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## **2-Butoxyethanol**

**CAS Registry Number: 111-76-2**

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## **Revision History**

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Revised DSD September 14, 2015: the odor-based value was withdrawn because 2-butoxyethanol does not have a pungent, disagreeable odor (TCEQ 2015).

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## Chapter 1 Summary Table

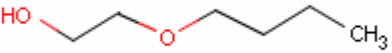
Table 1 provides a summary of health- and welfare-based values from an acute and chronic evaluation of 2-butoxyethanol (2-BE) can be found in Table 1. Table 2 provides summary information on 2-BE's physical/chemical data.

**Table 1 Health- and Welfare-Based Values**

Short-Term Values	Concentration	Notes
<sup>acute</sup> ESL [1 h] (HQ = 0.3)	2,900 µg/m <sup>3</sup> (600 ppb) <b>Short-Term ESL for Air Permit Reviews</b>	<b>Critical Effect(s):</b> eye, nose, and throat irritation in human volunteers
acute ReV (HQ = 1)	9,700 µg/m <sup>3</sup> (2,000 ppb)	<b>Critical Effect(s):</b> Same as above
<sup>acute</sup> ESL <sub>odor</sub>	---	Mild ethereal sweet odor
<sup>acute</sup> ESL <sub>veg</sub>	---	No data found
Long-Term Values	Concentration	Notes
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> (HQ = 0.3)	3,700 µg/m <sup>3</sup> (780 ppb) <b>Long-Term ESL for Air Permit Reviews</b>	<b>Critical Effect(s):</b> decreased in automated and manual hematocrit values, hemoglobin, and erythrocyte counts in rats and mice
chronic ReV (HQ = 1)	12,000 µg/m <sup>3</sup> (2,600 ppb)	<b>Critical Effect(s):</b> Same as above
<sup>chronic</sup> ESL <sub>linear(c)</sub>	---	No data found
<sup>chronic</sup> ESL <sub>veg</sub>	---	No data found

Abbreviations: **ppb**, parts per billion; **µg/m<sup>3</sup>**, micrograms per cubic meter; **h**, hour; **ESL**, Effects Screening Levels; **ReV**, Reference Value; <sup>acute</sup>**ESL**, acute health-based ESL; <sup>acute</sup>**ESL<sub>odor</sub>**, acute odor-based ESL; <sup>acute</sup>**ESL<sub>veg</sub>**, acute vegetation-based ESL; <sup>chronic</sup>**ESL<sub>linear(c)</sub>**, chronic health-based ESL for linear dose-response cancer effect; <sup>chronic</sup>**ESL<sub>nonlinear(c)</sub>**, chronic health-based ESL for nonlinear dose-response cancer effect; <sup>chronic</sup>**ESL<sub>nonlinear(nc)</sub>**, chronic health-based ESL for nonlinear dose-response noncancer effects; <sup>chronic</sup>**ESL<sub>linear(nc)</sub>**, chronic health-based ESL for linear dose-response noncancer effects; and <sup>chronic</sup>**ESL<sub>veg</sub>**, chronic vegetation-based ESL

**Table 2 Chemical and Physical Data**

Parameter	Value	Reference
Molecular Formula	$\text{H}_3\text{C}-(\text{CH}_2)_3-\text{O}-\text{CH}_2\text{CH}_2-\text{OH}$	ACGIH, 2002
Chemical Structure		ChemIDplus
Molecular Weight	118.17	ACGIH, 2002
Physical State	Liquid	ACGIH, 2002
Color	Colorless	ACGIH, 2002
Odor	Ethereal	ACGIH, 2002
CAS Registry Number	111-76-2	ACGIH, 2002
Synonyms	n-Butoxyethanol; Butyl Cellosolve; EGBE; Ethylene glycol monobutyl ether	ACGIH, 2002
Solubility in water	miscible with water and all commercial industrial solvents; 1.00E+06 mg/L	Verschueren, 2001; ChemIDplus
Log $P_{ow}$	0.74 (octanol-water)	Verschueren, 2001
Vapor Pressure	0.6 mmHg at 20°C	Verschueren, 2001
Relative Vapor Density (air = 1)	4.07	Verschueren, 2001
Density (water = 1)	0.90 g/cc at 20°C	Verschueren, 2001
Melting Point	< -70°C	Verschueren, 2001
Boiling Point	170°C	Verschueren, 2001
Conversion Factors	1 $\mu\text{g}/\text{m}^3 = 0.207 \text{ ppb}$ at 25°C 1 ppb = 4.83 $\mu\text{g}/\text{m}^3$	TS Staff

