Air Toxics Hot Spots Program

Draft Noncancer Reference Exposure Levels for Ethylene Glycol mono-n-Butyl Ether (EGBE)

Office of Environmental Health Hazard Assessment

Scientific Review Panel Meeting
Sacramento
December 14, 2016

EGBE: Preceding SRP Meeting

- **Proposed RELs:**
  - **Acute: 4700 µg/m³ (1000 ppb) – Human (sensory) irritation**
  - **8-hour: 164 µg/m³ (34 ppb) - Nasal olfactory epithelium degeneration in rats**
  - **Chronic: 82 µg/m³ (17 ppb) – same as 8-hour REL**

EGBE: Preceding SRP Meeting

- **Acute REL unchanged from previous March 2016 SRP Meeting**
- **8-Hour REL revised from 150 µg/m^3 (32 ppb) – As suggested by SRP at March 2016 meeting, $BMDL_{05}$ based on combined male and female rats rather than female rats only**
- **Chronic REL: revised from 77 µg/m^3 (16 ppb) – same basis as 8-hour REL**

EGBE: Preceding SRP Meeting

- **Key study for acute REL:**
- **Study: Carpenter, *et al.* (1956), which included 3 human volunteer inhalation studies.**
- **Study population: 2 to 4 human subjects per study from 3 studies.**
- **Exposure method: whole body exposure at 98, 113, or 195 ppm (473, 546, or 942 mg/m^3).**

EGBE: Preceding SRP Meeting

- **Key study for acute REL (continued):**

- **Exposure duration: 8 hours (98 and 195 ppm in chamber) or 4 hours (113 ppm in room).**
- **Critical effect: ocular and nasal (sensory) irritation.**
- **POD: LOAEL = 98 ppm (474 mg/m^3) was used to derive acute REL.**

EGBE Acute REL Derivation

- **Point of Departure: LOAEL, 474 mg/m^3 (98 ppm)**
- **No time adjustment**
- **LOAEL uncertainty factor (UF_L) = 10 (default)**
- **Interspecies uncertainty factor (UF_A) = 1**
- **Intraspecies toxicokinetic UF ($UF_{H\text{-}k}$) = 1 (site of action; no systemic effects)**
- **Intraspecies toxicodynamic UF ($UF_{H\text{-}d}$) = 10 (small sample size)**
- **Cumulative UF = 100**
- **Acute REL = 4700 µg/m^3 (1000 ppb)**

EGBE: Preceding SRP Meeting

- **Key study for 8-hour and chronic REL:**
- **Study: NTP (2000) 2-year EGBE inhalation study.**
- **Sample size and exposure: n = 50/sex/group, 6 hrs/day, 5 days/wk, for 2 years.**
- **Concentration: Rats: 0, 31, 62.5, and 125 ppm (0, 150, 302, and 604 mg/m^3); Mice: 0, 62.5, 125, and 250 ppm (0, 302, 604, and 1,208 mg/m^3).**

EGBE: Preceding SRP Meeting

- **Key study for 8-hour and chronic REL (continued):**

- **Nonneoplastic effects in rats: hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation in livers.**
- **Nonneoplastic effects in mice: forestomach ulcers and epithelial hyperplasia, hematopoietic cell proliferation and hemosiderin pigmentation in the spleen, hepatic Kupffer cell pigmentation, and bone marrow hyperplasia (males only).**

EGBE Eight-hour REL Derivation

- **Critical Effect: rat nasal hyaline degeneration**
- **Point of Departure: $BMDL_{05}$ = 8.2 ppm (39 mg/m^3)**
- **Time-adjusted exposure: 2.9 ppm (14 mg/m^3) (8.2 ppm x 6/24 x 5/7 x 20/10)**
- **Human Equivalent Concentration (HEC) = Time-adjusted Exposure × Regional Gas Dose Ratio (RGDR; 0.35) = 1 ppm (4.9 mg/m^3)**
- **Cumulative UF = 30**
- **Eight-hour REL = 164 µg/m^3 (34 ppb)**

EGBE Chronic REL Derivation

- **Critical Effect: Rat nasal hyaline degeneration**
- **Point of Departure: $BMDL_{05}$ = 8.2 ppm (39 mg/m^3)**
- **Time-adjusted exposure: 1.46 ppm (7 mg/m^3) = 8.2 ppm x 6/24 x 5/7**
- **Cumulative UF = 30**
- **Chronic REL = 82 µg/m^3 (17 ppb)**

EGBE REL Document
Production, Major Uses, and Occurrence

SRP Comment:

- **Update old production and usage information with more recent findings.**
- **Add information regarding measured EGBE concentrations outdoors. Include EGBE air concentrations following use of cleaning products, and add associated papers by Nazaroff.**
- **Present high EGBE concentrations measured indoors, not just mean values.**

EGBE REL Document
Production, Major Uses, and Occurrence

OEHHA Response:

