Compound	**Triethylene glycol dimethyl ether (TEGDME)**		***Data collection sheet (1/1)***
N°CAS 112-49-2 **1 ppm ~ 7.33 mg/m³**	**Harmonised CLP classification:** Repr.1B (H360Df)		
Organisation name	**AgBB**	**ANSES**	**Reach Registrants**
Risk value name	NIK (=LCI)	CLI (=LCI)	$DNEL_{(General\ population,\ long\text{-}term,\ inhalation,\ systemic)}$
Risk value (mg/m³)	0.007	0.02	19.9
Risk value (ppm)	0.00095	0.0027	2.7
Reference period	Chronic	Chronic	Chronic
Year	2018	2009	2018
Key study	Shih et al., 2000; Shih et al., 2003 (read-across using ethylene glycol monomethyl ether/EGME)	Miller et al., 1983 (read-across using ethylene glycol monomethyl ether/EGME)	Schwetz et al., 1992
Study type	Analysis of blood and sperm	Subchronic vapour inhalation study	Developmental toxicity oral study
Species	Human (29-53 workers of a copper clad laminate manufacturing plant)	Rats (Sprague-Dawley; 6-8 weeks old) Rabbits (New Zealand White; 6-7 months old)	Rabbits
Duration of exposure	Average duration of employment of 2.6-2.9 years	6 h/d, 5 d/w for13 weeks	GD 6 – 19
Critical effect	Haematological effects (decreased haemoglobin, packed cell volume and red blood cell count)	Decreased testes weight & degenerative changes in the testicular germinal epithelium	Developmental toxicity
Critical dose value	Average NOAEC	NOAEC (EGME)	NOEL
	7.4 mg/m³ (2.3 ppm)	93 mg/m³ (30 ppm)	75 mg/kg bw/d
Adjusted critical dose	NIK (EGME) = 3 µg/m³	CLI (EGME) = 20 µg/m³	$NOEC_{human}$
	NIK adopted from the EU-OEL for EGME of 3 µg/m³ (1 ppm)		NOAEL (oral, rabbit) x $1/sRV_{rabbit}$ x ABS(oral-rabbit)/ABS(inh-human) x sRV_{human}/wRV = 75 mg/kg bw/d x 1/0.376 m³/kg/d x 100%/100%

			= 199.5 mg/m^3
Single assessment factors	Molar adjustment factor = 178.23 / 76.09 = 2.34	N/A	UF_H 10
Other effects	N/A	Reduced body weight, haematological changes (pancytopenia), lymphoid tissue atrophy	Maternal toxicity
UF_H Intraspecies variability; UF_A Interspecies variability; UF_S Used subchronic study; UF_D Data deficiencies			

Compound	**Triethylene glycol dimethyl ether (TEGDME) C8H18O4**		***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	2019
General information			
CLP-INDEX-No.	4	INDEX	603-176-00-2
EC-No.	5	EINECS – ELINCS - NLP	203-977-3
CAS-No.	6	Chemical Abstracts Service number	112-49-2
Harmonised CLP classification	7	Human health risk related classification	Repr. 1B (H360Df)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	178.23 1 ppm = 7.33 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Hoffman et al., 1992
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rats
Route/type of study	12	Inhalation, oral feed, etc.	Oral
Study length	13	Days, subchronic, chronic	Subacute
Exposure duration	14	Hrs/day, days/week	Daily for 28 days
Critical endpoint	15	Effect(s), site of	Reduced thymus weight in females
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	62.5 mg/kg $_{bw}$xd
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	6
Route-to-route extrapolation factor	21	Oral-to-inhalation	1.23
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[1]
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic	10

[1] AF for allometric scaling is already included in line 21.

		Worker - General population	
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)*	2
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	369
POD/TAF	28	Calculated value (µg/m^3 and ppb)	169 µg/m^3 and 23.1 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m^3]	150
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for triethylene glycol dimethyl ether (TEGDME) are based on a project funded by the European Commission and carried out by Ramboll Environment & Health GmbH.