## Chapter 2 Major Uses or Sources

2-Butoxyethanol (2-BE) is used as a solvent in many industrial processes, including printing and paint manufacturing. 2-BE is useful as a solvent in water or organic solvent-based coating and is also found in many hard-surface cleaning products, cosmetic products, and hair dyes and colors (ACGIH 2001). It is also used as a solvent for nitrocellulose resins, spray lacquers, quick-drying lacquers, varnishes, enamels, varnish removers, and textiles (Lewis 2001).

## Chapter 3 Acute Evaluation

### 3.1 Health-Based Acute *ReV* and *ESL*

#### 3.1.1 Physical/Chemical Properties and Key Studies

2-BE is a liquid with an ethereal odor (refer to Section 3.2.1). The main chemical and physical properties of 2-BE are summarized in Table 2. It is highly water soluble.

The most consistently identified adverse effect of 2-BE exposure in several species of laboratory animals is hemolytic anemia. Humans are significantly less sensitive to the hemolytic toxicity of 2-BE than are typical laboratory species such as mice, rats, or rabbits. 2-BE produces dose- and time- dependent hemolysis of red blood cells in rats and mice, both *in vivo* and *in vitro* (Carpenter et al. 1956; Ghanayem and Sullivan 1993, Udden and Patton 1994, Udden 1995 in Agency for Toxic Substances and Disease Registry (ATSDR) 1998). The hematotoxicity is characterized in humans by decreased hemoglobin (Hb) content, progressive erythropenia, and hemoglobinuria. In animals, hematotoxicity is characterized by swelling and morphological alterations of erythrocytes, followed by hemolytic anemia, and decreases in circulating red blood cells (RBCs), Hb concentration, and hematocrit.

##### 3.1.1.1 Human Studies

In a study conducted by Carpenter et al. (1956), volunteers were exposed to 98, 113, or 195 ppm 2-BE for 4 to 8 h. Two men and one woman were exposed to 195 ppm for 8 h. Immediate nose and throat irritation followed by ocular irritation and disturbed taste were observed. All three subjects experienced discomfort due to the high level (195 ppm) of 2-BE. Twenty days after the 195 ppm experiment, two men and two women (three of these subjects, one man and two women, had had no previous contact with 2-BE vapor) were exposed to 98 ppm for 8 h <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub> with a 30-minute recess. Nasal irritation and a slight increase in nasal mucus discharge were observed. A lowest-observed-adverse-effect-level (LOAEL) of 98 ppm for throat, nasal and eye irritation was identified from this study.

In another study, no discomfort or clinical signs of adverse effects on pulmonary ventilation or respiratory frequency were reported in seven male volunteers exposed to 20 ppm 2-BE for 2 h during light physical exercise on a bicycle ergometer (Johanson et al. 1986). A freestanding no-observed-adverse-effect-level (NOAEL) of 20 ppm for discomfort and respiratory irritation was identified from this study and was used as the point of departure (POD).

### **3.1.1.2 Animal Studies**

Animal studies have reported effects on the kidney, hematopoietic system, and central nervous system from acute inhalation exposure to 2-BE. Inhalation exposures of groups of female rats to 62 ppm 2-BE for 4 h or 54 ppm for up to 30 days resulted in increased osmotic fragility of rat erythrocytes (Carpenter et al. 1956). This study also reported hemoglobinuria in rats and mice after inhalation exposure to 203 ppm and 200 ppm 2-BE, respectively, for 7 h.

In an inhalation study by Dodd et al. (1983), Fischer 344 rats were exposed to 0, 202, 523, or 867 ppm 2-BE for 4 h. Loss of coordination and shallow breathing, followed by death, occurred at 867 ppm.

Red-stained fluid in the urinary bladder and enlarged and discolored kidneys were observed at necropsy in animals that died during or following exposure to 523 or 867 ppm 2-BE. In a subsequent study (Dodd *et al.* 1983), Fischer 344 rats were exposed to 2-BE for 9 days (6 hrs/day) at 0, 20, 86, or 245 ppm. No effects on the hematologic parameters were observed in rats exposed to 20 ppm 2-BE. At the 86 ppm exposure, both sexes exhibited a significant effect on erythroid parameters, including decreased Hb and increased mean corpuscular volume (MCV). In addition, decreased mean corpuscular hemoglobin concentration (MCHC) was noted in females at 86 ppm. At the 245 ppm exposure, both sexes showed significantly depressed RBC count, Hb, and MCHC and significant increases in MCV, nucleated RBC count, and reticulocytes. A NOAEL of 20 ppm (6 hrs/day for 9 days) on hematologic parameters was identified from this study.

