

# Cal/OSHA Draft Substance Summary for the September 5, 2017 HEAC Meeting

**Substance name:** 2-butoxyethyl acetate

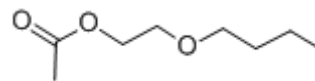
**CAS:** 112-07-2

**MW:** 160.20

Synonyms: 2-butoxyethyl ester, 2-butoxyethanol acetate, ethylene glycol monobutyl ether acetate, EGBA, Butyl Cellosolve acetate

Molecular formula: C<sub>8</sub>H<sub>16</sub>O<sub>3</sub>

Structural formula:



ppm to mg/m<sup>3</sup> conversion factors at 25 °C and 760 mm/Hg: 1 ppm = 6.55 mg/m<sup>3</sup>

Physical characteristics at room temp: Colorless liquid with a sweet, fruity odor.

Special physical characteristics if any: None.

Flammability and other hazards: Flash point 71°C; Auto-Ignition temp. 340°C

Major commercial form(s): Not known.

Uses/applications: Primarily used as a slow evaporating solvent for nitrocellulose lacquers, epoxy resins, and multicolor lacquers. Also used as a coalescing aid for polyvinyl acetate latex and in some ink and spot remover formulations.

## OELs

Source	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
Title 8 PEL	NA		
OSHA PEL	NA		
ACGIH TLV	20 ppm as TWA; 131 mg/M <sup>3</sup>	2003	<b>A3, confirmed animal carcinogen with unknown relevance to humans</b>
NIOSH REL	TWA 5 ppm (33 mg/M <sup>3</sup> -skin)		
NIOSH IDLH	100 ppm	1994	
MAK	Carcinogen category 2	2002	

## Other recommendations:

Source and date	Findings/Recommendations	Basis/source/ref(s)	Discussion and Assessment
OEHHA (2016)	Final draft Inhalation RELs - 4.7 mg/m <sup>3</sup> or 1 ppm (acute); 0.164 mg/m <sup>3</sup> or 0.034 ppm (8-hour); and 0.082 mg/m <sup>3</sup> or 0.017 ppm (chronic)	Ocular and nasal irritation (sensory irritation) for acute REL (Carpenter et al.; 1956); nasal hyaline degeneration of olfactory epithelium for 8-hour REL (NTP; 2000) and chronic REL (NTP; 2000).	Acute REL based on three whole-body human exposure studies of small sample size to identify a LOAEL; 8-hour REL and chronic REL based on 2 year whole-body inhalation exposure of rats (NTP, 2000); benchmark dose analysis performed and calculated BMCL05 values used as POD for chronic REL derivation.
US EPA (IRIS;	Inhalation chronic RfC 1.6 mg/m <sup>3</sup> .	Hemosiderin deposition in the liver (NTP; 2000).	The inhalation chronic RfC based on 2 year chronic study (NTP, 2000). A 10% extra risk for increase in

2010)			hemosiderin deposition in liver was used as a BMR (bench mark response) level and appropriate POD (point of departure) to calculate the RfC. UF = 10 for variability of human response.
NTP (2000)	Hematotoxic and mixed evidence of carcinogenicity.	Regenerative hemolytic anemia and subsequent effects on hematopoietic system in rats and mice in 14 week exposure study; and increase in incidences of neoplasms and nonneoplastic lesions in rats and mice in 2 year exposure study (NTP; 2000).	Anemia was concentration dependent; rats were more severely affected than mice; females were more severely affected than males; anemia in rats was macrocytic, normochromic, and responsive to increase in erythropoiesis, whereas it was normocytic in mice; Evidence of carcinogenic activity – none in male rats; equivocal in female rats based on increased combined incidences of benign and malignant pheochromocytoma of adrenal medulla; some in male mice based on increased incidences of hemangiosarcoma of liver; and some in female mice based on increased incidences of forestomach squamous cell papilloma or carcinoma.
ATSDR (Toxprofile; 1998)	Inhalation MRL 6 ppm (acute); 3 ppm (subacute); 0.2 ppm (chronic).	Hematotoxicity – acute (Tyl et al.; 1984); subacute (Dodd et al.; 1983); chronic (Haufroid et al.; 1992).	Acute, subacute, and chronic MRLs were respectively derived based on a NOAEL of 50 ppm in pregnant rats; NOAEL of 25 ppm in normal rats; and NOAEL in humans for statistically significant decreased hematocrit and increased mean corpuscular hemoglobin concentrations. The observed changes were still within the range of normal human variability.
IARC (2006)	Group 3 – not classifiable as to its carcinogenicity to humans.	Inadequate evidence in humans and limited evidence in experimental animals for its carcinogenicity (NTP; 2000).	Evidence of carcinogenic activity – none in male rats; equivocal in female rats based on increased combined incidences of benign and malignant pheochromocytoma of adrenal medulla; some in male mice based on increased incidences of hemangiosarcoma of liver; and some in female mice based on increased incidences of forestomach squamous cell papilloma or carcinoma.

