Compound	1,2-Diethoxyethane		*Data collection sheet (1/1)*	
N°CAS 629-14-1	**EU- Classification:** F (R11); R19; Repr. Cat.2 (R61); Repr. Cat.3 (R62); Xi (R36) **CLP:** Flam. Liq. 2 (H225); Eye Irrit. 2 (H319); Repr. 1A (H360Df)			
Organisation name	**National Toxicology Program**	**National Toxicology Program**	**AgBB NIK-AG**	**ANSES**
Risk value name	No risk value derived	No risk value derived	NIK	CLI
Risk value			10 µg/m^3	70 µg/m^3
Reference period			Chronic	Chronic
Year				
Key study	NTP (1987)/George et al. (1992)	NTP (1987)/George et al. (1992)		
Study type	Teratogenicity	Teratogenicity		
Species	CD-1 Mice	New Zealand White Rabbits		
Duration of exposure in key study	Gestation days 6-15	Gestation days 6-19		
Critical effect	Increased incidence of litters with malformed fetuses	Increased incidence of litters with malformed fetuses		
Critical dose value	NOAEL = 50 mg/kg bw/d	NOAEL = 25 mg/kg bw/d		
Adjusted critical dose				
Single assessment factors	No assessment made	No assessment made		
Other effects				

Compound	**1,2-Diethoxyethane EGDEE C6H14O2**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	150
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	603-208-00-5
EC No	5	EINECS – ELINCS - NLP	211-076-1
CAS No	6	Chemical Abstracts Service number	629-14-1
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 2 (H225); Eye Irrit. 2 (H319); Repr. 1B (H360Df)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	118.18 1 ppm = 4.86 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	George et al., 1992
Read across compound	10	Where applicable	
Species	11	Rat, human etc.	Mouse
Route/type of study	12	Inhalation, oral feed etc.	Oral
Study length	13	Days, subchronic, chronic	30 d (exposure on GD 6-15)
Exposure duration	14	Hrs/day, days/week	Daily gavage in water
Critical endpoint	15	Effect(s), site of	Foetal malformations
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	Adjusted NOAEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	87.5 mg/m^3
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	1
Route-to-route extrapolation factor	21		1[1]
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	3
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	7
	23 b	Kinetic + dynamic	2.5

[1] For mice, no standard route-to-route extrapolation factor is available. Route-to-route extrapolation is included in the POD (line 17), for details see line 32.

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)	525
POD/TAF	28	Calculated value (µg/m³ and ppb)	167 µg/m³ (34.4 ppb)
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	150
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for diisobutyl glutarate is based on a project funded by the German Environment Agency (UBA) (Werschkun, 2020).

The European Chemicals Agency (ECHA) has published an Annex XV dossier to identify 1,2-diethoxyethane (EGDEE) as a substance of very high concern based on its classification as Repr. 1B, H360Df (ECHA, 2012a). The substance has been on the candidate list since 2012. The underlying toxicological data are summarised in a supporting document (ECHA, 2012b). No other comprehensive risk assessment reports from international bodies could be found, and no registration dossier for 1,2-diethoxyethane is published on the ECHA dissemination site. Targeted searches were conducted in eChemPortal, HSDB, TOXLINE and PubMed to identify relevant information.

1,2-Diethoxyethane is at room temperature a colourless liquid with an ethereal odour. No information on an odour threshold could be found. Its metabolism proceeds via oxidation of the intermediate 2-ethoxyethanol to the main metabolite 2-ethoxyacetic acid, which is assumed to be responsible for causing the observed reproductive toxicity. Acute toxicity after inhalation was not investigated. Acute systemic toxicity after oral exposure is low. 1,2-Diethoxyethane acts as an irritant to the eyes and is classified as Eye Irrit. 2, H319.