In a study by Tyl et al. (1984), developmental, hematological, and renal effects were studied in pregnant Fischer 344 rats and New Zealand White rabbits exposed to 0, 25, 50, 100, or 200 ppm 2-BE for 6 hrs/day on gestational days 6-15 (rats) or days 6-18 (rabbits). Maternal, embryo and fetal toxicity were found in rats at 100 and 200 ppm. Maternal and embryo toxicity were also found in rabbits at 200 ppm. The study also showed a clear dose-response relationship for hematological and renal toxicity. Hematological determinations on dams showed significant reductions in RBC count, MCHC, and an increase in Hb per cell and size of the RBC in rats at 100 and 200 ppm, but not at 50 ppm. There were significant increases in Hb and hematocrit counts at 200 ppm. In contrast, increases in Hb and hematocrit were found in rabbits at 100 ppm, but not at 200 ppm. A NOAEL of 50 ppm for hematological effects in rats was identified from this study. In renal effects, clear evidence of hematuria or hemoglobinuria in 75% of the dams was observed in rats at the 100 and 200 ppm group during the exposure period. Red fluid on the tray paper, possibly evidence of hematuria, was observed in rabbits exposed to 100 and 200 ppm. A NOAEL of 50 ppm for renal effects in rats or rabbits was identified from this study. In addition, periocular wetness was observed in rats at all concentrations ( $\geq 25$  ppm) and in rabbits at 100 and 200 ppm. A LOAEL of 25 ppm for eye irritation in rats was identified in this study.

### **3.1.2 Mode of Action (MOA) Analysis and Dose Metric**

The MOA for hematotoxicity induced by 2-BE can be attributed to its metabolite, 2-butoxyacetic acid (2-BAA). In addition, respiratory effects, including changes in respiratory rate and hemorrhaging of the respiratory tissues, may be related to metabolic acidosis and hemolysis, respectively (ATSDR 1998, USEPA 1999). Since the key study is based on discomfort and

respiratory irritation in human volunteers, exposure concentration of the parent chemical will be used as the dose metric.

### 3.1.3 Point of Departure (POD) for the Key Study and Dosimetric Adjustments

A freestanding NOAEL of 20 ppm for discomfort and respiratory irritation was identified from the Johanson et al. (1986) study conducted in humans and was used as the POD adjusted for human equivalent concentration (POD<sub>HEC</sub>). Since the exposure duration of the key study is less than 8 h and concentration alone is the dominant determinant of mild respiratory irritation, no exposure duration adjustment is needed.

### 3.1.4 Extrapolation of POD<sub>HEC</sub> to Acute ReV and ESL

The acute Reference Value (ReV) of 2 ppm (9.7 mg/m<sup>3</sup>) was derived by applying an uncertainty factor (UF) of 10 for intrahuman variability and a UF of 1 for database uncertainty to the POD<sub>HEC</sub> of 20 ppm. The acute ESL of 600 ppb (2,900 µg/m<sup>3</sup>) was set according to the ESL guidance (TCEQ 2006) based on the acute ReV of 2 ppm multiplied by a hazard quotient (HQ) of 0.3 (Table 3).

**Table 3 Derivation of the Acute ReV and acute ESL**

Parameter	Summary
Study	Johanson et al. 1986
Study Population	7 healthy male volunteers
Study Quality	Medium
Exposure Method	exposure via inhalation at 20 ppm for 2 hrs during light physical exercise
Critical Effects	Respiratory effects, sensory irritation
POD	20 ppm (NOAEL)
Exposure Duration	2 h
Extrapolation to 1 hr	concentration-dependent effect, 1 hr concentration = 2 hr concentration (Section 3.1.3)
Extrapolated 1 hr concentration	20 ppm
Total uncertainty factors (UFs)	10
<i>Interspecies UF</i>	N/A
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	N/A
<i>Incomplete Database UF</i>	1
<i>Database Quality</i>	High
<b>Acute ReV [1 h] (HQ = 1)</b>	<b>9,700 µg/m<sup>3</sup> (2,000 ppb)</b>
<b>acute ESL [1 h] (HQ = 0.3)</b>	<b>2,900 µg/m<sup>3</sup> (600 ppb)</b>