Only a limited number of assessment reports on TEGDME were identified in the public domain. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) published an assessment on TEGDME as part of its assessment report on glycol ethers (ECETOC, 2005). A REACH registration dossier for the tonnage band 10-100 tonnes per annum is also available for TEGDME (ECHA, 2018). The Belgian competent authority (Belgian Federal Public Service) in cooperation with the Polish Competent Authority (Bureau for Chemical Substances) submitted an Annex XV report to ECHA to propose the identification of TEGDME as a substance of very high concern (SVHC) (ECHA, 2012a). Literature searches using PubMed, TOXNET and Google Scholar were conducted in order to identify relevant literature on TEGDME that is not addressed in the aforementioned data sources. All relevant data were used to evaluate and derive an EU-LCI value for TEGDME.

Rationale for critical effect/POD

Current LCI values from Germany and France are based on a read-across approach using ethylene glycol (mono) methyl ether (EGME) as the read-across substance. This is due to the understanding that TEGDME can be metabolised to yield EGME and its subsequent metabolite, methoxyacetic acid (MAA). However, the read-across approach using EGME was not considered for deriving an EU-LCI value for TEGDME for two main reasons:

- There are sufficient studies and experimental data on repeated exposure to TEGDME in multiple species. Even though in these repeated exposure studies TEGDME was administered orally, there is sufficient understanding of the toxicokinetics of TEGDME and ethylene glycol ethers such that a route-to-route extrapolation can be performed for the EU-LCI derivation.
- The developmental toxicity potency of various ethylene glycol ethers has been compared, and TEGDME is consistently known to have a lower potency, which is less likely to elicit developmental toxicity than the lower molecular weight ethylene glycol ether counterparts such as EGME and diethylene glycol dimethyl ether (DEGDME) (Schwetz et al., 1992; Hardin & Eisenmann, 1987). For example, one study showed that a single oral dose of 713 mg/kg bw/day of TEGDME in pregnant CD-1 mice on GD 11 resulted in neither maternal toxicity nor gross external foetal malformations (primarily paw defects) as examined on GD 18. By contrast, other ethylene glycol ethers such as EGME (304 mg/kg bw/day), ethylene glycol dimethyl ether (EGDME) (361 mg/kg bw/day) and DEGDME (537 mg/kg bw/day) all triggered significant paw defects (Hardin & Eisenmann, 1987).

For these reasons, the EU-LCI of TEGDME was derived *de novo* instead of taking a read-across approach using EGME.

As there were no animal or human data on inhalation exposure to TEGDME, the derivation of the EU-LCI for TEGDME is based on thymic effects observed in female rats after subacute oral exposure to TEGDME (Hoffman et al., 1992) as described in the ECETOC report (ECETOC, 2005) as well as in the REACH registration dossier for TEGDME (ECHA, 2018). In this study, Wistar rats (5/sex/group) were orally exposed to 0, 62.5, 250 or 1000 mg/kg bw/day of TEGDME for 28 days (subacute exposure). In male rats, retardation in growth rate, reduced water consumption, reductions in testes and thymus weight and thrombocytopenia were observed at 1000 mg/kg bw/day. Furthermore, histopathological examination revealed degenerative changes in the seminiferous epithelium and atrophy of the thymus at this highest dose. At 250 mg/kg bw/day, thymus reductions were also reported in females (no significant reduction in males) however, there were no histopathological findings. As the full text was not available to evaluate the severity of the thymus findings in female rats, the no-observed-effect-level (NOEL) was set at 62.5 mg/kg bw/day, and this was selected as the point of departure (POD) for the EU-LCI derivation.

Reproductive and developmental toxicity effects of TEGDME have been consistently observed in other species (Bossert et al., 1992; George et al., 1987; Hardin & Eisenmann, 1987; Hofmann et al., 1992; Plasterer et al., 1985; Schwetz et al., 1992). The published study of Schwetz et al. (1992) reported the lowest dose of TEGDME that triggered developmental effects in rabbits (described below). In addition, rabbits have been shown to be more sensitive than rodents to the developmental toxicity of TEGDME (George et al., 1987; Schwetz et al., 1992) as well as other ethylene glycol ethers such as EGME (Hanley et al., 1984; Miller et al., 1983).

