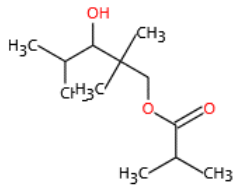
Compound	2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate	*Data collection sheet*
N°CAS 25265-77-4 **1 ppm (in air, 23°C) = 8.90 mg/m³**	**EU- Classification:** - **CLP:** -	
Organisation name	**REACH Registrant**	
Risk value name	DNEL	
Risk value (mg/m³)	14.5	
Risk value (ppm)	1.6	
Reference period	Chronic (consumer)	
Year	2019 (last modification)	
Key study	DNEL was derived by industry, no further information available	
Study type		
Species		
Duration of exposure in key study		
Critical effect	Systemic toxicity	
Critical dose value	Long-term inhalation DNEL for consumers (systemic effects) derived by industry	
Adjusted critical dose	Chronic	
Single assessment factors (see table R.8.6)	Not indicated, an overall assessment factor of 30 was applied	
Other effects		

Compound	**2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	850
EU-LCI status	2	Draft/final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2018
General information			
CLP-INDEX-No.	4	INDEX	Not listed
EC-No.	5	EINECS – ELINCS - NLP	246-771-9
CAS-No.	6	Chemical Abstracts Service number	25265-77-4
Harmonised CLP classification	7	Human health risk related classification	
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	216.32 1 ppm = 8.90 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Eastman, 1992
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rodent Male and female Sprague-Dawley rats
Route/type of study	12	Inhalation, oral feed, etc.	Oral via gavage
Study length	13	Days, subchronic, chronic	Subchronic (up to 51 days)
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	Liver weight increase with histopathological correlate at 300 mg/kg bw/day (LOEL)
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOEL
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	100 mg/kg bw/day corr. POD 87 mg/m³
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21	Oral → Inhalation *(R8-5)*	2
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)	100
POD/TAF	28	Calculated value (µg/m³ and ppb)	870 µg/m³ and 98 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	850
Additional comments	31		
Rationale section	32		



Background:
2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate (TMPD-MIB; trade name) is a colourless liquid with a faint odour, which is mainly used as a component of latex paints and as an intermediate in chemical syntheses. Indoor measurements reported TMPD-MIB median concentrations of < 2 µg/m^3 and maximum concentrations of up to 12000 µg/m^3.

At room temperature and atmospheric pressure, TMPD-MIB is a liquid with an approximate melting point <-70.25 °C, a boiling point of 255-261.5 °C and a vapour pressure of 1.3 Pa.

Toxicokinetics:
No toxicokinetic studies of TMPD-MIB after inhalative or oral exposure are available, but it is assumed that TMPD-MIB is metabolised similarly to the related compound 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TMPD-DIB). TMPD-DIB is rapidly absorbed, metabolised and eliminated in rats. Metabolisation is predominantly by O-glucuronidation, with a lesser degree of oxidation and subsequent glucuronidation (ECHA-disseminated dossier, 2018).

Human data:
There are no relevant data on the effects of TMPD-MIB on human health.

Acute toxicity:
The acute toxicity of TMPD-MIB is low, with acute oral LD50 values in rats of 6.86 ml/kg bw.
In an inhalation risk assay, six male or female rats in each dose group survived 8 hours of exposure to saturated vapours of TMPD-MIB.
In animal studies, TMPD-MIB was slightly irritating to skin and eyes, but did not show skin-sensitising properties (ECHA-disseminated dossier, 2018).

Repeated dose toxicity:
There are no data on toxicity following repeated exposure via inhalation.
TMPD-MIB was tested in a combined repeated dose and reproductive/developmental toxicity study according to OECD Test Guideline 422. Twelve male and twelve female Sprague-Dawley rats for each dose level were given doses of 0, 100, 300 and 1000 mg/kg bw/day via gavage. Females received between 40 and 51 doses during premating (14 days), mating (up to 14 days), pregnancy (21-22 days) and early lactation (4 days). All male animals received 51 doses.

Clinical signs of toxicity were limited to a dose-dependent reversible increase in post-dose sialorrhea in all treatment groups (1/24, 5/24, 22/24 animals in the 100, 300 and 1000 mg/kg bw/day dose groups, respectively). Sialorrhea may have been due to the taste of the test substance.