## **3.2 Welfare-Based Acute ESLs**

### **3.2.1 Odor**

2-BE has a mild, ethereal odor. An odor threshold (geometric mean) of 0.1 ppm has been reported (Amoore and Hautala 1983, AIHA 1989). Hellman and Small (1974) also report a 50% detection odor threshold of 100 ppb ( $483 \mu\text{g}/\text{m}^3$ ), a 50% recognition odor threshold of 350 ppb ( $1,690 \mu\text{g}/\text{m}^3$ ), and a 100% recognition odor threshold of 480 ppb ( $2,318 \mu\text{g}/\text{m}^3$ ). In addition, Nagata (1983) reports a 50% detection odor threshold value of 43 ppb. Since butoxyethanol does not have a pungent or disagreeable odor, an <sup>acute</sup>ESL<sub>odor</sub> was not developed (TCEQ 2015).

### **3.2.2 Vegetation**

No information was found to indicate that special consideration should be given to possible acute vegetation effects from 2-BE.

## **3.3 Short-term ESL**

This acute evaluation resulted in the derivation of the following values:

- acute ReV =  $9,700 \mu\text{g}/\text{m}^3$  (2,000 ppb)
- <sup>acute</sup>ESL =  $2,900 \mu\text{g}/\text{m}^3$  (600 ppb)

The short-term ESL for air permit evaluations is  $2,900 \mu\text{g}/\text{m}^3$  (600 ppb) (Table 1). The acute ReV of  $9,700 \mu\text{g}/\text{m}^3$  (2,000 ppb) is the acute comparison value for the evaluation of ambient air monitoring data (Table 1). The <sup>acute</sup>ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

# **Chapter 4 Chronic Evaluation**

## **4.1 Non-carcinogenic Potential**

### **4.1.1 Key Studies**

#### **4.1.1.1 Human Studies**

In an occupational exposure study by Haufroid et al. (1997), hematological effects were studied in 31 male workers exposed to low levels of 2-BE for 1 to 6 years in a beverage packing production plant. Twenty of the workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The geometric mean exposure concentration for the 31 workers was  $0.6 \pm 0.27$  ppm. Twenty-one unexposed men who worked for the same company, matched for sex, age, and smoking habits, served as controls. Urine was collected before the shift and at the end of the shift and analyzed for free 2-BAA, retinol binding protein, and creatinine. Blood was collected and measured for RBC counts, Hb, hematocrit, MCV, MCHC, haptoglobin, reticulocytes, and osmotic resistance. A significant correlation was observed between end shift urinary 2-BAA concentrations and 2-BE in air. There was no effect on hematologic, hepatic and renal parameters. A NOAEL of 0.6 ppm for decreased hemotocrit and increased MCHC was identified from this study based on the geometric mean of the exposed workers. However, in its toxicological review of 2-BE, the USEPA Integrated Risk

Information System (IRIS) (USEPA 1999) indicated that there were limitations of this occupational study. Some of the limitations noted were that the authors did not account for an important metabolic detoxification pathway, the higher alcohol consumption among exposed workers, and the lack of relation between hematologic results and parameters of internal exposure.

The ATSDR has used the NOAEL of 0.6 ppm (600 ppb) identified from the Haufroid et al. (1997) inhalation study to develop an inhalation chronic Minimal Risk Level (MRL). ATSDR divided the NOAEL by a cumulative UF of 3 (1 for extrapolation from animals to humans and 3 for human variability) to derive the chronic MRL of 966  $\mu\text{g}/\text{m}^3$  or 200 ppb (ATSDR 1998). No adjustment for intermittent to continuous exposure was applied, because 2-BE and its major metabolite, 2-BAA, are eliminated from the body within 24 h. A UF of 1 was applied for interspecies extrapolation in light of some evidence that humans are not more sensitive than experimental animals for 2-BE-induced hematological effects. A UF of 3 for human variability was used because the results of *in vitro* data suggest that 2-BE does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996 in ATSDR 1998).