## Health Summary

2-butoxyethyl acetate (2-BEA) causes irritation, central nervous effects and nausea in humans and hemolytic, hepatic and kidney effects in animals. Upon absorption into blood, 2-BEA is rapidly hydrolyzed to 2-butoxyethanol (2-BE) which undergoes rapid metabolism to butoxyacetic acid (BAA), the toxic metabolite of these two glycol ethers. BAA and its metabolites are well associated with the toxicological effects of 2-BE so the conclusion is drawn that 2-BEA will cause the same effects through its conversion to BAA. No health assessments of 2-BEA have been conducted so consequently the literature and health assessments of 2-BE were reviewed to assess the health effects of 2-BEA. Even though its use is wide-spread, there is limited human exposure data with which to assess the health effects of 2-BE. Human exposure data has demonstrated the irritancy of 2-BE under short-term controlled exposure studies. The toxicological effects of 2-BE have been extensively characterized in multiple species and in vitro and several PBPK models for 2-BE in rats and humans have been developed. There are also several workplace studies that collected biomonitoring data with which to evaluate the PBPK models. 2-BE was recently reviewed by several authoritative bodies (EU, 2006; US EPA, 2010, OEHHA 2016) resulting in health-based assessments based on a NTP 2-year study in rats and mice. The NTP 2000 study produced multiple data sets for benchmark dose modeling that were interpreted differently by USEPA-IRIS and OEHHA, resulting in different OELs. The two agencies also utilized different approaches to estimate reference levels for humans. USEPA used a PBPK model to estimate an internal dose in the rat and scaled that to humans while OEHHA applied uncertainly factors to the 5% effect determined through benchmark dose modeling of the animal data. Key details of the NTP studies and the pertinent sections of the USEPA and OEHHA assessments are provided for discussion. Reviews of volunteer exposure studies and workplace biomonitoring studies are also presented.

## Principal Study

NTP study, 2000: Toxicology and Carcinogenesis Studies 2-Butoxyethanol (CAS NO. 111-76-2) in F344/N Rats and B6C3F<sub>1</sub> Mice (Inhalation Studies)

Two-species, 2-year inhalation study on 2-BE in both genders of rats and mice. In this chronic study, animals were exposed to 2-BE 6 hours/day, 5 days/week at concentrations of 0, 31, 62.5, and 125 ppm (0, 150, 302, and 604 mg/m<sup>3</sup>) for groups of 50 F344/N rats and 0, 62.5, 125, and 250 ppm (0, 302, 604, and 1,208 mg/m<sup>3</sup>) for groups of 50 B6C3F<sub>1</sub> mice. The researchers stated that the highest exposure was selected to produce a 10–15% depression in hematologic indices. They reported that no effect on survival was observed in rats, but survival was statistically significantly decreased in male mice exposed to 125 or 250 ppm, compared with chamber controls (54, 52, and 78% respectively (NTP, 2000, 196293)). Although statistics were not reported for mean body weights, the rats exposed to 31 and 62.5 ppm had similar mean body weights to the control rats. Mean body weights of the exposed mice were generally less than those of controls, with females experiencing greater and earlier reductions. From week 17 to the end of the study, the mean body weights of 125 ppm female rats were generally less than those of controls. Nonneoplastic effects in rats included hyaline degeneration of the olfactory epithelium in males (13/48, 21/49, 23/49, 40/50) and females (13/50, 18/48, 28/50, 40/49) and Kupffer cell pigmentation in the livers of males (23/50, 30/50, 34/50, 42/50) and females (15/50, 19/50, 36/50, 47/50). The severity of the olfactory lesion was not affected by exposure. The Kupffer cell pigmentation is a result of hemosiderin accumulation and is a recognized secondary effect of the hemolytic activity of 2-BE (NTP, 2000). Specific aspects of the two studies are provided below.

**2-YEAR STUDY IN RATS:** Groups of 50 male and 50 female rats were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31.2, 62.5, or 125 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 27 male and 27 female rats were exposed to 0, 62.5, or 125 ppm for evaluation at 3, 6, and 12 months and nine male and nine female rats were exposed to 31.2 ppm for evaluation at 3 (hematology only) and 6 months. **Survival and Body Weights:** Survival of exposed male and female rats was similar to the chamber control groups. The mean body weights of females exposed to 125 ppm were generally less than the chamber control group. **Hematology and Bone Marrow Cellularity:** The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related mild macrocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females more affected than males. Significant increases in bone marrow cellularity and decreases in the myeloid/erythroid ratio relative to the chamber controls were observed at all time points in females exposed to 125 ppm, and a decrease in the myeloid/erythroid ratio was observed in males exposed to 125 ppm at 12 months. **Pathology Findings:** The incidence of benign or malignant pheochromocytoma (combined) of the adrenal medulla in females exposed to 125 ppm was not significantly increased compared to the chamber controls but exceeded the historical control range. Exposure-related increases in the incidences of hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation of the liver were observed in male and female rats.