Table 1: Statistically significant increases in organ weights, incl. incidence of histopathological findings

[mg/kg bw/day]	0	100	300	1000
Liver, males	13.3655	14.6095*	14.7002*	17.9233*
% increase	-	+8.5	+9.1	+25.4
Hepatocytomegaly, centrilobular	0/12	0/12	7/12	9/12
Liver, females	13.5971	14.5748	14.6530	16.4069*
% increase	-	+6.7	+7.2	+17.1
Hepatocytomegaly, centrilobular	0/12	0/12	3/12	9/12
Kidneys, males	3.3740	3.4807	3.5094	4.1283*
% increase	-	3.1	3.8	18.3
Hyaline droplet	0/12	0/12	12/12	12/12
Kidneys, females	2.3362	2.1063	2.4769	2.4214
% increase	-	-9.8	+5.7	+3.5
Hyaline droplet	0/12	0/12	0/12	0/12

*$p<0.05$

In the high dose group, test-substance-related signs of toxicity included a slight statistically significant decrease in feed consumption 4 days after the start of dosing. Organ weight differences included statistically significant increased relative kidney weights in male rats. An accumulation of histopathologically identified hyaline droplets points to a male rat-specific α2μ-globulin nephropathy, which has no relevance for human risk assessment.

In the high dose group, a biologically relevant and statistically significant increase in liver weights was described (+25.4% and +17.1% in males and females, respectively). Histopathological assessment of livers identified a high incidence of centrilobular hepatocytomegaly in males and females. In the mid dose, a lower incidence of centrilobular hepatocytomegaly was identified, together with a mild increase in liver weights. Liver weight increase in the low dose group was of questionable biological relevance and lacked a histopathological correlate.

Significantly reduced mean haemoglobin and creatinine values were also identified in the high dose group.

Although the adverse effects on the liver at the mid dose could be seen as an adaptive response, a liver weight increase with a histopathological correlate was considered biologically relevant for the derivation of the EU-LCI. The resulting POD was identified as 300 mg/kg bw/day (LOEL) or 100 mg/kg bw/day (NOEL), respectively.

Due to the ambiguous dose response of the observed liver weight increase, a Benchmark Dose Model was not suitable for the derivation of an alternative starting point. However, the identified value for the $BMD_{10}L_{95}$ of 90 mg/kg /day would substantiate the LOEL for a 10% increase in liver weight.

No impact on reproductive performance was identified (Eastman, 1992b; ECHA, 2018e).

The observations in this study were substantiated in a subacute toxicity study with 28-day oral dosing (ECHA, 2018).

Genetic toxicity/carcinogenicity:
There are no data available for the endpoint carcinogenicity.
TMPD-MIB tested negative in an Ames test as well in an *in vivo* micronucleus assay.

POD
The EU-LCI derivation is based on an oral NOEL value of 100 mg/kg bw/day due to an increase in liver weights which correlated with histopathologically identified centrilobular hepatocytomegaly (Eastman, 1992; ECHA, 2018).

Differences in respiratory volumes: the respiratory volume of the rat in 24 h corresponds to 1.15 m^3/kg bw. The correction factor is 1 ÷ 1.15 = 0.87.

Corrected POD: 87 mg/m³.

Assessment factors

For the calculation of the EU-LCI the default assessment factors were:

- 2 for study length, as the study duration of 51 days was considered to be equivalent to a subchronic study
- 2.5 for interspecies differences
- 10 for intraspecies differences
- 2 for route-to route extrapolation since 50% oral absorption in comparison with 100% absorption by inhalation is assumed in accordance to the ECHA Guidance Chapter R8 (2012).

Overall, a factor of 2 x 2.5 x 10 x 2 = 100 is calculated, resulting in an unrounded LCI value of 87 mg/m³ ÷ 100 = 870 µg/m³. The final EU-LCI value is 850 µg/m³.

References

Eastman (1992), Propanoic Acid, 2-Methyl-, Monoester with 2,2,4-Trimethyl-1,3-Pentanediol, Synonym: Texanol Ester-Alcohol, Combined Repeated Dose and Reproductive/Developmental Toxicity Study in the rat, Unpublished Eastman Kodak Report TX-92-57. Cited in: OECD (1996) OECD SIDS Texanol (CAS 25265-77-4).

ECHA (2018) Registration document isobutyric acid, monoester with 2,2,4-trimethylpentane-1,3-diol (CAS 25265-77-4). http://echa.europa.eu/de/registration-dossier/-/registered-dossier/14126 (last retrieved on 4.12.2019).

ECHA (2012) Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment (last retrieved on 4.12.2019).