Compound	Bis(2-methylpropyl) pentanedioate (Diisobutyl glutarate)	*Data collection sheet (1/1)*
N°CAS 71195-64-7	**EU- Classification:** not available **CLP:** not available (data lacking)	
Organisation name	**AgBB NIK-AG**	
Risk value name	NIK	
Risk value	100 µg/m³ (read-across from a mixture of dimethyl dicarboxylates, see below ('Remarks')	
Reference period	Chronic	
Year	2010	
Key study	Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of dibasic esters. Fund. Appl. Toxicol. 15 (2) 381-393.	
Study type	Subchronic inhalation study (OECD 413)	
Species	Rat	
Duration of exposure in key study	90 days (6 h/d, 5 d/wk)	
Critical effect	Degeneration of nasal olfactory epithelium	
Critical dose value	LOAEC: 20 mg/m³	
Adjusted critical dose	3.6 mg/m³	
Single assessment factors	Not specified	
Other effects		
Remarks	Read-across: The study was performed with a mixture of 66.5 % dimethyl glutarate, 16.9 % dimethyl succinate, and 16.5 % dimethyl adipate. The occupational exposure limit (MAK) value of 0.75 ppm (5 mg/m³) derived for this mixture was transformed into a worker DNEL value of 0.75 ppm (10 mg/m³) for diisobutyl glutarate by molar adjustment. This was then divided by 100 to obtain the NIK value, according to the former standard procedure of the AgBB.	

Diisobutyl glutarate and read across compound dimethyl glutarate

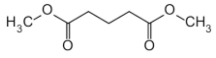
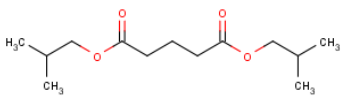
Compound	**Diisobutyl glutarate C13H24O4**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	35
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	
EC No	5	EINECS – ELINCS - NLP	275-257-7
CAS No	6	Chemical Abstracts Service number	71195-64-7
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	244.33 1 ppm = 10.05 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Dimethyl glutarate
Species	11	Rat, human etc.	
Route/type of study	12	Inhalation, oral feed etc.	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	Unrounded LCI for dimethyl glutarate
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	0.024 mg/m^3
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	-
Study length	20	sa→ sc→ c *(R8-5)*	-
Route-to-route extrapolation factor	21		-
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	-
	22 b	Severity of effect *(R 8-6d)*	-
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	-
	23 b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic Worker - general population	-

AF (sensitive population)	25	Children or other sensitive groups	-
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	-
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across	1.525
Rounded value	30	[µg/m³]	35
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).

Very little information is available on the toxicity of diisobutyl glutarate. Targeted database and literature searches were conducted in eChemPortal, the ECHA chemicals registry, HSDB, TOXNET and PubMed.

Similar to other dibasic esters (Bogdanffy et al., 1991), diisobutyl glutarate can be assumed to be metabolised to isobutanol and glutaric acid, which are both of very low systemic toxicity. The main health effect after inhalation of the ester is determined by the cytotoxicity of the acid after its release by carboxylesterase in the olfactory epithelium (Trela and Bogdanffy, 1991). As this effect will not be covered by route-to-route extrapolation, a read-across approach based on an available LCI value for another dialkyl glutarate, such as dimethyl glutarate is necessary. The rationale is that the toxicity of these two compounds is based on their common metabolite - glutaric acid - and is independent of the respective alcohol components.

Compound	Structure	Molar mass [g/mol]	EU-LCI value
Dimethyl glutarate		160.17	50 µg/m³ (ascribed) 25 µg/m³ (newly derived)
Diisobutyl glutarate		244.33	35 µg/m³ (read-across from dimethyl glutarate)

When applying the molar adjustment factor of 1.525 (244.33 ÷ 160.17) to the unrounded LCI value for dimethyl glutarate of 24.1 µg/m³ an initial value of 36.8 µg/m³ is obtained, which is rounded to 35 µg/m³ as the EU-LCI value for diisobutyl glutarate.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.

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 10.02.2021).

Compound	**Dimethyl glutarate C7H12O4**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	25[1]
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	-
EC No	5	EINECS – ELINCS - NLP	214-277-2
CAS No	6	Chemical Abstracts Service number	1119-40-0
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	160.17 1 ppm = 6.59 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Keenan et al. (1990)
Read across compound	10	Where applicable	Mixture of dibasic esters: 65.5 % dimethyl glutarate, 16.9 % dimethyl succinate, 16.5 % dimethyl adipate
Species	11	Rat, human etc.	Rat
Route/type of study	12	Inhalation, oral feed etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic (90 d)
Exposure duration	14	Hrs/day, days/week	6 h/d, 5 d/wk
Critical endpoint	15	Effect(s), site of	Degeneration of nasal olfactory epithelium
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	LOAEC
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	20 mg/m^3
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	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

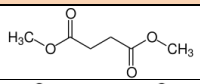
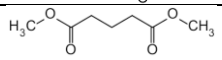
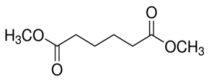
[1] Newly derived EU-LCI value. The current EU-LCI value of 50 µg/m^3 is an ascribed value.

