

# Cal/OSHA Draft Substance Summary for the March 6, 2018 HEAC Meeting

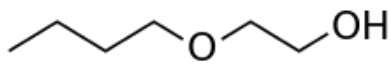
## Substance name: 2-butoxyethanol (2-BE) and 2-butoxyethyl acetate (2-BEA)

**CAS: 2-BE 111-76-2; 2-BEA 112-07-2**

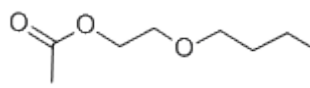
**MW: 2-BE 118.2; 2-BEA 160.20**

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

Molecular formula: 2-BE-C<sub>6</sub>H<sub>14</sub>O<sub>2</sub>

Structural formula: 

2-BEA-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: 2-BE- 1 ppm = 4.83 mg/m<sup>3</sup>

2-BEA- 1 ppm = 6.55 mg/m<sup>3</sup>

Physical characteristics at room temp: 2-BE Colorless liquid with a mild ether-like odor  
2-BEA Colorless liquid with a sweet, fruity odor.

Special physical characteristics if any: None.

Flammability and other hazards: 2-BE Flash point 61.7°C; Auto-Ignition temp. 245°C  
2-BEA Flash point 71°C; Auto-Ignition temp. 340°C

Major commercial form(s): Not known.

Uses/applications: 2-BE is a solvent for paints and surface coatings, as well as cleaning products and inks. In the petroleum industry, 2-BE is a component of fracturing fluids, drilling stabilizers, and oil slick dispersants for both water-based and oil-based hydraulic fracturing.

2-BEA is 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	2-BE: 20 ppm as TWA 2-BEA: NA		
OSHA PEL	2-BE: 50 ppm as TWA 2-BEA: 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; 2010)	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 hemosiderin deposition in liver was used as a BMR (benchmark 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

### Noncancer Effects

2- 2-BE causes irritation, central nervous effects and nausea in humans and hemolytic, hepatic and kidney effects in animals. Upon absorption into blood, 2-BE undergoes rapid metabolism to butoxyacetic acid (BAA), the toxic metabolite of 2-BE. BAA and its metabolites are well associated with the toxicological effects of 2-BE. Upon absorption into blood, 2-BEA is rapidly hydrolyzed to 2-BE so the conclusion is drawn that 2-BEA will cause the same effects through 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. There are also several workplace studies that collected biomonitoring data with which to evaluate the PBPK models.

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. The predominant toxic effect of 2-BE in animal models is on the hematologic system and includes elevated osmotic fragility of erythrocytes, hemolysis, decreased hematocrit, hemoglobinuria, hemoglobinemia, and hemolytic anemia. Most health risk assessments have used these hematopoietic effects of 2-BE as the basis for hazard and risk assessment (EPA 2010, ATSDR 2006, NTP 2000, WHO XXXX, ACGIH, ECETOC, 1994, NIOSH 1990). In the case of USEPA (2010), the toxic endpoint used for estimating the reference concentration was hemosiderin deposition in the liver which is a considered a secondary effect of the hemolysis. OEHHA (2017) used rodent olfactory hyaline degeneration as assessed through the formation of eosinophilic globules as the basis for the 8-hr and chronic RELs.

The most current of these recommendations rely on the results of a 2-year chronic inhalation study in rodents (NTP 2000) in which 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 B6C3F1 mice. Non-neoplastic 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 lesions 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). 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. Multiple hemolytic endpoints were examined; however a significant increase in the accumulation of hemosiderin in the liver Kupffer cells was considered to integrate these effects and was used for RfC derivation. The hemosiderin accumulation in the Kupffer cells increased in severity with increasing dose and exposure duration (sub-chronic to chronic), unlike the hemolytic endpoints. A NOAEL was not identified for this effect while a LOAEL of 31 ppm was identified in both male and female rats. Specific findings of the two studies are provided in the table below.