**2-YEAR STUDY IN MICE:** Groups of 50 male and 50 female mice were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 62.5, 125, or 250 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 30 male and 30 female mice were exposed to 0, 62.5, 125, or 250 ppm for evaluation at 3, 6, and 12 months. **Survival and Body Weights:** Survival of male mice exposed to 125 or 250 ppm was significantly less than that of the chamber control group. The mean body weights of exposed males were generally less than those of the chamber control group during the last 6 months of the study. The mean body weights of exposed female mice were less than those of the chamber control group; the

reductions were greater and occurred earlier than those observed in males. Hematology: The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related minimal normocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females affected slightly more than males. Pathology Findings: In females exposed to 250 ppm, incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma (combined) were significantly increased relative to the chamber controls, and these incidences exceeded the ranges in historical chamber controls. In 2-butoxyethanol exposed males, there were possible exposure-related increases in the incidences of squamous cell papilloma of the forestomach, although the increases were not significant and the incidences were within the historical control range for chamber controls. Accompanying these neoplasms in females and, to a lesser extent, in males were exposure-related increases in the incidences of ulcer and epithelial hyperplasia of the forestomach. In male mice exposed to 250 ppm, the incidence of hemangiosarcoma of the liver was significantly increased relative to chamber controls and exceeded the range in historical controls; in addition, there were possible exposure-related increases in the incidence of hepatocellular carcinoma. Incidences of hemosiderin pigmentation in the Kupffer cells were significantly increased in 125 and 250 ppm males and all exposed groups of females. The incidences of splenic hematopoietic cell proliferation and hemosiderin pigmentation were generally increased in males and females, and the incidences of bone marrow hyperplasia were increased in males. The incidences of hyaline degeneration of the olfactory and respiratory epithelia of the nose were increased in female mice.

## **OEL Derivations**

OEHHA, 2016

**Choice of Principal Study and Critical Effect:** In the key study (NTP, 2000), rats and mice subjected to a whole-body inhalation exposure of 0, 31.2, 62.5, or 125 ppm for two years displayed nasal olfactory epithelium lesions, liver Kupffer cell pigmentation, and forestomach epithelial hyperplasia and ulcers in both species. This study was chosen because it used a lifetime inhalation exposure, and provided the most sensitive toxicity endpoint not dependent on hemolytic anemia (humans tend to be resistant to 2-BE hematological effects). Benchmark dose analysis was used to calculate BMCL05 values (the 95% lower confidence interval at the 5% response rate), and corresponding NOAEL and LOAEL values for Nasal Olfactory Epithelium Lesions, Liver Kupffer Cell Pigmentation, Forestomach Epithelial Hyperplasia, and Forestomach Ulcer. We are using the BMCL05 values as the point of departure (POD) for OEL derivation. For each endpoint, the BMCL05 is derived from the models that provided the best visual and statistical fit to the data, particularly in the low dose region of the dose-response curve where the BMCL05 resides.

Of the chronic effects noted, the nasal olfactory epithelium lesions are more analogous to what would occur with human exposure to 2-BE than the other lesions. The primary cause of the nasal lesions is likely to be direct 2-BE irritation through the inhalation route (NTP, 2000). OEHHA focused on the regional (nose and upper respiratory tract) responses/changes, which is the most sensitive endpoint, and is more consistent with the acute inhalation effect of 2-BE in humans. Although liver Kupffer cell pigmentation would provide a lower BMCL05, this effect is secondary to hemolytic anemia, which is not considered by OEHHA to be relevant for 2-BE OEL derivation in humans. Regarding the forestomach effects in mice, humans do not have a similar organ, but it is conceivable that 2-BE could irritate the lining of the esophagus or stomach in humans. However, this endpoint was not as sensitive as the nasal olfactory epithelium lesions and there is evidence that humans would not be as sensitive as mice for upper gastrointestinal effects.

**BMD Approach/Selection of the POD:** Little difference was observed in the incidence of nasal lesions between male and female rats, compared to the gender differences for incidences observed for the other endpoints.

Therefore, combining male and female rats for BMCL05 estimation is applicable for the nasal endpoint. However, the BMCL05 results (7.6 ppm) in female rats were chosen as the point of departure (POD) for REL derivation because the BMCL05 was slightly lower with this set of data.