Well-documented teratogenicity studies were conducted under contract by the National Toxicology Program on CD-1 mice and New Zealand white rabbits (George et al., 1992; NTP, 1987a; NTP 1987b). Following oral exposure to 50, 150, 500, or 1000 mg/kg_{BW} x d during gestation days 6-15 (mice) and to 25, 50, or 100 mg/kg_{BW} x d during gestation days 6-19 (rabbits), adverse effects on foetal development (foetal malformations) were observed in both species well below the dose levels that caused maternal toxicity. Compared to the mouse with a NOAEL of 50 mg/kg_{BW} x d, lower effect levels were observed in the rabbit, with a LOAEL of 50 mg/kg_{BW} x d and a NOAEL of 25 mg/kg_{BW} x d. However, taking into account the differences in allometric scaling for the two species (AF 2.4 for rabbits as compared to AF 7 for mice), the mouse can in fact be considered the more sensitive species for the observed effect. The NOAEL in mice is therefore chosen as the point of departure (POD).

No adjustment for exposure duration or study length is needed, since the animals were exposed continuously during the timeframe considered critical for the studied endpoint. The POD is adjusted for route-to-route extrapolation by dividing the oral NOAEL in mice (50 mg/kg_{BW} x d) by a default factor of 2 to account for potential absorption differences between the oral and inhalation route, then multiplying by the standard human body weight (70 kg) divided by the standard human respiratory rate (20 m³/d). The resulting POD is 87.5 mg/m³.

Assessment factors were chosen as follows:

- Route-to-route extrapolation: 1 (as there is no standard extrapolation factor available for rabbits, route-to-route extrapolation was integrated into the POD, see above)

- Severity of effect: 3 (foetal malformations)
- Interspecies differences:
  7 for allometric scaling
  2.5 for remaining kinetic and dynamic differences
- Intraspecies difference: 10 (default value for the general population)

With a total assessment factor of 525 and a POD of 87.5 mg/m³, an initial value of 167 µg/m³ (34.4 ppb) is obtained and rounded to an EU-LCI value of 150 µg/m³.

Comparison of proposed EU-LCI with a derived EU-LCI from the teratogenicity study in rabbits

As mentioned above, an oral teratogenicity study in rabbits resulted in a NOAEL of 25 mg/kg_{BW} x d. If this study was used to derive an EU-LCI, the POD would be 44 mg/m³, calculated from the oral NOAEL, the default factor of 2 to account for potential absorption differences between the oral and inhalation route, and the standard human respiratory rate of 0.286 m³/kg x d. This POD is lower than the one obtained from the study in mice. However, assessment factors of 3 (severity of effect), 2.4 (allometric scaling), 2.5 (remaining interspecies differences) and 10 (intraspecies differences) result in a total assessment factor of only 180. Therefore a calculated value of 244 µg/m³ (50.2 ppb) is obtained and rounded to an EU-LCI value of 250 µg/m³, which is higher than the value derived from the mouse study. The proposed EU-LCI of 150 µg/m³ derived from the oral teratogenicity study in mice is preferred because it can be considered to be more protective.

References:

European Chemicals Agency (2012a): Annex XV dossier for 1,2-diethoxyethane. https://echa.europa.eu/documents/10162/c52546c1-89ad-4b0e-a141-b33bc279d853. Last accessed on 16 April 2020.

European Chemicals Agency (2012b): Support document for identification of 1,2-diethoxyethane as a substance of very high concern because of its CMR properties. https://echa.europa.eu/documents/10162/8c04401d-d0bb-409c-9250-c6e574f47305. Last accessed on 16 April 2020.

George, J.D.; Price, C.J; Marr, M.C.; Kimmel, C.A.; Schwetz, B.A.; Morissey, R.E. (1992): The developmental toxicity of ethylene glycol diethyl ether in mice and rabbits, Fundam. Appl. Toxicol. 19 (1): 15-25.

National Toxicology Program (1987a): Ethylene glycol diethyl ether (CAS No. 629-14-1) administered to CD-1 mice on gestational days 6 through 15, NTP Study No. TER87074 (abstract available only).

National Toxicology Program (1987b): Ethylene glycol diethyl ether (CAS No. 629-14-1) administered to New Zealand White rabbits on gestational days 6 through 19, NTP Study No. TER90075 (abstract available only).

Werschkun B. (2020): Toxicological basic data for the derivation of EU-LCI values for neopentyl glycol, diisobutyl succinate, dissobutyl glutarate, 1,2-dimethoxyethane and 1,2-diethoxyethane. UBA Texte 223/2020. https://www.umweltbundesamt.de/publikationen/toxicological-basis-data-for-the-derivation-of-eu (last accessed on 9.02.2021).