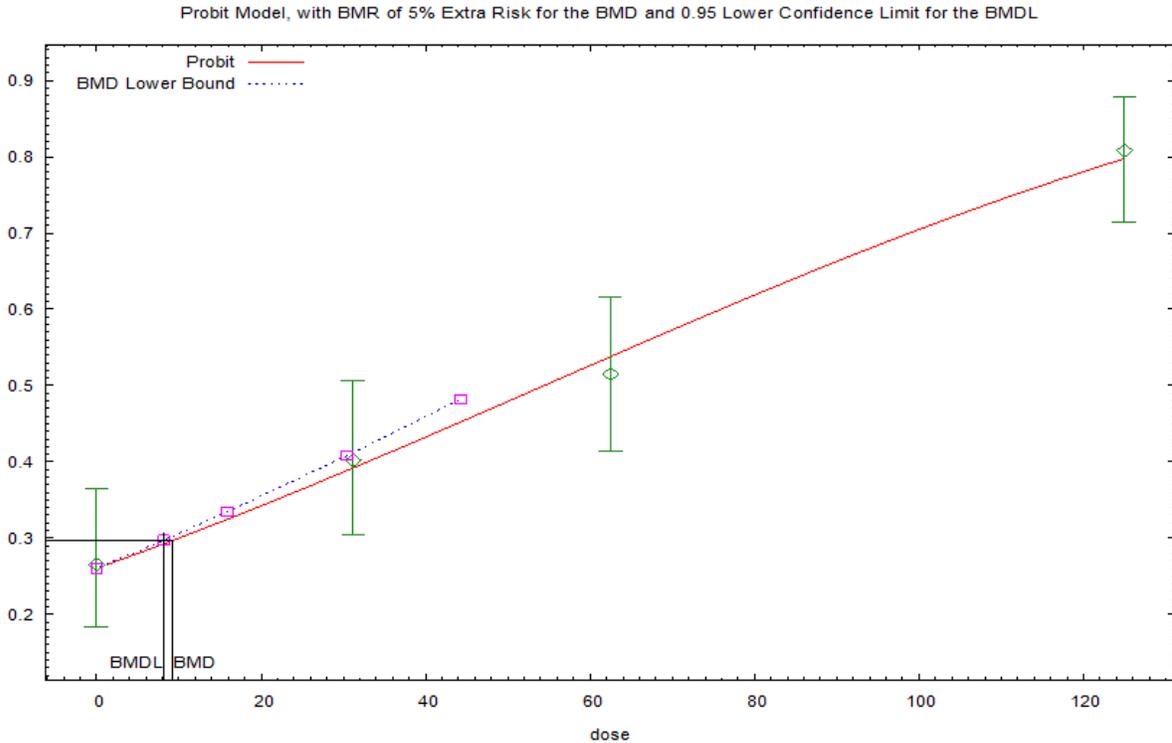
1651 the lining of the esophagus or stomach in humans via incidental or intentional ingestion.
1652 However, this endpoint in mice was not as sensitive as hyaline degeneration of the
1653 olfactory epithelium in rats (Table 10). Since this document is focusing on inhalation
1654 REL development, we are selecting nasal olfactory epithelium hyaline degeneration in
1655 rats as an endpoint to derive 8-hour and chronic RELs.

1656
1657 Logistic regression was performed by OEHHA to determine the relationship among rat
1658 sex, EGBE exposure concentration, and incidence of olfactory epithelial hyaline
1659 degeneration. A Wald test indicated that sex was not a significant factor for nasal
1660 olfactory epithelial hyaline degeneration in rats (Wald $X^2 = 0.20$; $p = 0.65$). Therefore,
1661 combining male and female rats for $BMCL_{05}$ estimation is applicable for the nasal
1662 endpoint in Table 10. In addition, the combined LOAEL of 151 mg/m^3 (31.2 ppm) for
1663 male and female rats is smaller than the LOAEL for males or females alone (302 mg/m^3 ;
1664 62.5 ppm). Table 11 lists the Benchmark Dose (BMD), BMD 95% lower confidence limit
1665 ($BMDL_{05}$), AIC and goodness-of-fit P-values for the several dichotomous models fit to
1666 male and female rat combined incidences of nasal olfactory epithelial hyaline
1667 degeneration. Figure 4 provides a graphic display of the dichotomous probit model fit to
1668 male and female rat nasal olfactory epithelium lesion incidence data.
1669