	Male F344/N Rats	Male F344/N Rats	Male B6C3F1	Female B6C3F1 Mice
Concentration	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 62.5, 125, and 250 ppm	Chamber control, 62.5, 125, and 250 ppm
Body Weight	Exposed groups similar to the chamber control group	125 ppm group less than the chamber control	Exposed groups generally less than the chamber control group	Exposed groups less than the chamber control group
Nonneoplastic Effects	Nose: olfactory epithelium, hyaline degeneration (13/48, 21/49, 23/49, 40/50)	Nose: olfactory epithelium, hyaline degeneration (13/50, 18/48, 28/50, 40/49)	Forestomach: ulcer (1/50, 2/50, 9/49, 3/48); epithelium hyperplasia (1/50, 7/50, 16/49, 21/48)	Forestomach: ulcer (15/50, 7/50, 13/49, 22/50); epithelium hyperplasia (6/50, 27/50, 42/49, 44/50)

	Liver: Kupffer cell pigmentation (23/50, 30/50, 34/50, 42/50)	Liver: Kupffer cell pigmentation (15/50, 19/50, 36/50, 47/50)	Liver: Kupffer cell pigmentation (0/50, 0/50, 8/49, 30/49) Spleen: hematopoietic cell proliferation (12/50, 11/50, 26/48, 42/49); hemosiderin pigmentation (0/50, 6/50, 45/48, 44/49) Bone Marrow: hyperplasia (0/50, 1/50, 9/49, 5/50)	Liver: Kupffer cell pigmentation (0/50, 5 25/49, 44/50) Spleen: hematopoietic proliferation (24/50, 29/50, 32/49, 35/50); hemosiderin pigmentation (39/50, 44/50, 46/49, 48/50)  Nose: olfactory epithelium, hyaline degeneration (6/50, 1 11/49, 12/50); respiratory epithelium, hyaline degeneration (17/50, 35/50, 26/49, 23/50)
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Several in vitro studies have compared 2-BE's hemolytic effects in human and rat red blood cells after acute exposures. Bartnik (1987) reported no hemolysis of human red blood cells exposed for three hours to BAA levels up to 15 mM. Hemolysis was observed in rat red blood cells, however, at BAA levels as low as 1.25 mM. Udden (2000) incubated human red blood cells with up to 2.0 mM BBA for four hours, and the authors observed none of the morphological changes observed in rat red blood cells at the same concentration. Udden (2002) reported a significant change in human red blood cell deformability at exposure to 7.5 and 10 mM BAA for 4 hours, whereas deformability in rat red blood cells was significantly increased at 0.05 mM BAA. Mean cellular volume in human blood samples was significantly increased at 10 mM BAA while mean cellular volume in rats was significantly increased at 0.05 mM BAA.

There are very few studies on the neurotoxicity of 2-BE. Recent studies have demonstrated neurotoxic effects of 2-BE in rats. Pomierny (2014) found that sub-cutaneous injections of 2-BE (2.5 mM/kg) in rats 5 days a week for 4 weeks. These studies showed that 2-BE reduced total antioxidant activity with a related increased lipid peroxidation in the frontal cortex but specific reduction in SOD and GPX were not observed. The authors suggest that this effect may be due to 2-BE effects on other antioxidant enzymes (GST) or non-enzymatic antioxidants (ascorbic acid, tocopherol). However, these mechanisms of BE action in the brain have not been studied and it cannot be concluded whether the increase of lipid peroxidation was the direct action of 2-BE on antioxidant enzymes or an indirect action connected with increase in the ROS production. In a similar study, 2-BE increased expression of the active form of caspase-3 and elevated levels of pyruvate and lactate in the examined brain regions (Pomierny 2016). The authors concluded that treatment with 2-BE induced the mitochondrial pathway of apoptosis, and disturbed glucose metabolism in rat brain. In a human neuroblastoma cell line, 2-BE increased markers of oxidative stress and apoptosis (Pomierny 2016).

## Carcinogenicity

The 2-year chronic inhalation study by the NTP (2000) observed a number of lesions and neoplasms in the two species. Forestomach tumors in female mice were observed at all exposure levels, but this effect has not been observed in any other species, including mice orally exposed to 2-BE. Though the incidence of this lesion increased with exposure, severity of the lesion did not increase with increasing dose. USEPA considered the forestomach tumors to be the result of a nonlinear mode of action and that metabolic and anatomic differences between mice and humans made this finding of questionable relevance (EPA, 2010). A high incidence of hepatocellular carcinomas was found in mice (10/50 [control], 11/50, 16/50, 21/50); however, the increase was associated with low survival in the high dose group and while the carcinoma incidence was significantly increased in the high dose group, when combined with adenomas there was no difference between neoplasms in controls and any dose group. With respect to pheochromocytomas reported in rats, given the marginal dose response, lack of tumor evidence in any other organ system of the rats, and reported difficulties in distinguishing pheochromocytomas from non-neoplastic adrenal medullary hyperplasia, this tumor type was not given significant weight in the qualitative or quantitative assessment of EGBE cancer potential (USEPA 2010). Results for neoplastic effects of 2-BE in the NTP study are summarized in the table below:

