Compound	Tetrahydrofuran					*Data collection sheet (1/2)*
N°CAS 109-99-9 **1 ppm ~ 2.97 mg/m³**	**CLP: Eye irrit. 2 (H319), STOT SE. 3 (H335), Carc.2**					
Organisation name	**AgBB (DE)**	**DFG (DE)**	**INRS (FR)**	**RIVM (NL)**	**AFS (SE)**	**SCOEL (EU)**
Risk value name	NIK (=LCI)	MAK (OEL 8h)	VLEP/VME	TCA	NGV (OEL TWA 8h)	OEL-8h TWA
Risk value (mg/m³)	1.5	150	150	0.035	150	150
Risk value (ppm)	0.50	50	50	0.012	50	50
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2015	1996	2006	2000	2015	1992
Key study	NIK derivation based on the review performed by the Committee on Hazardous Substances (AGS)	Ohashi et al., 1982b	Katahira et al., 1982a; Ikeoka et al., 1984; Ohashi et al., 1983 (based on SCOEL (EU), 1992)	Katahira et al., 1982a	Katahira et al., 1982a; Ikeoka et al., 1984; Ohashi et al., 1983 (based on SCOEL (EU), 1992)	Katahira et al., 1982a; Ikeoka et al., 1984; Ohashi et al., 1983
Study type		Subacute repeated inhalation	Experimental animal inhalation studies	Subchronic repeated inhalation	Experimental animal inhalation studies	Experimental animal inhalation studies
Species		Rats	Rats	Rats	Rats	Rats
Duration of exposure		4 h/day, 5 days/week, 3 weeks	Acute to subchronic	4 h/day, 5 days/week, 12 weeks	Acute to subchronic	Acute to subchronic
Critical effect		Slight damage to the nasal epithelium	Reduction in ciliary beating & irritation of the nose and eyes	Liver dysfunction & local irritation to respiratory tract mucous membrane	Reduction in ciliary beating & irritation of the nose and eyes	Reduction in ciliary beating & irritation of the nose and eyes
Critical dose value	OEL 150000 µg/m³	LOAEC: 100 ppm (297 mg/m³)	LOAEC: 100 ppm (297 mg/m³)	$NOAEC_{experimental}$: 295 mg/m³ (100 ppm)	LOAEC: 100 ppm (297 mg/m³)	LOAEC: 100 ppm (297 mg/m³)
Adjusted critical dose	N/A	N/A	N/A	$NOEC_{adjusted}$ = 295 x (4 h / 24 h) x (5 d / 7 d) = 35 mg/m³	N/A	N/A

Single assessment factors	For potential carcinogenic substances the OEL value is divided by 1000	UF 2	UF 2 (transient nature of the minimal effects observed)	UF_H+UF_A 100 x UF_S 10	UF 2 (transient nature of the minimal effects observed)	UF 2 (transient nature of the minimal effects observed)
Other effects	N/A	N/A	Liver dysfunction	N/A	Liver dysfunction	Liver dysfunction
UF_H Intraspecies variability; UF_A Interspecies variability; UF_S Used subchronic study; UF_D Data deficiencies; UF_L Used LOAEL						

Compound	**Tetrahydrofuran**				***Data collection sheet (2/2)***
N°CAS 109-99-9 1 ppm ~ 2.97 mg/m³	**CLP: Eye irrit. 2 (H319), STOT SE. 3 (H335), Carc.2**				
Organisation name	**ACGIH (US)**	**EPA (US)**	**NIOSH (US)**	**OSHA (US)**	**REACH Registrants**
Risk value name	TLV-TWA	RfC	REL TWA (10 h)	PEL TWA (8 h)	$DNEL_{(General\ population,\ inhalation,\ long\text{-}term,\ systemic)}$
Risk value (mg/m³)	147	2	590	590	13
Risk value (ppm)	50	0.67	200	200	4.3
Reference period	Chronic	Chronic	Chronic	Chronic	Chronic
Year	2005	2012	1992	1994	2018
Key study	Katahira et al., 1982a	NTP, 1998	ACGIH, 1970		NTP, 1998
Study type	Subchronic repeated inhalation	Subchronic repeated inhalation	N/A	N/A	Subchronic repeated inhalation
Species	Rats	Rats and mice	N/A	N/A	Rats and mice
Duration of exposure	4 h/day, 5 days/week, 12 weeks	6 h/day, 5 days/week, 14 weeks	N/A	N/A	6 h/day, 5 days/week, 14 weeks
Critical effect	Local irritation to respiratory tract mucous membrane	Absolute liver weight in male mice	Anaesthetic effects Mild upper respiratory tract irritation	N/A	Acanthosis and inflammation of the forestomach in rats
Critical dose value	NOEC: 100 ppm (297 mg/m³)	$BMCL_{10}$ = 246 mg/m³ (82.8 ppm)	N/A	N/A	NOAEC: 600 ppm (1782 mg/m³)
Adjusted critical dose	N/A	N/A	N/A	N/A	[1800 x (6 h/d / 24 h/d) x (5 d/w / 7d/w)] / 25