In the study by Schwetz et al. (1992), TEGDME (0, 75, 125, 175, or 250 mg/kg bw/day) was orally administered by gavage on gestation day 6 through 19 (14 days) to pregnant New Zealand white rabbits (n = 15-25 per group). Treated females were euthanised on gestation day 30. Uterine contents were examined, and live foetuses were examined for morphological alterations. The study found no significant clinical signs of toxicity and no increase in maternal mortality. Maternal body weight and gravid uterine weight were significantly reduced at 250 mg/kg bw/day, but maternal weight gain during treatment was significantly depressed when doses exceeded 175 mg/kg bw/day. There was no TEGDME-related effect on mean foetal body weight, but prenatal mortality was significantly increased at 250 mg/kg bw/day, which was primarily due to an increased incidence of resorption of implanted embryos. In addition, at 175 and 250 mg/kg bw/day, significant increases in the incidence of malformed foetuses per litter and in the incidence of litters with malformed foetuses were also observed. The most frequently observed malformations in foetuses of normal size included anonychia (missing toenails with no digital abnormalities), an abnormally small spleen, and hydronephrosis. Exposure to 75 or 125 mg/kg bw/day of TEGDME showed no evidence of reproductive or developmental toxicity, and therefore, the dose of 125 mg/kg bw/day of TEGDME was considered the NOAEL for developmental toxicity.

The study of Hoffman et al. (1992) was selected as the key study instead of the study of Schwetz et al. (1992) because the POD for the Hoffman et al. (1992) study (NOEL of 62.5 mg/kg bw/day) is lower than that for the Schwetz et al. (1992) study (NOAEL of 125 mg/kg bw-day). Also, applying the required assessment factors for both studies revealed that the EU-LCI value using the Hoffman et al. (1992) study would result in a lower EU-LCI that would also be protective of the developmental effects observed in the Schwetz et al. (1992) study (see Appendix 1 for the comparative analysis).

To perform the route-to-route extrapolation of TEGDME from oral exposure to inhalation, an understanding of the toxicokinetics of TEGDME as well as a general understanding of glycol ethers is needed. This information was extrapolated from existing data from DEGDME, a structural analogue of TEGDME with the same functional groups and with a difference of one ethyl group. In general, glycol ethers are readily absorbed and widely distributed following oral or inhalation exposure, and it has been shown that DEGDME absorbed via oral exposure is readily excreted from the body, primarily via the urine (Cheever et al. 1988; ECETOC, 2005; Richards et al., 1993; WHO, 2002). For example, from a single oral dose of 6.84 mg/kg bw/day of [^{14}C]-DEGDME in male Sprague-Dawley rats, 83.1% of the administered radioactivity was found in the urine 24 hours after exposure. A higher dose of 684 mg/kg resulted in a slightly lower degree of urinary excretion of 77.5%. Within 96 hours of exposure in rats for both doses, nearly 96% of the administered radioactive dose was recovered in urine, faeces and expired air and with less than 2.5% found in the carcass (Cheever et al., 1988). It is believed that mixed function oxidases such as cytochrome P450 (CYP450) enzymes are required to initiate the metabolic reaction (O-demethylation)

of DEGDME (ECETOC, 2005), and CYP450 enzymes are expressed in both human nasal mucosa and the liver (Zhang et al., 2005).

With this considered, taking the oral toxicokinetics data from Cheever et al. (1988) study, it can be assumed that at least 93.5% (96% recovered dose – 2.5% of the dose found in the carcass) of the oral dose would be absorbed. Taking a worst-case scenario of 100% absorption of inhalation and following the guidelines on route-to-route extrapolation published by ECHA (2012b), the NOAEC is corrected by the difference in route-specific absorption (93.5% oral/100% inhalation).

The NOEL from the repeated subacute oral exposure study in rats was converted to the corresponding inhalation concentration in humans according to ECHA (2012b) as shown below:

$NOEC_{human}$: oral NOEL x 1/sRVrat x (Absorption oral-rat/Absorption inhal-human)
62.5 mg/kg bw-day ÷ 1.15 m^3/kg bw x 93.5/100 = 50.8 mg/m^3

Assessment factors (AF)

Standard default assessment factors were applied for study length and interspecies as well as intraspecies differences. As mentioned above, an additional AF of 2 was included to account for the potential increased formation of MAA if the exposure was combined with CYP2E1 inducers such as ethanol and phenobarbital and the higher capacity of humans to metabolise TEGDME to MAA than rodents (see Appendix 2 below).

- Study length: 6
- Interspecies differences: 2.5 (for kinetics + dynamics)
- Intraspecies differences: 10
- Other adjustment factors: 2

The total assessment factor is 369.

This resulted in a calculated value of 169 µg/m^3 (23.5 ppb) and a derived EU-LCI for TEGDME of 150 µg/m^3.