Summary of the 2-Year Carcinogenesis Toxicology Study of 2-BE

	Male F344/N Rats	Male F344/N Rats	Male B6C3F1	Female B6C3F1 Mice
Concentrations	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 62.5, 125, and 250 ppm	Chamber control, 62.5, 125, and 250 ppm
Neoplastic effects	None	None	Liver: hemangiosarcoma (0/50, 1/50, 2/49, 4/49)	Forestomach: squamous cell papilloma (0/50, 1/50, 2/50, 5/50); squamous papilloma or carcinoma (0/50, 1/50, 2/50, 6/50)
Uncertain findings	None	Adrenal Medulla: benign or malignant pheochromocytoma (3/50, 4/50, 1/49, 8/49) (Not significantly different from controls.	Forestomach: squamous cell papilloma (1/50, 1/50, 2/49, 2/49) Liver: hepatocellular carcinoma (10/50, 11/50, 16/49, 21/49)	None
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Some evidence	Some evidence

The latest USEPA review of 2-BE (USEPA 2010) indicates 2-BE is "not likely to be carcinogenic to humans" at continuous exposure to concentrations at or below 0.33 ppm based on laboratory animal evidence, mode-of-action information, and limited human study information. The assessment concluded that tumorigenic responses in rodents were likely from a non-linear mechanism and that these responses were not likely to occur in humans absent the non-neoplastic hematologic effects.

### **Human exposure data**

Multiple inhalation toxicokinetic studies have exposed volunteers to 20 – 50 ppm for periods up to four hours 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 human study by Johanson and Boman (1991) in which four male 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 males and six rats were simultaneously exposed to 113 ppm for 4 hr. Symptoms in the males included nasal and eye irritation, disagreeable metallic taste, occasional belching and slight increase in nasal mucous discharge. Hematologic changes were observed in the rats but not in males. In a second experiment, two males and one female 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 female also developed a headache for 24 hours. Hematologic changes were not observed in the humans but were in the three exposed female rats. In a third study, two males and two females were exposed to 100 ppm for 8 hours. All experienced vomiting and headaches but no hematologic 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-BE and its metabolite BAA. The respiratory uptake of 2-BE averaged 10.1  $\mu\text{mol}/\text{min}$  or 57 % of the inspired amount. The concentration in blood reached a plateau level of 7.4  $\mu\text{mol}/\text{L}$ . None of the subjects complained of or showed any signs of adverse effects that could be related to the exposure to 2-BE. 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). 2-BE retention averaged 67.0, 68.9 and 77.6 % for the three exposure conditions. Respiratory elimination of 2-BE 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 2-BE and the total elimination of BAA.

### **Occupational Studies**

The relationship of 2-BE exposure and BAA excretion was evaluated in a group of 5 females 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 (Haufröid, 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 2-BE and BAA levels on erythrocyte lineage were investigated by studying red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin 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. The blood changes were considered consistent with hemolysis observed in animals; however, both changes were in the range of normal population values (ATSDR, 1998) for this small exposed group ( $n = 31$ ). None of the red blood cell end points were correlated with internal exposure as assessed by urinary free 2-BAA. ATSDR considered 0.60 ppm from this study 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 days 1 and 5 of the work week (Hung et al, 2011). The high exposure group also experienced a dermal exposure to 2-BE 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.

In a study of workers in a screen printing department exposed to 2-BE and other solvents (Song, 2017), significant increases in white blood cell counts, reticulocyte percentages, and corrected reticulocyte count (i.e., reticulocyte index) were found in the exposed group compared to controls. Workers were exposed to 2-BE (1.4 – 3.4 ppm), 2-ethoxyethanol (2.5 ppm), ethylbenzene (4 ppm), xylene (1.3 – 2.7 ppm), cyclohexanone (1.5-3.7 ppm), and trimethylbenzene (0.016 – 0.5). No significant differences were found between the exposed group and control group in mean hb, Hct, MCV, MCH, MCHC, RBC and platelet counts, and lymphocyte percentage. However, white blood cell (WBC) counts, reticulocyte counts, and RI were higher in the exposed group than in the control group, and the differences were statistically significant. The risk of reticulocytosis was 16.3 times (95% CI: 1.53–173.27) higher in the exposure group compared to that in the control group. However, other variables, including age, sex, drinking, smoking, lymphocyte, platelet counts, hemoglobin, and MCV, were not significant risk factors for reticulocytosis.