- **Checked ACC and ACS publications. The most recent annual EGBE production in the U.S. was added.**
- **Outdoor concentrations of EGBE measured by Daisey *et al.* (1994) and Nazaroff (Nazaroff and Weschler, 2004; Singer *et al*. 2006) were added.**
- **Maximum concentrations of EGBE from various studies have been included.**

EGBE REL Document
Production, Major Uses, and Occurrence

SRP Comment:

- **Clarify Hot Spots reporting, and add California emission trends.**

OEHHA Response:

- **California Toxics Inventory (CTI) EGBE emissions (tons/year) are presented. CTI provides emissions estimates by stationary (point and aggregated point), area-wide, on-road mobile (gasoline and diesel), off-road mobile (gasoline, diesel, and other), and natural sources.**

EGBE REL Document
Toxicokinetics

SRP Comment:

- **General comment – reorganize the Section to increase consistency and clarity.**
- **Emphasize the importance of inhalation exposure, and discuss the study by Corley *et al.* (1956) first; then, summarize the study limitations of Johanson and Boman (1991) that used finger pricks versus venous blood draws.**
- **Include papers by Hung *et al.* (2011) and Korinth *et al.* (2007) regarding toxicokinetics and occupational dermal exposure to EGBE.**

EGBE REL Document
Toxicokinetics

OEHHA Response:

- **Section 4 "Toxicokinetics" has been reorganized as requested.**
- **Discussions of the Corley *et al.* (1956) and Johanson and Boman (1991) papers can be found in the revised Section 4.1, "Toxicokinetic Studies in Humans."**
- **Hung *et al*. and Korinth *et al*. summaries were added to Section 4.1.**

EGBE REL Document
Toxicokinetics

SRP Comment:

- **In the "Metabolism and Elimination" section, provide a table of the different studies, and separately discuss differences due to species, age, and metabolite patterns.**

EGBE REL Document
Toxicokinetics

SRP Comment Continued:

- **Include an additional table of metabolites with percentages of each excreted from mice, rats, and humans, and change the structural formulas in Figure 3 to conform to ACS journals (*i.e.* use skeletal formulas).**
- **Evaluate butoxyacetic acid (BAA) as a biomarker of exposure, and clarify the term, "urine half-life."**

EGBE REL Document
Toxicokinetics

OEHHA Response:

- **Added subsections 4.3 (Species Differences in Metabolism and Elimination of EGBE) and 4.4 (Age- and Sex-Related Differences in Rodents).**
- **Added Table 4 (species-specific urinary metabolites), and modified EGBE metabolism structures (now Figure 3) as requested.**
- **Clarified total urinary BAA as the most appropriate biomarker of EGBE exposure, and "urinary elimination half-life" was defined.**

EGBE REL Document
Toxicokinetics

SRP Comment:

- **Unclear description of metabolism and urinary EGBE and BAA conjugates in rats and humans.**

OEHHA Response:

- **Metabolism discussion revised and clarified in response to comments.**

EGBE REL Document
Toxicokinetics

OEHHA Response Continued:

- **Description of urinary metabolites of EGBE have been discussed in greater detail. In rats, free-BAA is the primary metabolite, but small amounts of EGBE-glucuronide and EGBE-sulfate conjugates are also secreted in urine.**
- **In humans, urinary secretion of BAA is mainly in the form of BAA conjugates with glutamine. A smaller amount is excreted as free-BAA.**

EGBE REL Document
Acute Toxicity

SRP Comment:

- **Include separate subsections for:**
  1. **acute and chronic animal studies,**
  2. **controlled human exposure studies,**
  3. **accidental inhalation, dermal, and acute oral ingestion (poisoning) case-studies,**
  4. **and add a table of toxic sequelae.**
- **Discuss human exposure studies by Bauer *et al.* (1992), Hung *et al.* (2010), and Rella *et al.* (2012).**

EGBE REL Document
Acute Toxicity

OEHHA Response:

- **Added Subsections 5.1.1 and 5.1.2 in the revised document summarize human inhalation studies, including occupational and chamber studies, and high-dose oral exposures, respectively.**
- **Table 5 added - summarizes clinical responses observed in several human oral poisoning case studies.**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

SRP Comment:

- **Qualitative evaluation is needed of the studies presented including their strengths and weaknesses.**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

SRP Comment Continued:

- **Example: the key acute REL study, Carpenter *et al.* (1956), is limited by unstated purity of the test substance, imprecise performance of inhalation exposures, questionable test substance measurement methods with unknown error, and poor reporting.**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

OEHHA Response:

- **Limitations and advantages of the Carpenter *et al.* (1956) study and other human chamber studies are now discussed in Section 8.1.**
- **Added discussion of potential impurities and measurement method (gas interferometer)**
- **Additional support for basing the acute REL on the Carpenter *et al*. study is presented. For example:**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

OEHHA Response Continued:

- **Human toxicokinetic studies (e.g., Johanson *et al.*, 1986) had better methods, but tested a single dose, only established a free-standing NOAEL, had small "n" values, and focused mainly on ADME. There is a high risk of missing some adverse effects.**
- **Carpenter *et al.* (1956) had 3 dose groups, was designed to examine irritant effects, addressed both subjective and objective symptoms, and established a LOAEL.**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

