Compound	Hexylene glycol (2-methyl-2,4-pentanediol)	*Data collection sheet*
N°CAS 107-41-5	**EU-Classification:** Xi; R36/38 **CLP:** Skin irrit. 2 (H315), Eye irrit. H319	

Organisation name	**CARB**	**DFG**	**REACH Registrants**
Risk value name	8-hour REL	MAK	DNEL
Risk value (µg/m³)	0.28 (0.058 ppm)	49 (10 ppm)	7.8 (1.6 ppm)
Reference period	acute (8 h)	Chronic (worker)	Chronic (DNEL $_{\text{Gen. Pop. long term}}$)
Risk value (mg/m³) / Short term (15 min)		100 (20 ppm)	-
Year	2010	1997, 2000, 2001	2017
Key study	Union Carbide Corporation (1976)	Silverman et al. (1946)	Fabreguette (1999)
Study type	Subacute exposure study, 2 weeks	Acute exposure study, 15 min (245 mg/m³)	Subchronic study, oral
Species	Rat	Human	Rat
Duration of exposure in key study	7 h/d, 5 d/week, 9 d	15 min	7 d/week, 90 d
Critical effect	Lesions of the respiratory epithelium	Eye irritation	Highest dose tested
Critical dose value	LOAEC 676.2 mg/m³ (140 ppm)	LOAEC: 245 mg/m³	NOAEC 450 mg/(kg KG x d)
Adjusted critical dose	422.6 mg/M³ (676.2 X 7/8 X 5/7), RGDR: 4 → Human Concentration Adjustment: 1690 mg/m³	-	-
Single assessment factors (see table R.8.6)	UF_L 10 x UF_H 10 x UF_A 2 x √10 x UF_S 10 x UF_D 1 = 6000	Not indicated	UF_H 10 x UF_A 2.5 x UF_S 2 x= 50
Other effects			
Remarks			Route-to-route-extrapolation factor 1.15 m³/(kg bw x d), no differences in oral and inhalation absorption assumed

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies

Compound	Hexylene glycol (2-methyl-2,4-pentanediol)		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	3500
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value was issued	2018
General information			
CLP Index No	4	INDEX	603-053-00-3
EC No	5	EINECS – ELINCS - NLP	203-489-0
CAS No	6	Chemical Abstracts Service number	107-41-5
Harmonised CLP classification	7	Human health risk-related classification	Skin irrit. 2, Eye irrit.
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	118.18 1 ppm = 4.9 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	ECHA (2017) Reproduction / Developmental Toxicity Screening Test (2010)
Read-across compound	10	Where applicable	-
Species	11	Rat etc. / human	Rat, Sprague-Dawley (10/sex/dose)
Route/type of study	12	Inhalation, oral feed, etc.	Oral (gavage)
Study length	13	Days, subchronic, chronic	Males: 4 weeks before pairing, during the pairing period (3 weeks), until final sacrifice of the females, at least 10 weeks in total
Exposure duration	14	Hours/day, days/week	once/day, daily
Critical endpoint	15	Effect(s), site of	Hepatotoxicity
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc.	NOAEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	200 mg/(kg bw x d)
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure hours/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		1.15 m^3/(kg bw x d) (rat) (assuming identical resorption rates for oral and inhalation exposure)
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)*	1
	23 b	Kinetic + dynamic	2.5
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)	1.15 m^3/(kg bw x d) x 50
POD/TAF	28	Calculated value (µg/m^3 and ppb)	3480 µg/m^3 and 710 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	3500
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for hexylene glycol is based on a project funded by the German Environment Agency (Voss, 2018).

Rationale for critical effects

The data base of studies on effects in humans is extremely limited. A study on human volunteers with acute exposure to 245 mg/m^3 (50 ppm) of the test substance for 15 minutes led to eye, but not respiratory tract irritation in most of the 12 exposed males and females. No NOAEC was reported in this study (Silverman et al., 1946). No data are available for the effects of repeated inhalation of hexylene glycol in humans.

In the only available study of animals with repeated inhalation, short-term exposure to 700 mg/m^3 of an inhalable aerosol for 9 days (7 hours/day, with a two-day break in between after day 5) led to minimal effects on the epithelium in the trachea of exposed rats and the single exposed rabbit (very slight submucosal haemorrhage, congestion, slight hyperplasia). No effects were observed in the lungs or other organs or on body weight.