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)	840
POD/TAF	28	Calculated value (µg/m³ and ppb)	23.8 µg/m³ and 3.61 ppb
Molar adjustment factor	29	Used in read-across	1.011
Rounded value	30	[µg/m³]	25
Additional comments	31		
Rationale section	32		

For dimethyl glutarate, no comprehensive risk assessment reports from international bodies could be found. Occupational limit values are based on read-across from a mixture of dibasic esters including dimethyl glutarate. A REACH registration dossier for dimethyl glutarate is available on the ECHA dissemination site (ECHA, 2020). Targeted literature searches were conducted in HSDB, TOXLINE and PubMed to identify additional relevant information. No additional information on (sub)chronic inhalation studies with the substance could be found.

Dimethyl glutarate is liquid at room temperature. Its odour is reported as 'sweetish'. No information on an odour threshold could be found.

It is metabolised to methanol and glutaric acid by carboxylesterase in the nasal olfactory epithelium (Bogdanffy et al., 1991). The release of carboxylic acid causes dose-dependent cytotoxicity (Trela and Bogdanffy, 1991) that results in degenerative changes in the nasal mucosa (Keenan et al., 1990). As this effect will not be covered by route-to-route extrapolation, a read-across approach based on an available inhalation study for similar short-chain dimethyl dicarboxylates, such as succinate and adipate is necessary. The rationale is that the difference in chain length between these homologues is no larger than two CH_2 units and the free acids are of similar acidity, as characterised by their pK_A values.

Compound	Structure	Molar mass [g/mol]	Acidity of the free acid		EU-LCI value
			pK_{A1}	pK_{A2}	
Dimethyl succinate		146.14	4.16	5.61	50 µg/m³ (ascribed) 20 µg/m³ (newly derived)
Dimethyl glutarate		160.17	4.32	5.42	50 µg/m³ (ascribed) 25 µg/m³ (newly derived)
Dimethyl adipate		174.20	4.43	5.42	50 µg/m³ (ascribed)

A mixture of dimethyl succinate (16.9 %), dimethyl glutarate (65.5 %), and dimethyl adipate (16.5 %) was investigated in a subchronic inhalation toxicity study similar to OECD guideline 413 (Keenan et al., 1990). Sprague-Dawley rats were exposed to concentrations of 0, 20, 76, or 390 mg/m³ for 6 hours per day, 5 days per week over 13 weeks. Although it is reported that the test substance was administered as a vapour, it must be assumed, based on other studies with similarly high concentrations (ECHA, 2020), that most of it was actually present as an aerosol. However, as deposition of the vapour in the nasal mucosa is reported to occur instantly with efficiency rates of around 98 % (Morris et al., 1991), there seems to be no reason to expect a difference in toxicity between aerosol and vapour in this case. All test concentrations caused degeneration or atrophy of the olfactory epithelium in female rats. In male rats, these effects were only observed in the two highest dose groups. After a 6-week recovery period, regenerative processes and signs of tissue repair such as respiratory metaplasia, disorganisation of the olfactory epithelium and decreased numbers of neuronal cells were noted. Animals exposed to 390 mg/m³ showed slight reductions in body

weight gain. The NOAEC for systemic toxicity was therefore 76 mg/m³. For local effects, the LOAEC was 20 mg/m³. This value is used as the point of departure (POD) for the determination of an EU-LCI value for dimethyl glutarate based on read-across from the mixture of dimethyl dicarboxylates as specified above.

Assessment factors were chosen as follows:

- 5.6 to adjust for exposure duration (from 6 h/d on 5 d/wk to 24/7)
- 2 for the extrapolation from subchronic to chronic
- 3 to account for the uncertainty of the dose-response by using a LOAEC instead of a NOAEC
- 2.5 for interspecies differences (default value for kinetic and dynamic differences)
- 10 for intraspecies differences (default value for the general population)

The total assessment factor of 840 and the POD of 20 mg/m³ gave an initial value of 23.8 µg/m³ (3.61 ppb) for the mixture of dimethyl esters. The application of a molar adjustment factor of 1.011 for read-across – calculated by dividing 160.17 by [(0.169 x 146.14) + (0.655 x 160.17) + (0.165 x 174.20)] – resulted in an initial value of 24.1 µg/m³, which is rounded to the EU-LCI value of 25 µg/m³ for dimethyl glutarate. This newly derived EU-LCI value is lower than the current ascribed value of 50 µg/m³. It may be considered conservative as it is based on local effects that have been characterised as predominantly mild and may be presumed to be reversible.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

European Chemicals Agency (2020): Registration dossier for dimethyl glutarate. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/5377. Last accessed on 10.02.2021.

Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of bibasic esters, Fundam. Appl. Toxicol. 15 (2), 381-393.

Morris, J.B.; Clay, R.J.; Trela, B.A.; Bogdanffy, M.S. (1991): Deposition of dibasic esters in the upper respiratory tract of the male and female Sprague-Dawley rat, Toxicol. Appl. Pharmacol. 108 (3), 538-546.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.