OEHHA Response Continued:

- **For REL derivation, a study with a LOAEL is preferred over a study with only a free-standing NOAEL (OEHHA, 2008).**
- **A new table (Table 9) added compares NOAELs and LOAELs for RBC hemolysis in rodent EGBE exposure studies.**

EGBE Acute REL
Limitations/advantages of Carpenter *et al.* (1956)

OEHHA Response Continued:

- **The NOAEL and LOAEL in rodents from Carpenter *et al.* (1956) study were roughly 2-fold greater compared to NOAELs and LOAELs in later rodent studies by Tyl *et al.* (1984), NTP (2000), and Dodd *et al.* (1983).**

EGBE Acute REL
Comparing Carpenter and Johanson Studies

SRP Comment:

- **Given the sub-par quality of the Carpenter *et al.* (1956) study using today's standards, it may be helpful to discuss how the draft acute REL would change if the Johanson *et al.* (1986) study was used and whether the study is more appropriate for setting the acute REL.**

EGBE Acute REL
Comparing Carpenter and Johanson Studies

OEHHA Response:

- **We added a discussion comparing the two studies. Using the Johanson *et al.* (1986) 20 ppm free-standing NOAEL as a POD, an intraspecies UF = 10 is applied resulting in an acute REL of 2 ppm (9.7 mg/m^3).**
- **This value is twice the REL value of 1 ppm (4.8 mg/m^3) that was derived from the Carpenter *et al.* (1956) study (refer to the last paragraph of Section 8.1).**

EGBE 8-hour and Chronic RELs
REL development: NTP historical control data

SRP Comment:

- **How does incidence of nasal olfactory epithelial hyaline degeneration, liver Kupffer cell pigmentation, forestomach epithelial hyperplasia, and forestomach ulcer in the NTP (2000) study compare to historical NTP controls?**

EGBE 8-hour and Chronic RELs
REL development: NTP historical control data

OEHHA Response:

- **Referring to pathology tables for all routes/vehicles on the NTP historical control database, there were no incidence data for the biological endpoints in question. Historical incidence data were available primarily for tumor and cancer endpoints.**

(Refer to https://ntp.niehs.nih.gov/results/dbsearch/historical/index.html)

EGBE 8-hour and Chronic RELs

REL development: Dose-response relationships

SRP Comment:

- **Perform a trend test on NTP incidence data to show a monotonic relationship between the dose and response.**
- **Add the sex variable to test whether there is a significant difference between male and female rats. If there is no difference, combine data from male and female rats, and model them such that the 31.2 ppm (151 mg/m^3) exposure dose is the LOAEL for the nasal hyaline degeneration endpoint.**

EGBE 8-hour and Chronic RELs
REL development: Dose-response relationships

OEHHA Response:

- **Cochran-Armitage trend test *p*-values from the BMDS (US EPA, 2015) have been added to Table 8 to show dose-response relationships.**
- **Logistic regression was performed to determine the relationship between rat sex, EGBE exposure, and incidence of olfactory epithelial hyaline degeneration.**

EGBE 8-hour and Chronic RELs
REL development: Dose-response relationships

OEHHA Response Continued:

- **A Wald test indicated that sex was not a significant factor for nasal olfactory epithelial hyaline degeneration in rats.**
- **Combining male and female rats for $BMCL_{05}$ estimation is applicable for the nasal endpoint.**

EGBE 8-hour and Chronic RELs Development

OEHHA Response continued:

- **Incidences of nasal olfactory epithelia hyaline degeneration from male and female rats in the NTP 2-year study (2000) were combined.**
- **The $BMDL_{05}$ from combined male and female rat data serves as a POD to develop 8-hour and chronic RELs.**
- **The calculated 8-hour and chronic RELs are 164 µg/m³ (34 ppb) and 82 µg/m³ (17 ppb), respectively.**

EGBE
Other Changes to the Document

- **Clarified ambiguous terminology (*e.g.*, "significant" and "reasonably").**
- **Some mouse parameter data were excluded in Table 10, as trend tests suggested there were no significant dose responses.**
- **No significant differences were observed by pair-wise comparison for the severity of hyaline degeneration in high-dose exposures between male and female rats ($p > 0.05$).**

Questions?

EGBE REL Document
Toxicokinetics

SRP Comment:

- **Text from the original EGBE REL document stated, "Because butoxyacetic acid is excreted in the urine in both rats and humans following ethylene glycol to butoxyethanol exposure, it has been suggested that the production of BAA through the formation of BAL by ADH is applicable in both rats and humans."**
- **"I didn't even understand what that was saying. Any species with alcohol and aldehyde dehydrogenase is likely to take this through the aldehyde and into the acid. So it's sort of a throw-away sentence."**

OEHHA Response:

- **This section has been clarified in response to comments.**