#### **4.1.1.2 Animal Studies**

##### **4.1.1.2.1 NTP (1998)**

In a portion of the National Toxicology Program (NTP) two-species, 2-year inhalation study on 2-BE (NTP 1998), groups of F344 rats were exposed to 0, 31, 62.5, and 125 ppm, and groups of B6C3F1 mice were exposed to 0, 62.5, 125 and 250 ppm (6 hrs/day, 5 days/week). Mice and rats were examined at 3, 6, and 12 months (8-10 animals/duration) for hematologic effects. In rats, statistically significant decreases in automated and manual hematocrit values, Hb, and erythrocyte counts were observed in the 31 ppm females exposed for 3 and 6 months and in males exposed to 62.5 ppm for 12 months. MCV was increased following 31 ppm and higher exposures at 3 months in both males and females. In mice, statistically significant decreases in those same hematologic endpoints were also observed in the 125 ppm females and the 250 ppm males and females exposed for 3, 6, and 12 months. No changes in MCV were observed, except for an increase in the 250 ppm females exposed for 12 months. The results showed that female rats appear to be more sensitive to hematologic effects of 2-BE than other animals. A LOAEL of 31 ppm for hematologic effects in female rats, the most sensitive species and sex, was identified from this inhalation study and represented a LOAEL for a 3- and 6-month exposure.

In a separate subchronic portion of this study (NTP 1998), both groups of F344 rats and B6C3F1 mice (10 animals/sex) were exposed to 0, 31, 62.5, 125, 250 and 500 ppm of 2-BE 6 h/day, 5 days/week for 14 weeks and were then evaluated for hematologic effects. A mild to moderate regenerative anemia were observed at all concentrations in female rats, at the highest three concentrations in male rats, and at the two highest concentrations in both sexes of mice. Alterations in hematologic parameters were observed at the LOAEL of 31 ppm in female rats and 62.5ppm in male rats. The 31 ppm exposure level was considered a NOAEL for male rats and for male and female mice. Therefore, the dose-response data on the hematologic effects in female rats from the NTP (1998) subchronic (14 weeks and 6 months) studies were selected by the USEPA IRIS as the basis for an inhalation reference concentration (RfC) (USEPA 1999).

#### 4.1.1.2.2 Dodd et al. (1983)

In a subchronic inhalation study of hematological effects in rats (Dodd et al. 1983), Fischer 344 rats (16 rats/sex/group) were exposed to 0, 5, 25, or 77 ppm 2-BE 5 days per week, 6 h per day, for 13 weeks. Slight, but statistically significant decreases in RBC (13% below control) and Hgb, accompanied by an increase in MCHC (11% above control), were observed in the females exposed to 77 ppm after 6 weeks of the exposure regimen. At the conclusion of the 13-week exposure regimen, however, the hematologic effects seen in the females had lessened (RBC was 7% below control) or returned to control value ranges. Male rats of the 77 ppm group exhibited slight (5 % below control) but statistically significant decreases in RBC counts after the conclusion of 13-week exposure regimen. There were no significant biological effects in the 5 or 25 ppm-exposed rats. A subchronic NOAEL of 25 ppm in both male and female rats, and a LOAEL of 77 ppm in male rats representative of a 13-week exposure for hematological effects were identified from this study.

The California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) has published an inhalation chronic Reference Exposure Level (REL) of 200  $\mu\text{g}/\text{m}^3$  (40 ppb) for 2-BE based on an inhalation study of hematological effects in rats conducted by Dodd et al. (1983) (OEHHA 1997). A subchronic NOAEL of 25 ppm for hematological effects in rats identified from this study was used. To convert from intermittent exposure to continuous exposure, the subchronic NOAEL was multiplied by 6/24 h and 5/7 days. The converted subchronic NOAEL of 4.5 ppm was then divided by a cumulative UF of 100 (1 for extrapolation from animals to humans, 10 for extrapolation from subchronic to chronic exposure, and 10 for human variability) to derive the chronic REL. No UF was applied for interspecies extrapolation in light of some evidence that humans are not more sensitive than experimental animals for 2-BE-induced hematological effects.

#### 4.1.2 MOA Analysis and Dose Metric

Section 3.1.2 contains a discussion of the MOA of 2-BE. Although the hematologic effects induced by 2-BAA have not been established conclusively, the MOA for changes in hematologic parameters induced by 2-BE have been attributed to its metabolite, 2-BAA (IARC 2006). A physiological based pharmacodynamic (PBPK) model was used by IRIS (USEPA 1999) to estimate the internal dose surrogate ( $C_{\text{max}}$  2-BAA in blood). The calculated  $C_{\text{max}}$  for 2-BAA in blood corresponding to the female rat LOAEL of 31 ppm 2-BE was 285  $\mu\text{M}$  and was used by IRIS to calculate the human equivalent concentrations (HECs).