**OEL Derivation:** To derive the 8-hour OEL, the average experimental exposure was adjusted for 8-hour exposures, seven days/week. The assumption is that the rats show both mixed active and inactive periods during exposure, and a time adjustment is made to simulate an active 8-hour working period during which the off-site worker is exposed. The concentration is first adjusted down to 24-hour continuous exposure ( $6/24$  hours  $\times$   $5/7$  days per week), then multiplied by 2 ( $20\text{m}^3/10\text{m}^3$ ) to represent an active individual breathing half the air breathed in a day during an active working 8-hour period when exposure occurs, compared to what a resident would breathe over a 24-hour period. Adjustments for differences in minute volume and for relative areas of human and rat extrathoracic regions of the respiratory tract resulted in a human equivalent concentration of 0.95 ppm (OEHHA, 2008c). An interspecies Uncertainty Factor (UF) =  $\sqrt{10}$  was used. This was composed of a toxicokinetic UF of 1 because we utilized the HEC dosimetric adjustment and the toxicological endpoint is a port of entry effect. We retained a UF of  $\sqrt{10}$  to account for interspecies tissue sensitivity differences. The intraspecies toxicokinetic and toxicodynamic UFs were both assigned  $\sqrt{10}$ . No additional adjustment was made for early life exposures, since the effect of concern is at the portal of entry. The cumulative UF was 30 which results in an 8-hour OEL of 0.032 ppm ( $0.15\text{ mg/m}^3$ ) and this value is just slightly higher than 2-BE's odor threshold (0.10 ppm). The derivation is outlined below.

Study: NTP, 2000 Study population Rats (50 animals/group/gender)

Exposure method: Discontinuous whole-body inhalation exposure to 0, 31.2, 62.5, 125 ppm

Critical effects: Nasal hyaline degeneration of olfactory epithelium

LOAEL: 31.2 ppm

BMCL05: 7.6 ppm (Logistic model from female rats)

Exposure continuity: 6 hours/day, 5 days/week

Exposure duration: 2 years

Time-adjusted exposure: 2.714 ppm ( $7.6\text{ ppm} \times 6/24 \times 5/7 \times 20/10$ )

Human Equivalent Concentration: 0.950 ppm (gas with extrathoracic respiratory effects, RGDR = 0.35)

LOAEL uncertainty factor: 1 (with use of a BMCL05)

Subchronic uncertainty factor: 1

Interspecies uncertainty factor: Toxicokinetic (UFA-k) 1 Toxicodynamic (UFA-d)  $\sqrt{10}$

Intraspecies uncertainty factor: Toxicokinetic (UFH-k)  $\sqrt{10}$  Toxicodynamic (UFH-d)  $\sqrt{10}$

Cumulative uncertainty factor: 30

Eight-hour Reference Exposure Level: 0.032 ppm ( $0.15\text{ mg/m}^3$ )

USEPA, 2010

**Choice of Principal Study and Critical Effect:** Only one human occupational exposure study to low levels of 2-BE is available, which did not observe changes outside the normal clinical ranges in hepatic, renal, or hematologic parameters (Haufrond et al., 1997). The animal studies considered for selection as principal studies include the 14-week and 2-year inhalation studies by NTP (2000) in rats and mice, the developmental toxicity study by Tyl et al. (1984) in rats and rabbits, the developmental toxicity study by Nelson et al. (1984) in rats, and the subchronic study by Dodd et al. (1983) in rats. The NTP (2000) study was selected as the principal study because it was conducted in two species and provides data for different durations and for more dose groups than the other studies. The developmental toxicity studies identified effects at doses higher than the doses associated

with the critical effects identified in the NTP (2000) study and were not used for quantitative purposes. While the subchronic study by Dodd et al. (1983) was well-conducted, the NTP (2000) study contained more dose groups, more animals per group, and a longer duration of exposure. Thus, Dodd et al. (1983) was not used for quantitative purposes. Two endpoints from the NTP (2000) study—the hemolytic endpoint from the 14-week inhalation study and the hemosiderin deposition endpoint from the 2-year inhalation study— were used for the critical effect. The hemolytic endpoints in the 1999 2-BE Toxicological Review were used to derive the reference values, but were not used to derive the values in this updated assessment. New MOA information published since the 1999 2-BE Toxicological Review is included in this document, and this information supports the hemosiderin deposition endpoint as an important key event in the proposed MOA.