Single assessment factors	UF 2 („A TLV-TWA of 50 ppm is recommended to reduce the potential for number of effects that occur or are seen as study NOELs at 100 to 200 ppm in test animals")	UF_H 10 x UF_A 3 x UF_S 1 x UF_D 3 x UF_L 1	N/A	N/A	UF_H 10 x UF_A 2.5
Other effects	Liver dysfunction	CNS (narcosis)	N/A	N/A	CNS (narcosis)
UF_H Intraspecies variability; UF_A Interspecies variability; UF_S Used subchronic study; UF_D Data deficiencies; UF_L Used LOAEL					

Compound	**Tetrahydrofuran**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	500
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	603-025-00-0
EC-No.	5	EINECS – ELINCS - NLP	203-726-8
CAS-No.	6	Chemical Abstracts Service number	109-99-9
Harmonised CLP classification	7	Human health risk related classification	Eye irrit. 2 (H319) STOT SE 3 (H335) Carc.2
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	72.10 1 ppm = 2.97 mg/m3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	NTP, 1998
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	F344/N rats and B6C3F1 mice
Route/type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic
Exposure duration	14	Hrs/day, days/week	6 h/day, 5 days/week for 14 weeks
Critical endpoint	15	Effect(s), site of	Increased absolute liver weight of male mice supported with observation of centrilobular cytomegaly
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	BMCL05
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	144.05 mg/m3 (48.5 ppm)
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	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	
	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)	280
POD/TAF	28	Calculated value (µg/m³ and ppb)	514.44 µg/m³ and 173 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	500
Additional comments	31		
Rationale section	32		

Data compilation and evaluation for tetrahydrofuran are based on a project funded by the European Commission and carried out by Ramboll Environment & Health GmbH (formerly BiPRO GmbH).

A number of organisations or national agencies have published comprehensive assessments of tetrahydrofuran (THF) which were considered for the EU-LCI derivation (ACGIH, 2005; DFG, 2013; EPA, 2012; OECD, 2000). There are also two REACH registration dossiers for THF (ECHA, 2018). A targeted literature search using PubMed and Google Scholar was also conducted with the aim of identifying any relevant literature on the inhalation exposure of THF that is not addressed in these data sources. The entire body of data was used for the evaluation and derivation of an EU-LCI value for THF.

European and national authorities and organisations have consistently recommended 50 ppm (150 mg/m³) as the occupational exposure limit value (e.g. TWA-8 h) for THF. This is primarily based on local respiratory effects and/or nasal effects (such as ciliary beating) observed upon exposure to THF at concentrations as low as 100 ppm (297 mg/m³) (Ikeoka et al., 1984; Katahira et al., 1982a; Ohashi et al., 1982b). However, for the derivation of its tolerable concentration in air (TCA), the Dutch authorities (RIVM) selected the Katahira et al. (1982a) study as the only key study, with a NOAEC of 100 ppm (297 mg/m³) for liver dysfunction and irritation of nose epithelium as the point of departure, resulting in a derived TCA of 35 µg/m³ (12 ppb). These studies are not considered eligible for the EU-LCI derivation, however, since the critical effects are primarily local effects of inhalation exposure to THF and there is data available on chronic exposure to THF in experimental animals.

Rationale for key study/POD

As there is no human data on chronic exposure to THF, derivation of the EU-LCI for THF is based on the repeated inhalation study in rats and mice conducted by the US National Toxicology Program (NTP, 1998). The NTP study had two phases, a subchronic and a chronic inhalation exposure phase to THF in both rats and mice of both sexes. This NTP study was used by the US EPA for their derivation of the reference concentration of THF.

For the subchronic exposure, rats and mice of both sexes were exposed to 0, 66, 200, 600, 1800 or 5000 ppm (0, 196, 594, 1782, 5346 or 14850 mg/m³, respectively) THF via inhalation for 6 hours/day, 5 days/week for 14 weeks. At 5000 ppm (i.e. 14850 mg/m³), rats of both sexes exhibited lower thymus and spleen weights, ataxia and higher incidence of hyperplasia (acanthosis) as well as inflammation in the forestomach. Female rats exposed to 5000 ppm also had lower liver weights. For mice, narcotic effects were experienced by both sexes at 1800 and 5000 ppm concentrations. Increased liver weights were reported at ≥ 600 ppm and ≥ 1800 ppm for male and female mice, respectively. There was also increased incidence of minimal to mild centrilobular cytomegaly in mice of both sexes exposed to 5000 ppm. At this highest concentration, uterine atrophy in females and degeneration of the inner cortex of the adrenal gland in both sexes were observed. Male mice exposed to 600 ppm or higher had lower thymus weights (Chhabra et al., 1990; NTP, 1998).

