Compound	**2-Butoxyethanol (EGBE)**		***Data collection sheet***	
N° CAS 111-76-2 1 ppm = 4.91 mg/m³	**CLP:** Acute Tox 4 (H302), Acute Tox 4 (H312), Skin Irrit. 2, Eye Irrit. 2, Acute Tox 4 (H332)			
Organisation name	**ATSDR**	**US EPA**	**Santé Canada**	**Reach registrants**
Risk value name	Chronic Inhalation MRL	Inhalation RfC	CA	DNEL
Risk value (mg/m³)	1	1.6	11	49
Risk value (ppm)	0.2	0.3	2.2	
Reference period	chronic	chronic	chronic	
Year	1998	2010	1999	
Key study	Haufroid et al., 1997	NTP (2000), NTP technical report on the toxicology and carcinogenesis studies of 2-butoxyethanol	NTP 1998	
Study type	chronic study in workers	chronic (rat and mouse) inhalation study	chronic inhalation study	
Species	human (31 male workers)	F344/N rats and $B6C3F_1$ mice	F344 rats	
Duration of exposure in key study	1 to 6 years	6 h/d, 5 d/w for 2 years	6 h/d, 5 d/w for 2 years	
Critical effect	decrease in haematocrit values and increase in mean corpuscular haemoglobin concentration	hemosiderin deposition in the liver	haemolytic anemia (macrocytic and normochromic)	
Critical dose value	NOAEL: 0.6 ppm	NOAEL: 31 ppm		long term inhalation DNEL for consumers (systemic effects) derived by industry (ECHA-website

				registered substances), no transparent information about derivation of DNEL
		LOAEL: 62.5 ppm	LOAEL: 150 mg/m^3 (31 ppm)	
Adjusted critical dose		PBPK and $BMCL_{10}$		
		$BMCL_{HEC}$: 16 mg/m^3		
Single assessment factors (see table R.8.6)	AF_H 3 = 3	AF_H 10 = 10	0.5 x 0.1 x 3.2 x 3.2 = 0.5	no information on DNEL derivation
Other effects				
Confidence		medium/high	medium	
AF_L used LOAEL; AF_H intraspecies variability; AF_A interspecies variability; AF_S used subchronic study; AF_D data deficiencies				

Compound	**2-Butoxyethanol (EGBE)**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	1600
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2016
General Information			
CLP Index No	4	INDEX	603-014-00-0
EC No	5	EINECS – ELINCS - NLP	203-905-0
CAS No	6	Chemical Abstracts Service number	111-76-2
Harmonised CLP classification	7	Human health risk-related classification	Acute Tox 4 (H302, Acute Tox 4 (H312), Skin Irrit. 2, Eye Irrit. 2, Acute Tox 4 (H332)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	118.2 1 ppm = 4.86 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP (2000)
Read-across compound	10	Where applicable	
Species	11	Rat etc. / human	F344/N rats and B6C3F1 mice
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	104 weeks
Exposure duration	14	Hours/day, days/week	6h/d, 5d/w
Critical endpoint	15	Effect(s), site of	Hemosiderin deposition in the liver
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	BMC10L95
POD value	17	[mg/m^3] or [ppm] or [mg/kg_{BW}×d]	133 µmol hour/L
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	HECs of 3.4 ppm (16 mg/m^3)
Study Length	20	sa→ sc→ c *(R8-5)*	1
Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	HECs of 3.4 ppm (16 mg/m^3)
	23 b	Kinetic + dynamic	1
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1

Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	10
POD/TAF	28	Calculated value (µg/m^3 and ppb)	1600 µg/m^3 and 242 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	1600
Additional comments	31		
Rationale section	32		

The reference concentration (RfC) proposed by the US EPA in 2010 seems the most relevant. The pivotal study was published in 2000 by NTP. 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. Groups of 50 male and 50 female rats and mice 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 haematology and bone marrow analyses, additional groups of 27 (per sex) rats and 30 (per sex) mice 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 (haematology only) and 6 months (NTP, 2000).

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 lower than those of the chamber control group. 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 lower than those of the chamber control group during the last 6 months of the study. The mean body weights of exposed female mice were lower than those of the chamber control group; the reductions were greater and occurred earlier than those observed in males.

In rats, the most consistent exposure-related effect on the haematopoietic system was an exposure concentration-related mild macrocytic, normochromic, regenerative anaemia 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. In mice, the most consistent exposure-related effect on the haematopoietic system was an exposure concentration-related minimal normocytic, normochromic, regenerative anaemia present at 3, 6, and 12 months, with females affected slightly more than males.

In rats, 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.

In female mice 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 haemangiosarcoma 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 haemosiderin pigmentation in the Kupffer cells were significantly increased in 125 and 250 ppm males and all exposed groups of females. The incidences of splenic haematopoietic cell proliferation and haemosiderin 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 (NTP, 2000).

Derivation of the EU LCI

The US EPA selected the AUC as the appropriate dose metric due to the nature of the endpoint, haemosiderin deposition. This endpoint increased in severity with increased duration (subchronic to chronic) and is believed to be the result of the cumulative exposure to EGBE as opposed to a peak event.

A BMCL10 of 133 µmol hour/L for haemosiderin staining in the liver of male rats chronically exposed to EGBE (NTP, 2000) was used as the POD.

A human PBPK model (Corley et al., 1997) was used to back-calculate to an HEC of 16 mg/m³ (3.4 ppm) for the BMCLHEC.

An assessment factor of 10 was selected to account for the uncertainty associated with the variability of the human response to the effects of EGBE.

A final value of 1600 µg/m³ is proposed as EU LCI.

The odour, mild and ether-like, is defined by a threshold at 0.1 ppm (500 µg/m³) (geometric mean) (OEHHA, 2015; AIHA, 1989).

References

AIHA (1989). Odour thresholds for chemicals with established occupational health standards American Industrial Hygiene Association AEAR89-108.

Corley RA; Markham DA; Banks C; Delorme P; Masterman A; Houle JM (1997). Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. Fundam Appl Toxicol, 39: 120-130.

NTP (2000) Toxicology and carcinogenesis studies of 2-butoxyethanol (Cas No. 111-76-2) in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program Technical Report Series No. 484. National Toxicology Program, Research Triangle Park NC, USA.

OEHHA (2015). Ethylene Glycol mono-n-Butyl Ether. Reference Exposure Levels. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Appendix D1. Public Review Draft. August 2015. Air Toxics Hot Spots Program. Air, Community, and Environmental Research Branch. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency.

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