The primary effects of 2-BE exposure were hematological effects and were observed in both species and genders tested. Female rats (NTP, 2000) appeared to be most sensitive among animals studied. A mild-to-moderate regenerative anemia was observed in females exposed to all concentrations, with a LOAEL of 31 ppm identified for hematological effects in male and female rats and no NOAEL. Exposure-related trends were noted for reticulocyte count, RBC count, MCV, Hb concentration, and Hct. The hematological endpoints were considered for the derivation of the OEL; however, they presented a number of difficulties. It was not clear which of the hematological endpoints (changes in RBC count, reticulocyte count, MCV, Hb concentration, and Hct) observed in 2-BE-exposed animals should be used to derive an OEL. In the case of BMD analysis, the proper benchmark response (BMR) level for the BMD derivation was uncertain. In addition, while these hematologic effects were observed in both the subchronic and chronic studies and persisted with exposure duration, they did not progress in severity in the subchronic-to-chronic study. Further, better model fits were obtained from the BMD analysis of the subchronic study, which used two more exposure concentrations than the chronic study. For these reasons, the hematologic responses from the 14-week subchronic study were chosen for use in the BMD analyses of this endpoint. Selection of the most appropriate hematologic endpoints for use in the BMD analysis also required consideration of 2-BE's MOA for hemolysis. The suggested MOA of 2-BE hemolysis is based on data indicating that BAA, an oxidative metabolite of 2-BE and the first hypothesized event in the MOA, is likely to be the causative agent in hemolysis. The second event in the MOA is erythrocyte swelling and cell lysis, which is believed to be preceded by an increase in the osmotic fragility and a loss of deformability of the erythrocyte. This results in decreased values for RBC count, Hb, and Hct and in response, an increase in the production of immature RBCs (reticulocytes) by the bone marrow. Although changes in reticulocyte and nucleated erythrocyte counts sometimes represent the largest measurable differences between exposed animals and unexposed control animals, this parameter is highly variable and does not always exhibit a dose-dependent trend. While these endpoints can be indirect markers of RBC lysis, they are governed by multiple feedback control processes that can be both very sensitive and variable. Therefore, a change in reticulocyte or nucleated erythrocyte count is not considered a suitable endpoint for deriving the OEL. Until more is known about the molecular interaction between BAA and specific cellular molecules, it is reasonable to assume that changes in MCV and RBC count are measurements of precursor events in response to both oral and inhalation 2-BE exposure. Therefore, dose response information on MCV and RBC count are key endpoints used in the BMD analyses and were considered for derivation of the OEL for 2-BE. While the toxicokinetic data suggest that MCV should theoretically be the earlier indicator of hemolytic effects from 2-BE exposure, recent studies suggest that the relationship between the rate of MCV increase and RBC count decrease may not be consistent across exposure protocols. In the gavage studies of Ghanayem et al. (1987) and the inhalation studies of NTP (2000), Hct, a measure of RBC volume relative to blood volume, tended to decrease along with RBC count and Hb at all exposure levels for which a hematologic effect was observed. However, Hct did not change as RBC count and Hb decreased following drinking water exposures (NTP, 1993). Thus, the loss of erythrocytes in the drinking water studies (reduced RBC

count) may have been offset by a concurrent increase in the size of the individual cells (increased MCV). This was not the case in the gavage and inhalation studies. For these reasons, greater weight is given to reduced RBC count, as opposed to increased MCV. While the hemolytic effects appeared to be among the earliest effects from 2-BE exposure, the hemosiderin deposition endpoint was selected as the critical effect. This effect was found to occur in both species and genders of animals tested, with rats being the more sensitive species; the effect also occurred in the 14-week subchronic NTP inhalation study. The suggested MOA of 2-BE-induced liver effects is based on the observation that the hemolytic effects led to compensatory erythropoiesis and significant increases in blood degradation products, including an increased accumulation of hemosiderin in the liver Kupffer cells of 2-BE-exposed animals. The hemosiderin accumulation seen in the Kupffer cells was found to increase in severity with increasing dose and exposure duration, unlike the hemolytic endpoints, such as decreased Hct, which did not progress from 3 to 12 months. Thus, hemosiderin deposition in Kupffer cells in the rat liver is believed to be a sequela to the hematologic effects. Because of the progression of this effect with chronic exposure, hemosiderin is deemed to be the most sensitive effect. A NOAEL was not identified, while a LOAEL of 31 ppm was identified in both male and female rats. The 2-year chronic inhalation study by the NTP (2000) observed forestomach ulcers in female mice at all exposure levels, but this effect has not been observed in any other species, including mice exposed orally to 2-BE. Though the incidence of this lesion increased with exposure, severity of the lesion did not increase with increasing dose.

**BMD Approach/Selection of the POD:** For the purposes of deriving an OEL for 2-BE, hemosiderin staining data were evaluated in male and female rats from the 2-year chronic study by NTP. The current BMD technical guidelines suggest the use of 10% extra risk as a BMR level for quantal data, as this is at or near the limit of sensitivity in most cancer bioassays and in some noncancer bioassays as well. Because the hemosiderin staining endpoint was observed in control animals and a 10% increase in incidence was within the observable range of the data, 10% extra risk was considered an appropriate BMR and a BMCL10 an appropriate POD for derivation of the OEL. The AUC was selected as the appropriate dose metric due to the nature of the endpoint, hemosiderin deposition. This endpoint increased in severity with increased duration (subchronic to chronic) and is believed to be the result of the cumulative exposure to 2-BE as opposed to a peak event.

Consideration of the available data has led to the selection of the 2-year inhalation study (NTP, 2000) and increased hemosiderin staining in the liver of male F344 rats as the principal study and critical effect for deriving the chronic OEL for 2-BE. This is a high-quality study and, when coupled with information on the MOA, U.S. EPA concluded that this is a precursor to an adverse effect and is appropriate for use in deriving the OEL. A BMCL10 of 133  $\mu\text{mol}\cdot\text{hour}/\text{L}$  for hemosiderin staining in liver of male rats chronically exposed to 2-BE (NTP, 2000) was used as the POD to calculate the OEL. A human PBPK model was used to back-calculate to a HEC of 16  $\text{mg}/\text{m}^3$  (3.4 ppm) for the  $\text{BMCL}_{\text{HEC}}$ .