#### 4.1.3 POD for the Key Study and Dosimetric Adjustments

As mentioned in Section 4.1.1.1, there were limitations of Haufroid et al. (1997) occupational study. The IRIS review finds there are no reliable human chronic health effects data available. Thus, the subchronic/chronic LOAEL of 31 ppm for hematologic effects in female rats identified by NTP (1998) was used as the critical effect for deriving the  $^{\text{chronic}}\text{ESL}_{\text{nonlinear (nc)}}$ . The TS believes that the LOAEL of 31 ppm based on the NTP (1998) animal study is a more conservative and appropriate POD than a chronic NOAEL based on the Haufroid et al. (1997) human study or a subchronic NOAEL based on the Dodd et al. (1983) animal study. However, experimental *in vivo* and *in vitro* data indicate that pharmacodynamically, humans are less

sensitive than rats to the hematological effects of 2-BE (Carpenter et al. 1956; Ghanayem and Sullivan 1993, Udden and Patton, 1994, Udden, 1995 in ATSDR 1998 and USEPA 1999).

Based on the NTP (1998) study and other animal studies, female rats appear to be more sensitive to the hematologic effects of 2-BE than other animals. In addition, model analyses of the data from the NTP (1998) study predicted steeper dose-response curves for RBC count (as an indicator of cell lysis). Thus, the LOAEL of 31 ppm for hematologic effects in female rats and dose-response information on RBC count were used as the basis for a RfC by the IRIS (USEPA 1999). USEPA (1999) calculated the HECs using 4 different methods. They were as follows: standard default  $150 \text{ mg/m}^3$  (31 ppm); physiologically-based pharmacokinetic (PBPK)  $474 \text{ mg/m}^3$  (98 ppm); benchmark concentration ( $\text{BMC}_{05}$ )  $130 \text{ mg/m}^3$  (27 ppm); and PBPK and  $\text{BMC}_{05}$  combined  $380 \text{ mg/m}^3$  (79 ppm). Refer to USEPA (1999) for detailed information on their methods of analysis and RfC derivation. Consistent with USEPA (1999), the TS used the  $\text{POD}_{\text{HEC}}$  of  $380 \text{ mg/m}^3$  (79 ppm) based on PBPK and  $\text{BMC}_{05}$  modeling combined.

#### 4.1.4 Adjustments to the $\text{POD}_{\text{HEC}}$

The MOA by which 2-BE produces decreases in RBC count is considered a threshold, nonlinear MOA. Therefore, UFs were applied to the  $\text{POD}_{\text{HEC}}$  of  $380 \text{ mg/m}^3$  (79 ppm) to derive a ReV.

Consistent with USEPA (1999), the TS selected a UF of 10 for human variability ( $\text{UF}_H$ ) to account for possible childhood and gender susceptibility, and individuals with enhanced metabolism or decreased excretion of 2-BAA and individuals whose RBC walls are less resistant to the lysis caused by 2-BAA. While the TS usually does not use a LOAEL to NOAEL UF ( $\text{UF}_L$ ) if the  $\text{BMC}_{05}$  modeling value is used (TCEQ 2006), a UF of 3 was conservatively selected for a LOAEL to NOAEL UF ( $\text{UF}_L$ ) because the BMC used in the derivation of the RfC was based on a more serious hematologic endpoint, i.e., RBC lysis as measured by a decrease in RBC count (USEPA 1999). A UF of 1 for intraspecies uncertainty ( $\text{UF}_A$ ) was used because a PBPK model was used to account for toxicokinetic and toxicodynamic differences between animals and human. A UF of 1 was selected for extrapolating the results from a subchronic study to chronic exposures ( $\text{UF}_{\text{Sub}}$ ) because a PBPK model was used and 2-BE and its major metabolite, 2-BAA, do not accumulate so chronic effects would not be expected to differ significantly from subchronic effects. The NTP (1998) reports a significant increase in the severity of hemolytic effects beyond 1-3 weeks of inhalation exposure time to 2-BE would not be expected (also see Section 4.1.3). A database UF of 1 ( $\text{UF}_D$ ) was used because the chronic database for 2-BE is considered adequate. Confidence is considered high on the RfCs derived from internal dose measures (combined PBPK/BMC method) because pharmacokinetic difference between rats and humans were accounted for using PBPK models.