For the chronic exposure, F344/N rats and B6C3F1 mice of both sexes were exposed to 0, 200, 600 or 1800 ppm (0, 594, 1782 or 5346 mg/m³, respectively) THF for 6 hours/day, 5 days/week for 105 weeks. Poor

survival rates were observed in all exposed male rat groups with an increased incidence (not statistically significant) of renal tubule epithelial adenomas and carcinomas. The survival rate was also poor for male mice exposed to 1800 ppm due to sequelae associated with narcosis. Increased non-neoplastic lesions of the urinary tract were observed in these exposed male mice, but the authors hypothesised that this might be a consequence of prolonged wetting of preputial fur during exposure-related narcosis. At 200 ppm, there was a significant increase in nephropathy in male mice compared to controls. Female mice exposed to the highest concentrations (1800 ppm) had higher incidence of hepatocellular adenomas and/or carcinomas. The increase showed a concentration-related trend with statistical significance reached at 1800 ppm. On the other hand, there was no increased incidence in neoplastic lesions in either female rats or male mice. The NTP study concluded that there was some evidence of carcinogenic activity in male rats, no evidence of carcinogenic activity in female rats and male mice and clear evidence of carcinogenic activity in female mice (Chhabra et al., 1998; NTP, 1998).

Among the observed effects in this study, the increase in absolute liver weight in male mice observed in the subchronic part of the NTP study was selected as the critical endpoint for the EU-LCI derivation. The rationale behind this selection is based on the following arguments.

1. **The tumour incidence in male rats and female mice reported in the 2-year study has been questioned in terms of relevance in humans.** It is known that kidney tumours due to formation of alpha-2u-globulin and presence of protein casts/hyaline droplets in male rats are species- and sex-specific and do not occur in humans. The liver tumours in female mice have also been questioned due to high species susceptibility for this type of tumour and the absence of tumours at other sites of the body in combination with the lack of genotoxic potential of THF. Furthermore, there is currently no evidence pointing to THF as a potential cancer risk in humans (see Appendix for further discussion on this topic).

2. **The subchronic study investigated and reported more effects and concentrations (six including control in the subchronic study, four in the chronic study), including both higher (5000 ppm or 14850 mg/m^3) and lower (66 ppm or 196 mg/m^3) concentrations.** The subchronic study also reported less severe effects than tumour formation at similar doses; thus, selecting the critical effect from the subchronic phase of the NTP study provides a more conservative EU-LCI value.

3. **In a number of animal studies, the liver has been shown to be a target organ upon inhalation exposure to THF.** Effects such as decreased hepatic enzymatic activity, increased liver weight and histopathological observations such as centrilobular cytomegaly have been attributable to inhalation exposure to THF (Chhabra et al., 1990; Elovaara et al., 1984; NTP, 1998). In the subchronic exposure part of the NTP study, there was a clear concentration-response relationship, with the statistically significant increased absolute (and relative) liver weight starting at 600 ppm (1782 mg/m^3). Histopathological assessment of the liver tissues showed a mild degree of centrilobular cytomegaly with statistical significance reached only at the highest concentration of 1800 ppm (5346 mg/m^3).

   The chronic phase of the NTP study did observe an increase in nephropathy in male mice exposed to 200 ppm (594 mg/m^3) THF compared to control, but there was no clear concentration-response relationship. This effect was not selected as the critical effect for the EU-LCI derivation as there is a stronger indication of progressive liver damage (i.e. increased liver weight leading to centrilobular cytomegaly) from inhalation exposure to THF.

   The CNS is also a target organ of THF inhalation exposure, as effects have been reported not only in the NTP (1998) but also in other repeated inhalation studies. In the NTP study, however, no incidence data available was for the CNS effects (observed only at 1800 and 5000 ppm, or 5346 and 14850 mg/m^3 respectively, in mice), so only the NOAEC of 600 ppm (1782 mg/m^3) could be used as the point of departure (POD) for this effect. Because the effect of increased liver weight showed a statistically significant concentration-response relationship starting at 600 ppm, the benchmark concentration approach was used to determine which approach would result in a lower POD. This means that the derived EU-LCI would protect against CNS effects, which were observed at higher concentrations than liver effects.