No information on the odour threshold of TEGDME was available in the public domain. It should be mentioned that TEGDME has a very low vapour pressure of 0.003 kPa at 20 °C, and the exposure of the general population to TEGDME occurs primarily through dermal contact with products containing TEGDME such as adhesives, brake fluids and paint remover.

Appendix 1: Comparative analysis of derived EU-LCI values between the Hoffman et al. (1992) and Schwetz et al. (1992) studies

Taking the Schwetz et al. (1992) study on the developmental toxicity of TEGDME would result in a POD of 125 mg/kg bw/day (NOAEL). The NOAEL from the developmental toxicity oral study in rabbits can be converted to the corresponding inhalation concentration in humans as shown below:

$NOAEC_{human}$: 125 mg/kg bw-day ÷ 1.15 m^3/kg bw x 93.5/100 = 101.6 mg/m^3

Standard default assessment factors would be applied for interspecies as well as intraspecies differences. Because of the critical effect of foetal malformations, an AF of 5 would be applied to account for the severity of effects (ECETOC, 2010). According to ECETOC (2010), an AF of 3 for developmental effects would usually be applied. In the case of TEGDME, the AF for severity of effect would be increased to 10 to account for the species difference in the metabolism of TEGDME as well as for the higher potential of metabolising TEGDME to MAA in pregnant mothers (see Appendix 2 below).

- Severity of effect: 10
- Interspecies differences: 2.5 (for kinetics + dynamics)
- Intraspecies differences: 10

The total assessment factor is 250.

This resulted in a calculated value of 406 µg/m^3 and a derived EU-LCI for TEGDME of 400 µg/m^3. The derived EU-LCI value of 150 µg/m^3 from the Hoffman et al. (1992) study would protect against the developmental toxicity of TEGDME.

Appendix 2: Scenarios of increased formation of the reproductive toxicant MAA from TEGDME exposure in humans

Based on the understanding of the toxicokinetics of DEGDME, TEGDME is believed to primarily undergo O-demethylation to form the metabolite [2-(2-methoxyethoxy)ethoxy]acetic acid, which is presumed not to be teratogenic. However, the minor metabolic pathway of TEGDME involving oxidative cleavage of the inner ether bond to form EGME and MAA can occur. MAA is a well-reported reproductive and developmental toxicant, and the increased probability of this minor metabolic pathway occurring may arise from two scenarios: exposure to TEGDME during pregnancy and combined exposure to TEGDME and CYP450 2E1 inducers such as ethanol and phenobarbital.

Toxicokinetic studies of DEGDME in rats have shown that 2-methoxyethoxyacetic acid is the predominant urinary metabolite (e.g. ≥ 67% after 48 or 96 h exposure), whereas MAA is a minor metabolite (about 6% of the urinary metabolite). However, the proportion of MAA in urine changes in pregnant animals. For example, pregnant CD-1 mice orally exposed to 3.73 mmol/kg bw/day (500 mg/kg bw/day) DEGDME on gestation day 11 had urinary levels of MAA (28 ± 1% of the administered dose) and 2-methoxyethoxyacetic acid (63 ± 2% of the administered dose over a 48 h period). The parent DEGDME and metabolite MAA were also detected in the embryonic tissues from these animals and embryos harvested (Daniel et al., 1991; WHO, 2002). This suggests that pregnant mothers upon DEGDME (or TEGDME) exposure might have a higher body burden of MAA.

The formation of EGME and MAA from the higher molecular weight glymes such as DEGDME and TEGDME are believed to occur via an oxidative cleavage reaction mediated by CYP450 enzymes (Cragg, 2001; Richards et al., 1993; Tirmenstein, 1993). Microsomes isolated from phenobarbital or ethanol (CYP450 2E1 inducers) pre-treated rats exhibited an increased capacity to cleave DEGDME to EGME, whereas this ethanol-induced conversion of DEGDME to EGME was not observed when the reaction contained the CYP450 2E1 inhibitor isoniazid (Tirmenstein, 1993). This means that combined exposure to glymes such as TEGDME and CYP450 2E1 and inducers such as ethanol and phenobarbital could also result in increased cleavage of the inner ether linkage, resulting in increased formation of EGME and MAA. Lastly, it is postulated that human liver microsomes might be more capable of metabolising DEGDME and TEGDME to EGME and MAA than rats (Tirmenstein, 1993; WHO, 2002).

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