1670 **Table 11. BMDS dichotomous models fit to incidence of hyaline degeneration of**
 1671 **the olfactory epithelium in male and female rats after inhalation exposure to**
 1672 **EGBE for 2 years (NTP, 2000)**

Model Name	BMD mg/m ³ (ppm)	BMDL ₀₅ mg/m ³ (ppm)	Goodness- of-fit p-value	AIC	Scaled residual
Multistage	27.0703 (5.6046)	21.9928 (4.5534)	0.1972	485.392	0.549
Gamma	79.0087 (16.3579)	26.0642 (5.3963)	0.4104	484.765	0.522
Logistic	46.0019 (9.5242)	40.0318 (8.2882)	0.8236	482.479	0.115
LogLogistic	93.8720 (19.4352)	40.8242 (8.4522)	0.2900	485.205	0.704
LogProbit	101.6430 (21.0441)	48.4367 (10.0283)	0.2441	485.441	0.726
Probit	44.9094 (9.2980)	39.4300 (8.1636)	0.8492	482.417	0.109
Weibull	71.9713 (14.9009)	27.2101 (5.6336)	0.4890	484.567	-0.158
Quantal-Linear	27.0703 (5.6046)	21.9928 (4.5534)	0.1972	485.392	0.549

1673 Note: Results are from benchmark dose analysis using BMDS version 2.6 (EPA, 2015). We selected the
 1674 best available model based on a smaller AIC and larger goodness-of-fit P-value among the different
 1675 models. In this case, the Probit model (bold) was the most appropriate model. AIC = Akaike Information
 1676 Criterion. Scaled residual is for the dose group nearest the BMD.
 1677



1678
 1679 **Figure 4.** Dichotomous Probit model fit to nasal olfactory epithelium incidences in male
 1680 and female rats after inhalation exposure to EGBE for 2 years (NTP, 2000)
 1681

1682 The point of departure (the $BMCL_{05}$) was adjusted for 8-hour exposures, seven days/wk.
 1683 The assumption is that the rats show both mixed active and inactive periods during
 1684 exposure, and a time adjustment is made to simulate an active 8-hour working period
 1685 during which the off-site worker is exposed. The concentration is first adjusted down to
 1686 24-hour continuous exposure ($6/24$ hours \times $5/7$ days per week), then multiplied by 2
 1687 ($20m^3/10m^3$) to represent an active individual breathing half the air breathed in a day
 1688 during an active working 8-hour period when exposure occurs, compared to what a
 1689 resident would breathe over a 24-hour period.

1690
 1691 Adjustments for differences in MV and for relative areas of human and rat extra-thoracic
 1692 regions of the respiratory tract resulted in a human equivalent concentration of
 1693 $14.15 \text{ mg}/m^3$ (2.9 ppm) (OEHHA, 2008). We used an interspecies $UF = \sqrt{10}$. This was
 1694 composed of a toxicokinetic UF of 1 because we utilized the HEC dosimetric adjustment
 1695 and the toxicological endpoint is a port of entry effect. We retained a UF of $\sqrt{10}$ to
 1696 account for interspecies tissue sensitivity differences. The intraspecies toxicokinetic and
 1697 toxicodynamic UFs were both assigned $\sqrt{10}$. No additional adjustment was made for
 1698 early life exposures, since the effect of concern is at the portal of entry and thus age-
 1699 related differences in toxicokinetics do not likely influence response. The cumulative UF

1700 was 30 which results in an 8-hour REL of 0.165 mg/m³ (0.034 ppm) and this value is
 1701 just slightly lower than EGBE’s odor threshold 0.483 mg/m³ (0.10 ppm).
 1702