**OEL Derivation—Including Application of Uncertainty Factors:** A factor of 10 was selected to account for the uncertainty associated with the variability of the human response (UFH) to the effects of 2-BE. Potentially susceptible subpopulations include individuals with enhanced metabolism or decreased excretion of BAA and individuals whose RBC membranes are more susceptible to the lysis caused by BAA, the precursor step to developing hemosiderin staining in the liver. Human in vitro studies suggest that the elderly and patients with fragile RBCs would not be more sensitive to the hemolytic effects of 2-BE than normal adults. Laboratory animal studies suggest that older animals are more sensitive than neonates and that females are more sensitive than males. Additionally, human responses to 2-BE have not been observed under a broad range of exposure conditions (e.g., repeated or long-term exposures) and potentially sensitive subjects (e.g., individuals predisposed to hemolytic anemia or infants). A factor of 1 was selected to account for the uncertainty associated with

interspecies variability resulting from toxicodynamic and toxicokinetic differences between animals and humans (UFA). In this assessment, the toxicokinetic uncertainty is addressed by the determination of an Human Equivalent Concentration in a combination of measured internal blood levels in the test animals and PBPK modeling. Thus, a value of 1 was selected for the toxicokinetic portion of the UFA. Regarding toxicodynamics, in vivo and in vitro studies indicate that humans may be significantly less sensitive than rats to the hematological effects of 2-BE. For this reason, a value of 1 was selected for the toxicodynamic portion of the UFA.

A factor to account for extrapolation from subchronic to chronic exposure (UFS) was not needed because the OEL was derived from a chronic inhalation study. A factor to account for the extrapolation from a LOAEL to a NOAEL (UFL) was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a benchmark response (BMR) for BMD modeling. In this case, EPA concluded a 10% increase in hemosiderin staining, indicating a precursor to an adverse effect, is appropriate for use in deriving the OEL. A factor of 1 was selected to account for deficiencies in the database (UFD). Studies that are available include chronic and subchronic studies for two species (rats and mice), and several reproductive and developmental studies, including a two-generation reproductive toxicity study. There are also limited human studies available following short-term inhalation exposure. A total UF of 10 (10 for UFH, 1 for UFA, and 1 for UFD) was used in the derivation of the OEL. The combined PBPK and BMC modeling method using hemosiderin as an endpoint was used to derive the OEL. In addition, MOA information was used to inform the choice of the critical effect. The OEL for 2-BE based on hemosiderin deposition in the liver was calculated as follows:

$$\text{OEL} = \text{BMCL}_{\text{HEC}} \div \text{UF} = 16 \text{ mg/m}^3 \div 10 = 1.6 \text{ mg/m}^3 \text{ Thus, the OEL is } 1.6 \text{ mg/m}^3 .$$

$$\text{Adjusting for occupational exposure: } 1.6 \times 24 \text{ hrs}/8\text{hrs} = 4.8 \times 1 \text{ ppm}/6.55 \text{ mg/m}^3 = 0.732 \text{ ppm}$$

### **Human exposure data**

Controlled volunteer studies:

Multiple inhalation toxicokinetic studies have exposed volunteers to 20 – 50 ppm for periods up to four hour without causing symptoms. These studies are usually conducted in exposure chambers with subjects at rest. 2-BE was not irritating to the eyes or respiratory tract at 20 ppm for 2 hours (Johanson *et al.*, 1986a) or 25 ppm for 10 minutes (Johanson *et.* 1999). A study by Johanson and Boman (1991) in which four male volunteers human volunteers were exposed to 50 ppm 2-BE for 2 2-hour intervals separated by a 30 minutes of clean air did not report any symptoms. In a repeat study (Jones *et al.*, 2003) no signs of irritation were reported after exposure of four volunteers to 50 ppm 2-BE for 2 hours on 9 separate occasions. Carpenter (1956) conducted numerous studies in humans. Two men and six rats were simultaneously exposed to 113 ppm for 4 hr. Symptoms in the men included nasal and eye irritation, disagreeable metallic taste, occasional belching and slight increase in nasal mucuous discharge. Hematological changes were observed in the rats but not in men. In a second experiment, two men and one woman were exposed to 195 ppm for 2 4-hr periods, separated by 30 min. The responses of all three subjects included immediate irritation of the nose and throat, followed by eye irritation and disturbed taste. The woman also developed a headache for 24 hours. No hematological changes were observed in the humans but were in the three exposed female rats. In a third study, two men and two women were exposed to 100 ppm for 8 hours. All experienced vomiting and headaches but no hematological effects (Carpenter, 1956).