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

A PEL of 5 ppm for 2-BE and 2-BEA is recommended for discussion based on the consistent findings of hematologic effects of 2-BE in multiple species and its observation in humans. Small but significant declines in two hematologic parameters were observed in workers exposed to  $0.6 \pm 0.27$  ppm for 1-6 years compared to controls (Haufroid, 1997) and the accumulation of hemosiderin in liver Kupffer cells has been observed in 2-BE poisoning cases. The validity of hematologic effects as the most sensitive endpoint for 2-BE has been established in multiple studies across routes of exposure, concentration and time and with several hematological parameters. In addition, PBPK rodent and human models are in good agreement and provide a degree of certainty for the extrapolation to workplace exposures.

The proposed PEL uses the  $BMCL_{HEC-ENV}$  derived in USEPA (2010), adjusts that value to occupational exposure (24/8) and applies an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3. The interspecies factor is set to 1 based on the lesser sensitivity of human blood cells to the hematologic effect of 2-BE (Udden 2000; Udden, 2002) than that of rodents. With in vitro testing, concentrations of BAA must be in excess of 7.5 mM in human blood for pre-hemolytic changes to occur. Comparable effects in rat blood occur at in vitro concentrations approximately 150-fold lower. The intraspecies uncertainty factor of 3 was based on evidence from in vitro hemolytic tests of human blood from sensitive human subpopulations (elderly, patients with congenital hemolytic disorders, children) showing no difference from controls when incubated with up to 2 mM BAA for 4 hours. Using these factors, the PEL is calculated as:

$PEL = 16 \text{ mg/m}^3 \times 24/8 \times 5/5 \div 1 \div 3 = 16 \text{ mg/m}^3$ . Converted to ppm:  $16 \text{ mg/m}^3 \times 1 \text{ ppm}/4.83 \text{ mg/m}^3 = 3.3 \text{ ppm}$ . Round to 5 ppm.

Without an intraspecies uncertainty factor, the PEL is 10 ppm.



The hematologic changes in Haufroid are within population ranges for males reported in the 2011-2012 NHANES. Five of the 9 hematologic parameters from Haufroid and corresponding values from NHANES are shown in the following table:

Blood parameter	NHANES 2011-2012 (n = 1603, M)	Haufroid			
		Mean	Controls (21)	Mean	Exposed (31)
Hct %	38.7 – 51.4	45.5	40.6 – 50.4	43.9	39.9 – 50.7* (p= 0.03)
Hg (g/dL)	13.1 – 17.5	15	13.5 – 17.0	14.8	13.6 – 17.1
MCHC (g/dL)	32.3 – 35.3	32.9	31.1 – 35.6	33.6	31.8 – 35.6* (p= 0.02)
Rbc (x10 <sup>6</sup> /ul)	4.07 – 5.70	5.02	4.56 – 5.52	4.92	4.42 – 5.63
Mean Cell Volume fL	77.6 – 98.9	90.8	83.7 – 102.8	89.4	82.2 – 101.3

BAA leads to rbc swelling and lysis, ultimately resulting in a decline in cell number. The two significant changes observed in Haufroid are consistent with that MOA – a 3.5% reduction in rbc volume (hematocrit) with a corresponding 2.1% concentrating effect of hemoglobin within the volume (MCHC) as cell number declines. While BAA can plausibly be the cause of these blood changes, these changes are well within the normal population range and other parameters were unaffected. The distribution of Hct% from Haufroid does indicate that some of the workers were borderline anemic. The NHANES III survey (1994-1998) found that 95% of men over 18 years had a hemoglobin concentration that was greater than 13.5g/dl or 39.9% Hct, while 95% of women greater than 18 years had hemoglobin levels of 12.0g/dl or 35.7% hematocrit. These levels were established as the defining levels for iron deficiency anemia and are consistent with other population-based studies. The FDA standard for the lower level for hemoglobin for blood bank donor eligibility is 12.5 g/dL or 38% hematocrit for both men and women (USFDA, 2008).

Assuming the Hct decline in Haufroid was due to BAA, the difference between the control Hct mean from Haufroid (45.5) and the low end of the NHANES (38.7) could be used to extrapolate the effect seen in Haufroid to higher exposures. That difference is 6.8% while the decline observed in Haufroid was 1.6%. Dividing 6.8 by 1.6 yields 4.25, which can be considered a multiplier of the Haufroid exposure concentration that would reduce Hct% to the lowest value seen in NHANES. The corresponding concentration would be: 4.25 x 0.6 ppm = 2.55 ppm. It would be appropriate to round this value up to 5 ppm as the in vitro human rbc hemolysis under exposure to BAA is nonlinear (Udden 2000).