1703 **8.3 EGBE Chronic Reference Exposure Level**

<i>Study</i>	NTP, 2000
<i>Study population</i>	Rats (50 animals/group/gender)
<i>Exposure method</i>	Discontinuous whole-body inhalation exposure of 0, 151, 302, or 604 mg/m ³ (0, 31.2, 62.5, or 125 ppm)
<i>Critical effects</i>	Nasal hyaline degeneration of olfactory epithelium
<i>LOAEL</i>	151 mg/m ³ (31.2 ppm)
<i>NOAEL</i>	Not observed
<i>BMC₀₅</i>	39.4 mg/m ³ (8.16 ppm; Probit model from male and female rats)
<i>Exposure continuity</i>	6 hrs/day, 5 days/wk
<i>Exposure duration</i>	2 years
<i>Time-adjusted exposure</i>	7.04 mg/m ³ (1.46 ppm) (ppm = 8.16 ppm x 6/24 x 5/7)
<i>Human Equivalent Concentration</i>	2.46 mg/m ³ (0.510 ppm; gas with extra-thoracic respiratory effects, RGDR = 0.35)
<i>LOAEL uncertainty factor</i>	NA
<i>Subchronic uncertainty factor</i>	1
<u><i>Interspecies uncertainty factor</i></u>	
<i>Toxicokinetic (UF_{A-k})</i>	1
<i>Toxicodynamic (UF_{A-d})</i>	√10
<u><i>Intraspecies uncertainty factor</i></u>	
<i>Toxicokinetic (UF_{H-k})</i>	√10
<i>Toxicodynamic (UF_{H-d})</i>	√10
<i>Cumulative uncertainty factor</i>	30
<i>Reference Exposure Level</i>	82 µg/m ³ (17 ppb)

1704
 1705 The chronic REL is based on the same study as the 8-hour REL (NTP, 2000) and uses
 1706 the same benchmark dose analysis with a POD of 40 mg/m³ (8.2 ppm). In this instance
 1707 the time adjusted exposure reflects conversion of an intermittent to a continuous
 1708 exposure. The same uncertainty factors apply to give a cumulative UF of 30 and a
 1709 chronic REL of 83 µg/m³ (17 ppb).
 1710

1711 Occupational exposure limits for EGBE have been established by various agencies in
 1712 the US NIOSH based an 8-hour TWA Recommended Exposure Limit of 24 mg/m³ (5

1713 ppm) on tissue irritation, CNS depression, and adverse effects on the blood and
1714 hematopoietic systems. Both the Occupational Safety and Health Administration
1715 (OSHA) and the American Conference of Governmental Industrial Hygienists (ACGIH)
1716 established a TWA of 120 mg/m³ (25 ppm, based on the risk of hematologic and other
1717 systemic effects associated with exposure to EGBE. These values were established
1718 more than 20 years ago (NIOSH, 1992).

1719

1720 **9. Evidence for Differential Sensitivity of Children**

1721

1722 No human inhalation studies were found that addressed differential sensitivity of
1723 children relative to adults exposed to EGBE in terms of eye and upper respiratory
1724 irritation. In experimental animals, no evidence was found for differential sensitivity in
1725 developmental studies, as both maternal toxicity and fetotoxicity occurred at similar
1726 exposure concentrations. Regarding the hemolytic action of EGBE, an animal oral
1727 gavage study found that adult (9-13 weeks) male rats (12/12, 100%) were more
1728 sensitive to the hemolytic effects of EGBE at 125 mg/kg in water than young (4-5
1729 weeks) male rats (1/11, 9.1%) (Ghanayem *et al.*, 1987). In humans, *in vitro* studies in
1730 RBCs from children and healthy adults showed no difference in their resistance to the
1731 hemolytic effects of BAA (Udden, 1994; Udden, 2002). Due to the sensory irritant action
1732 of EGBE exposure, asthmatics including children may be more sensitive to EGBE
1733 exposure compared to the general population. Otherwise, there is currently insufficient
1734 evidence to consider EGBE a chemical for which children are more sensitive compared
1735 to the general population.

1736

1737 Several epidemiological studies indicate that indoor factors might cause asthma in
1738 childhood. The most consistent finding for induction of asthma in childhood is related to
1739 exposure to environmental tobacco smoke, and living in homes close to busy roads or
1740 homes damp with visible molds. More research is needed to clarify the potential risk for
1741 exposure to volatile and semi-volatile organics due to renovation activities or cleaning
1742 (Heinrich, 2011). Further study is needed to identify whether EGBE contributes to
1743 increased childhood asthma in the home environment.

1744

1745

1746 **10. References**

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