$$\begin{aligned}\text{Chronic ReV} &= \text{POD}_{\text{HEC}} / (\text{UF}_H \times \text{UF}_L \times \text{UF}_A \times \text{UF}_{\text{Sub}} \times \text{UF}_D) \\ &= 79 \text{ ppm} / (10 \times 3 \times 1 \times 1 \times 1) \\ &= 2.6 \text{ ppm} \\ &= 2,600 \text{ ppb}\end{aligned}$$

Accordingly, by applying a cumulative UF of 30 to the aforementioned  $\text{POD}_{\text{HEC}}$ , the ReV is 2,600 ppb.

The <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub> of 780 ppb (3,800 µg/m<sup>3</sup>) was set according to the ESL guidance (TCEQ 2006) based on the chronic ReV multiplied by a HQ of 0.3 (Table 4).

**Table 4 Derivation of the Chronic ReV and <sup>chronic</sup>ESL<sub>nonlinear(nc)</sub>**

Parameter	Summary
Study	NTP (1998) and USEPA (1999)
Study Population	Rats and mice (10/sex/exposure level)
Study Quality	High
Exposure Method	Whole-body chamber inhalation
Critical Effects	Hematologic effects
POD (original female rats study)	31 ppm (LOAEL)
Exposure Duration	6 h/day, 5 days/week for 3 to 12 months
POD <sub>HEC</sub> Dosimetry adjustment from animal concentration to HEC	79 ppm (380 mg/m <sup>3</sup> ) (combined PBPK/BMC <sub>05</sub> method)
Total UFs	30
<i>Interspecies UF</i>	1
<i>Intraspecies UF</i>	10
<i>LOAEL UF</i>	3
<i>Subchronic to chronic UF</i>	1
<i>Incomplete Database UF</i>	1
<i>Data Quality</i>	High
<b>Chronic ReV (HQ = 1)</b>	<b>12,000 µg/m<sup>3</sup> (2,600 ppb)</b>
<sup>chronic</sup> ESL <sub>nonlinear(nc)</sub> (HQ = 0.3)	<b>3,800 µg/m<sup>3</sup> (780 ppb)</b>

#### 4.2 Carcinogenic Potential

No studies were found demonstrating carcinogenic effects in humans or animals after oral or inhalation exposure to 2-BE. NTP (1998) reported no evidence of carcinogenic activity in male F344/N rats and equivocal evidence in female F344/N rats. Under the 1986 USEPA Guideline for Carcinogen Risk Assessment, 2-BE is deemed to be a *possible human carcinogen* based on limited laboratory animal evidence and a lack of human studies (USEPA 1986, 1999). Using the weight-of-evidence narrative recommended in the 2005 cancer guidelines (USEPA 2005), the TCEQ has classified 2-BE as “Data are inadequate for an Assessment of Human Carcinogenic Potential” (TCEQ 2006). 2-BE is evaluated by IARC as *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC 2006).

#### 4.3 Welfare-Based Chronic ESL

No information was found to indicate that special consideration should be given to possible vegetation effects from 2-BE.

#### 4.4 Long-term ESL

This chronic evaluation resulted in the derivation of the following values:

- chronic ReV = 12,000  $\mu\text{g}/\text{m}^3$  (2,600 ppb)
- $\text{chronicESL}_{\text{nonlinear(nc)}} = 3,800 \mu\text{g}/\text{m}^3$  (780 ppb)

The long-term ESL for air permit reviews is the  $\text{chronicESL}_{\text{nonlinear(nc)}}$  of 3,800  $\mu\text{g}/\text{m}^3$  (780 ppb) (Table 1). For the evaluation of long-term ambient air monitoring data, the chronic ReV of 12,000  $\mu\text{g}/\text{m}^3$  (2,600 ppb) is used for the evaluation of ambient air monitoring data (Table 1). The  $\text{chronicESL}_{\text{nonlinear(nc)}}$  (HQ = 0.3) is not used to evaluate ambient air monitoring data.

The long-term ESL is much higher than the short-term odor-based ESL of 210  $\mu\text{g}/\text{m}^3$  (43 ppb) (Table 1). Thus, if the 1-h modeling concentrations meet the short-term ESL, no acute and chronic adverse effects are expected to occur as a result of exposure to 2-BE emissions from a permit application facility.

### Chapter 5 References

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