Several studies with repeated (up to subchronic) oral exposure of rats revealed largely adaptive effects of hexylene glycol on the liver (increased liver weight with hepatocellular hypertrophy). In a reproduction/developmental toxicity screening test (OECD Guideline 421) with Sprague-Dawley rats (10 M + 10 F/group), 0, 200, 500 or 1000 mg/(kg bw x d) hexylene glycol was given by gavage for 4 weeks before mating, during mating, gestation and the beginning of the lactation period (until day 4 after parturition) (total exposure period for M and F at least 10 weeks). Minimal to slight dose-related hepatocellular hypertrophy was recorded in male Sprague-Dawley rats given 200 mg/(kg bw x d) and in males and females given 500 or 1000 mg/(kg bw x d). This correlated with increased liver weights. In addition, minimal altered cell foci were recorded in males given 500 or 1000 mg/(kg bw x d), consisting of clear cell focus or foci, associated with basophilic cell foci in one of the males given 1000 mg/kg/day. These findings were considered to be adverse after 3 months of treatment since these changes could be consistent with pre-neoplastic lesions (ECHA, 2017).
Carcinogenicity studies or *in vivo* genotoxicity studies with hexylene glycol are not available. *In vitro* genotoxicity studies provide no evidence of a genotoxic potential.

Rationale for starting point

The only inhalation toxicity study with repeated exposure may be used as supportive, but in itself is considered insufficient to evaluate the toxicity of hexylene glycol and the derivation of an EU-LCI. Therefore, the derivation of an EU-LCI is based on data from a guideline study with oral exposure. This procedure is justified, as the critical effect is a systemic toxic effect, and toxicokinetic data do not provide evidence against a route-to-route-extrapolation.
The NOAEL of 200 mg/(kg bw x d) for adverse hepatic effects (minimal altered cell foci) in male rats observed in an oral Reproduction / Developmental Toxicity Screening Test (ECHA, 2017) served as a POD for the derivation of an EU-LCI value. The study is not published but is described in sufficient detail in the REACH registration dossier and considered 'reliable without restrictions', RL 1 (ECHA, 2017).

Rationale for assessment factors

- Route-to-route extrapolation factor: 1.15 m^3/(kg bw x d) (rat)

- Adjusted study length factor: 2 (subchronic exposure)
- Allometric scaling (rat to human): already included in route-to-route extrapolation
- Interspecies differences: 2.5 (default value for systemic effects)
- Intraspecies differences: 10 (default value).

The total assessment factor is 50 x 1.15 m^3/(kg bw x d), leading to an EU-LCI value of 200 mg/(kg bw x d) : 1.15 m^3/(kg bw x d): 50 = 3480 µg/m^3 which was rounded to 3500 µg/m^3.

The derived EU-LCI value is supported by derivations from other studies:
In a developmental toxicity study (exposure on GD 6-15) with oral exposure of rats, a dose-dependent transitional reduction of body weight gain was observed on GD 6-7 in pregnant dams with a NOAEL of 300 mg/(kg b.w. x d). A slight but still significant transitional effect on weight gain at this dose was not considered adverse, therefore, the lowest dose of 30 mg/(kg bw x d) was assessed as a NOEL. From the NOAEL, a value of 10000 µg/m^3 can be derived; the NOEL would lead to a value of 1000 µg/m^3.

From the study on subacute inhalation in rats, a value of about 1000 µg/m^3 could be derived using the following factors: LOAEC to NOAEC: 3; 7hours/24 x 5days/7days for continuous exposure; subacute to chronic: 6, interspecies: 1; intraspecies: 10; total factor: 864. The effects on the respiratory system in this study were mild, and the calculation described was considered to be conservative.

Therefore, the derived EU-LCI of 3500 µg/m^3 will also be protective against local effects on the respiratory system. The derived EU-LCI is far below the concentration reported to cause eye irritation in humans at brief exposure. The derived value is also below the reported odour threshold of 19 mg/m^3 (3.9 ppm) by AIHA (2013). Thus, odour perception seems unlikely at the proposed EU-LCI.

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