Several controlled studies have examined the effect of physical exertion on 2-BE kinetics and symptoms. Seven male volunteers were exposed to 2-butoxyethanol to 20 ppm during light physical exercise (50 W) on a bicycle



ergometer (Johanson, 1986). The exposure took place in an exposure chamber and lasted 2 h. Expired air was collected at regular time intervals for estimation of the respiratory uptake of the solvent. Arterialized capillary blood and urine were sampled during and after the exposure period and analyzed for 2-butoxyethanol and its metabolite butoxyacetic acid. The respiratory uptake of 2-butoxyethanol averaged 10.1 /lmin or 57 % of the inspired amount. The concentration in blood reached a plateau level of 7.4  $\mu\text{mol/L}$ . None of the subjects complained of or showed any signs of adverse effects that could be related to the exposure to 2-butoxyethanol. Furthermore, no effects were observed in the electrocardiograms. During the exposure, no consistent changes in pulmonary ventilation, respiratory frequency, or heart rate were seen. Three male subjects were exposed by facemask to 25.2 ppm or 12.6 ppm at rest and 12.6 ppm at 30W of exercise, 50 min/hr for 4 hr (Van Vlem 1987). retention averaged 67.0, 68.9 and 77.6 % for the three exposure conditions. Respiratory elimination of and BAA at the 3 exposure conditions was 0.66 to 0.69 at rest and 0.24% at 30W. Recovered BAA at the three conditions was 27, 27 and 13.6% respectively. The authors concluded that workload influenced the respiratory elimination of and the total elimination of BAA.

## Occupational Studies

The relationship of BAA excretion and EBGE exposure was evaluated in a group of 5 women working at a silkscreen operation (Veulemans 1987). Half-shift personal monitoring (urine) was conducted for 5 days. Following a 12-day interruption, monitoring continued for an additional 7 days. Mean weekly exposure to 2-BE averaged 0.65 ppm. The urine samples showed higher post-shift concentrations of BAA in all cases compared with pre-shift concentrations. Pre-shift concentrations ranged from less than 1 to 5.5 mg/liter, whereas post-shift values ranged from approximately 8 to 11 mg/liter. No accumulation of BAA was seen during the workweek. On the third Monday morning of monitoring, following 2 days off, no BAA was detected, indicating complete clearance of BAA over the weekend.

A cross section of 31 male workers, aged 22–45 were exposed to  $0.6 \pm 0.27$  ppm for 1–6 years (Haufroid, 1997). Twenty 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 effects of and BAA levels on erythrocyte lineage were investigated by studying red blood cell (RBC) count, Hb, Hct, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin 17 concentration (MCHC), haptoglobin (Hp), reticulocyte count, and osmotic resistance (OR), a measure of osmotic fragility. Also studied were serum glutamic-oxaloacetic and glutamicpyruvic transaminases and renal creatinine and urinary retinol binding protein parameters. In addition, there was coexposure to methyl ethyl ketone. Single determinations of BAA in post-shift urine samples were used to assess exposure to low levels of 2-BE. No differences were observed for RBC counts, Hb, MCV, MCH, Hp, reticulocyte count, or between exposed and control workers. The only statistically significant change observed in exposed workers when compared with a matched control group ( $n = 21$ ) was a 3.3% decrease in Hct ( $p = 0.03$ ) and a 2.1% increase in MCHC ( $p = 0.02$ ). Urinary concentrations of BAA ranged from 0.3 to 51.4 mg./g creatine after shift (average = 12.2) in workers exposed to 0.76 ppm and from 0.6 to 20.4 mg/g creatine after shift in workers exposed to 0.46 ppm. A significant correlation ( $r = 0.55$ ,  $p = 0.0012$ ) was observed between end shift urinary BAA and 2-BE in air. There was no effect on red blood cell number, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, haptoglobin, reticulocyte number, osmotic resistance and hepatic and renal parameters. Two small but statistically significant differences in hematology values were observed: a significant decrease ( $p=0.03$ ) in hematocrit values and a significant increase ( $p = 0.02$ ) in mean corpuscular hemoglobin concentration. These changes were considered consistent with hemolysis observed in animals however both changes were in the range of normal clinical values (ATSDR, 1998). None of the red blood cell end points were correlated with internal exposure as assessed by urinary free 2-butoxyacetic acid.

ATSDR considered 0.60 ppm to be a NOAEL to derive a Minimum Risk Level of 0.2 ppm after applying a uncertainty factor of 3 for human variability.