As the latest review by UESPA indicates 2-BE is not likely a human carcinogen at the RfC (0.33 ppm), no account of the carcinogenicity of 2-BE is considered in the PEL. From USEPA IRIS, 2010:

“Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005, 086237), EGBE (2-BE) is deemed "not likely to be carcinogenic to humans" at environmental concentrations at or below the RfD and RfC, based on laboratory animal evidence, mode-of-action information, and limited human study information. The available data indicate that carcinogenic effects from EGBE (2-BE) are not likely to occur in humans in the absence of the critical noncancer effects, including hepatic hemosiderin staining and irritant effects at the portal of entry, and are not likely to be carcinogenic to humans exposed at levels at or below the RfC and RfD values established in this assessment.”

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-BE and 2-BEA. A skin notation is recommended for 2-BE and 2-BEA. ACGIH has recommended that the skin notation not be included on the basis that 2-BE causes hemolytic effects to which are not sensitive and a PBPK analysis showing the inhalation route is much more significant. This reasoning does not address the high skin permeability of 2-BE and the contribution to total dose from this route of exposure which can be substantial.

### **Usage information: EPA TSCA Chemical Data Reporting (CDR), EPA Toxics Release Inventories (TRI), other sources:**

In 2015, there were 34 TSCA CDR records for 2-BE (usage in excess of 25,000 lbs) in U.S. Of these, there were 3 in California. There are 137 businesses in the State of California CERS database reporting use of 2-BE. The average daily amount of 2-BEA reported by these businesses is 15, 55 and 1000 gallons for the 50, 75 and 99 percentiles.

In 2015, there were 21 TSCA CDR records for 2-BEA (usage in excess of 25,000 lbs) in U.S. Of these, there were 2 in California. There are 184 businesses in the State of California CERS database reporting use of 2-BEA. The average daily amount of 2-BEA reported by these businesses is 40, 275 and 19,000 gallons for the 50, 75 and 99 percentiles.

### **Measurement information**

#### **2-BE:**

OSHA Method: OSHA 83

Estimated LOD/LOQ: LOD is 7.22 µg/sample.

Reliable quantitation limit and detection limit is the same at this level and is 31 parts per billion.

NIOSH Method: 1403 (alcohols IV) shows an LOD of 1.0 µg/sample.

#### **2-BEA**

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 for either substance.

### **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 PELs proposed are 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 2015, Federal OSHA estimated that approximately 2.5% of employers using beryllium would incur a cost of \$10,000 per typical employer and \$3,000 per small (<20 employees) employer annualized over 10 years. as a result of the reduction to the PEL for beryllium and beryllium compounds in their 1910.1000, Tables Z-1 as well as three separate substance specific standards for general industry, construction industry, and shipyards. (<https://www.gpo.gov/fdsys/pkg/FR-2017-01-09/pdf/2016-30409.pdf>). This proposal is to reduce the PEL for 2-BE and 2-BEA with no additional substance specific requirements. As such, we anticipate only a small percentage of affected employers will incur a onetime cost to evaluate the workplace, upgrade or install new engineering controls, and train employees on the changes. Although the cost should be significantly less for these changes, we will use the above annualized figures as a onetime cost by multiplying by 10 years giving us the average cost of \$100,000 per typical affected employer and \$30,000 per small affected employer. Additionally Federal OSHA estimated 2.5% of the employers using beryllium would incur these costs, Previous Federal OSHA estimates (1989) placed the number at 11% of employers using listed chemicals would incur the costs to comply with the reduction of PELs for over 300 substances. To utilize the worst-case scenario, we will use 11% of employers using 2-BE and/or 2-BEA will be affected by the increased costs to comply. Based on this, 11% of the approximately 321 employers in California estimated to be using these substances leaves approximately 35 employers that would incur a cost. Since approximately 71% of these are small businesses that leaves 25 small employers that would incur the \$30,000 cost and the remaining 10 larger employers would incur the \$100,000 cost for a total of \$1,752,000 in one-time costs as a result of this proposed amended 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 Permissible Exposure Limits for 2-BE and 2-BEA that are 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 PELs will result primarily from reduced hemolytic effects among exposed workers.

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