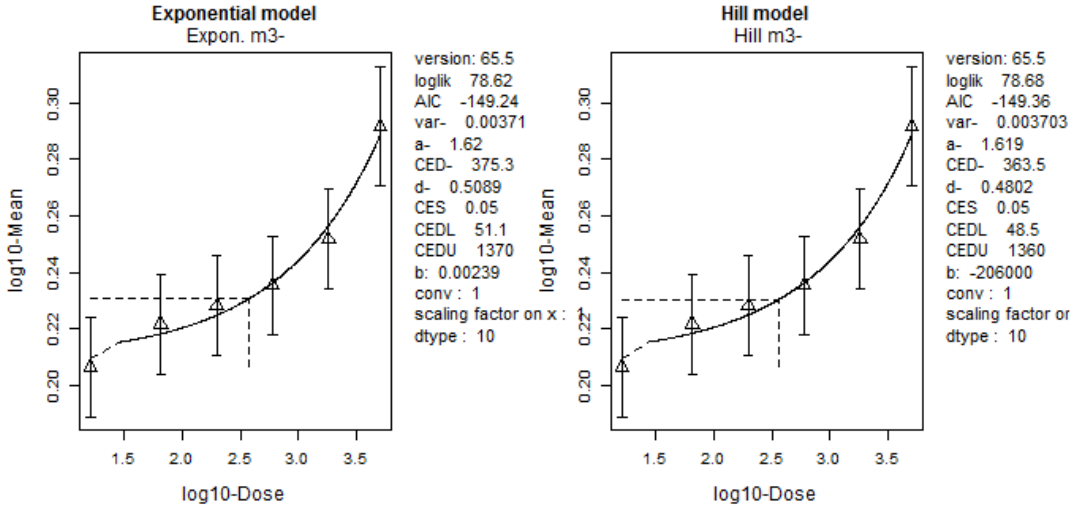
Therefore, selection of increased absolute liver weight with the supporting evidence of centrilobular cytomegaly in the male as the critical effect is considered a conservative endpoint for deriving the EU-LCI for THF.

The average absolute liver weights at the different concentrations are shown below:

Concentration [ppm]	Abs. liver weight [g]	Standard error	No of examined mice
0	1.613	0.037	10
66	1.667	0.022	10
200	1.695	0.037	10
600	1.722*	0.031	10
1 800	1.789*	0.035	10
5 000	1.964*	0.060	7

* statistically significant ($p < 0.05$) compared to control (0 ppm)

As there is a clear concentration-response relationship with this endpoint, a benchmark concentration approach was taken. Taking into consideration the EFSA guidance document on benchmark dose/concentration (EFSA Scientific Committee et al., 2017) and the nature of the study design (continuous data), the calculation of $BMCL_{05}$ was performed using the PROAST v. 65.5 software developed by the RIVM in the Netherlands. The benchmark response was set at the default value of 5% change with no additional assumptions. Model 3 was the selected model with the lowest Akaike information criterion (AIC). The figure below shows the data of the two fitted (exponential and Hill) models.



There was hardly any difference between the two models, and so the model with the lower AIC and $BMDL_{05}$ was selected (i.e. the Hill model), and the $BMDL_{05}$ of 48.5 ppm (144.05 mg/m^3) was selected as the POD.

Assessment factors

Standard default assessment factors were applied to adjust for exposure duration, study length, interspecies and intraspecies differences. The assessment factors applied are:

- exposure duration: 5.6
- study length: 2
- interspecies difference: 2.5
- intraspecies difference: 10

The total assessment factor is 280.

This resulted in a calculated EU-LCI value of 514.44 µg/m^3 and a derived EU-LCI for THF of 500 µg/m^3.

The EU-LCI value (170 ppb; 500 µg/m^3) is below the lowest reported odour threshold for THF (2 ppm, i.e. 6 mg/m^3) (Amoore & Hautala, 1983).

Appendix: Tetrahydrofuran as a carcinogen

The 2-year NTP carcinogenicity study showed increased incidence of renal tubule epithelial adenomas and carcinomas in male rats and hepatocellular adenomas and/or carcinomas in female mice (NTP, 1998). However, the human relevance of these tumours has been questioned by authorities (EPA, 2012; Health Council of the Netherlands, 2012). The involvement of alpha-2u globulin in kidney tumours of male rats is a species- and sex-specific effect that is not found in humans. The high species susceptibility of liver tumours in female mice, the absence of tumour formation in other organs and the lack of genotoxic potential of THF are also concerns that lead to doubts as to the relevance in humans of THF-induced liver cancer. Also, there are currently no human studies showing the carcinogenic potential of THF. Lastly, the lack of genotoxic potential as well as its rapid metabolism/elimination from the body suggests that THF is a weak, nongenotoxic carcinogen that would have an exposure threshold, and therefore, the derived EU-LCI of 500 µg/m^3 for THF is considered to protect against potential human health effects of THF.

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