In a study of biological indicators of exposure in a bike manufacturing plant, 80 workers were categorized into three exposure groups and personal air samples, urine sample and blood samples acquired pre- and post-work on and days 1 and 5 of the work week (Hung et al, 2011). The high exposure group also experienced a dermal exposure to the other two groups did not. The high exposure group whose hands were in direct contact with a dilute aqueous solution of 2-BE were exposed to an average of 1.7 ppm of 2-BE in air. Only 7 workers in the other groups had detectable levels in their air samples with an average of 0.45 ppm. Correlation of 2-BE in air and post-shift urinary BAA levels (after hydrolysis) was poor. Post-shift total BAA levels in urine on Monday and Friday (446.8 and 619.4 mg/g creatinine) were around 223% and 310% of the ACGIH proposed Biological Exposure Index (BEI; 200 mg/g creatinine). For the high exposure group, no significant difference was observed in exposure to 2-BE in air between day 1 and day 5. The mean pre-shift BAA on Friday was significantly higher than that on Monday. The pre-shift Monday and post-Friday BAA urine levels in the low exposure group were 20.1 and 60.8 mg/g creatinine, respectively. Using a PBPK model, the authors estimated that with the Day 1 exposure of 1.89 ppm, the predicted value of total BAA is about 20 mg/g creatinine, about 5% of the actual value observed in the high exposure group.

### **HEAC Health-based assessment and recommendation**

A PEL of 1.0 ppm for 2-BEA is recommended for discussion based on the consistent findings of hematological effects of 2-BE in multiple species and in humans. The validity of this endpoint has been established in multiple studies across routes of exposure, concentration and time and with several hematological endpoints. In addition, PBPK rodent and human models are in good agreement and provide a degree of certainty for the extrapolation to workplace exposures. The relationship between hyaline degeneration and 2-BE is not as strong and is not universally accepted by other regulatory agencies. A more thorough examination of this endpoint to assist a weight of evidence determination by the committee can be undertaken. Because there can be appreciable dermal absorption of 2-BE, an ACGIH Biological Exposure Index of 200 mg/L has been established for this substance. The workplace studies show a wide range of BAA levels in workers, some that exceed the BEI, so including this as guidance in the standard may facilitate workplace monitoring for 2-BEA. A skin notation is recommended.

### **Usage information: EPA Inventory Update Reporting (IUR), other sources**

The CalEPA CERS database reports approximately 103 users in California. Primary users include chemical manufacturers, paint, ink and coating manufacturers, glass, window, door, plastics and resin manufacturers, automotive repair, aerospace, and educational settings.

### **Measurement information**

OSHA Method: OSHA 83

Estimated LOD/LOQ: LOD is 7.54 µg/sample.

Reliable quantitation limit and detection limit is the same at this level and is 24 parts per billion.

NIOSH Method: 8316 (butoxyacetic acid in urine) biological indicator of exposure.

Based on this information, there are no anticipated concerns with analytical feasibility.

### **Recommended Workplace Controls**

Providing suitable control measures such as ventilation to control exposure can be accomplished using existing equipment as most systems have the ability to control to the proposed levels.

## **Economic Impact Analysis/Assessment**

The Division has made a determination that this proposal is not anticipated to result in a significant, statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states. This proposal will not have any effect on the creation or elimination of California jobs nor result in the creation or elimination of existing businesses or affect the expansion of existing California businesses. The Division anticipates that any potential costs will be balanced by avoiding or minimizing the costs inherent in workers' compensation claims, lost work time, and productivity losses that would have been caused by exposure related illness of employees.

The PEL proposed is consistent with recent scientific findings, of which professional health and safety staff and consultants of these employers and others with significantly exposed employees should be aware. Many of these entities already seek to control employee exposures to chemicals to levels below existing PELs in the interest of business continuity and minimization of tort and workers compensation liability. In 1989, Federal OSHA estimated that approximately 11% of employers using the listed chemicals would incur a one-time cost of approximately \$60,000/employer as a result of the revision or addition of PEL's for 376 chemicals in their 1910.1000, Tables Z-1, Z-2, and Z-3

([https://www.osha.gov/pls/oshaweb/owasrch.search\\_form?p\\_doc\\_type=PREAMBLES&p\\_toc\\_level=1&p\\_keyvalue=Air~Contaminants](https://www.osha.gov/pls/oshaweb/owasrch.search_form?p_doc_type=PREAMBLES&p_toc_level=1&p_keyvalue=Air~Contaminants)). Even though this estimate was done in 1989, since we are only changing one chemical in this proposal, the average cost of \$60,000 per affected employer and \$31,000 per small affected employer is considered a high estimate. Based on the assumptions used in the final rule, 12% of the estimated 103 employers in California expected to be using 2-BEA, leaves approximately 13 employers that would incur this \$60,000 cost for a total of \$780,000 in one-time costs as a result of this proposed PEL. Although they did not quantify the benefits, Federal OSHA also estimated that these costs would be more than offset by savings incurred from improved employee health and productivity

Setting a Permissible Exposure Limit for 2-BEA that is up-to-date and consistent with current scientific information and state policies on risk assessment will send appropriate market signals to employers with respect to the costs of illness and injury, which chemicals can impose on workers and their families, the government, and society at large. With appropriate market signals, employers may be better able to choose chemicals for use in the workplace that impose less of a burden on workers and society. There are no anticipated benefits to the state's environment.

The economic benefits from the proposed PEL will result primarily from reduced hemolytic effects among exposed workers.

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