Annex VI report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **TETRAHYDROFURAN**

EC Number: 203-726-8

CAS Number: 109-99-9

Submitted by: **France**

Date: **June 2009**

Version: **2**

CONTENTS

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Tetrahydrofuran

EC Number: 203-726-8

CAS number: 109-99-9

Registration number (s): -

Purity: 99.5-99.9%

Impurities: Peroxide (as hydrogen peroxide) (unknown concentration) [JT Baker Chemical, 1986] can be formed when THF is exposed to air. Some grades may contain an inhibitor such as butyl hydroxy toluene (CAS No. 128-37-0), at less than 1%, to prevent peroxide formation (SIDS, 2000)

Proposed classification based on Directive 67/548/EEC criteria:

F; R11-19
Carc.Cat.3; R40
Xi; R36/37

Proposed classification based on GHS criteria:

Flam. Liq. 2 – H225
EUH 019
Carc. 2 – H351
Eye Irrit. 2 – H319
STOT single 3 – H335

Proposed labelling:

R-phrases: R11- R19 - R36/37 - R40
Symbol(s) : F; Xn
S-phrases : S2- S16- S29- S33- S46

Proposed specific concentration limits (if any): none

Proposed notes (if any): Note H

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name:	Tetrahydrofuran
	Synonyms: Butylene oxide, Cyclotetramethylene oxide, Diethylene oxide, 1,4-epoxybutane, Ethyl ethylene oxide, 2-Ethyloxirane, Furanidine, Oxacyclopentane, Oxolane, Tetramethylene oxide, THF
EC Name:	203-726-8
CAS Number:	109-99-9
IUPAC Name:	Tetrahydrofuran

1.2 Composition of the substance

Chemical Name:	Tetrahydrofuran
EC Number:	203-765-0
CAS Number:	7722-84-1
IUPAC Name:	Tetrahydrofuran
Molecular Formula:	C_4H_8O
Structural Formula:	
Molecular Weight:	72.12 g/mol
Typical concentration (% w/w):	-
Concentration range (% w/w):	99.5-99.9%

Chemical Name:	Hydrogen Peroxide
EC Number:	231-765-0
CAS Number:	7722-84-1
IUPAC Name:	Hydrogen peroxide

Molecular Formula: H_2O_2

Structural Formula:

Molecular Weight: 34 g/mol

Typical concentration (% w/w): -

Concentration range (% w/w): <0.5%

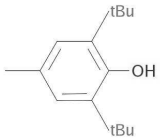
Classification

The following harmonised classification of hydrogen peroxide was agreed at the 19th ATP:

According to 67/548/CEE	*According to CLP*
R5 O; R8 Xn; R20/22 C; R35 with specific concentration limits: Xn; R20: C ≥ 50 % Xn; R22: C ≥ 8 % C; R35: C ≥ 70 % C; R34: 50 % ≤ C < 70 % Xi; R37/38: 35 % ≤ C < 50 % Xi; R41: 8 % ≤ C < 50 % Xi; R36: 5 % ≤ C < 8 % O; R8: C ≥ 50 % R5: C ≥ 70 %	Ox. Liq. 1 – H271 Acute Tox. 4* – H332 Acute Tox. 4* – H302 Skin Corr. 1A – H314 with specific concentration limits: Ox. Liq. 1; H271: C ≥ 70 %**** Ox. Liq. 2; H272: 50 % ≤ C < 70 %**** Skin Corr. 1A; H314: C ≥ 70 % Skin Corr. 1B; H314: 50 % ≤ C < 70 % Skin Irrit. 2; H315: 35 % ≤ C < 50 % Eye Dam. 1; H318: 8 % ≤ C < 50 % Eye Irrit. 2; H319: 5 % ≤ C < 8 % STOT SE 3; H335; C ≥ 35 %

Considering that H_2O_2 is hypothetically present in THF in concentration lower to 0.5% (based on THF minimal purity), no

additional classification applies for THF due to this impurity.

Chemical Name:	Butyl Hydroxy Toluene
EC Number:	204-881-4
CAS Number:	128-37-0
IUPAC Name:	2,6-di-tert-butyl-p-cresol
Molecular Formula:	$C_{15}H_{24}O$
Structural Formula:	
Molecular Weight:	220.34 g/mol
Typical concentration (% w/w):	-
Concentration range (% w/w):	<1%
Classification:	No harmonised classification

1.3 Physico-chemical properties

REACH ref Annex, §	Property	IUCLID section	Value
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Tetrahydrofuran is a colorless, mobile volatile liquid with a faintly fruity, ether-like odor (Odour threshold: 20-50 ppm [Hara, 1987]) and a pungent taste **(**Sax's Dangerous Properties of Industrial Materials, 2004)
VII, 7.2	Melting/freezing point	3.2	-108°C (Merck Index, 1996)
VII, 7.3	Boiling point	3.3	66°C (760 mm Hg) (Merck Index, 1996)
VII, 7.4	Relative density	3.4 density	0.89 (at 20°C) (IUCLID dataset, 2000)
VII, 7.5	Vapour pressure	3.6	17300 Pa (at 20°C) (IUCLID dataset, 2000)
VII, 7.6	Surface tension	3.10	No data
VII, 7.7	Water solubility	3.8	Miscible **(**Sax's Dangerous Properties of Industrial Materials, 2004**)**
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	Calculated and measured: 0.46 (IUCLID dataset, 2000)
VII, 7.9	Flash point	3.11	Open cup: -20°C Closed cup: -14.5°C (BASF AG, 1993)
VII, 7.10	Flammability	3.13	THF is highly flammable Hazardous decomposition products: Toxic gases and vapors may be released in a fire involving THF.
VII, 7.11	Explosive properties	3.14	Lower limit: 2% Upper limit: 11.8% (IUCLID dataset, 2000) THF is thermally explosive when peroxides are formed (concentrations exceeding 1%)
VII, 7.13	Oxidising properties	3.15	No data
VII, 7.14	Granulometry	3.5	No data
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	No data
XI, 7.16	Dissociation constant	3.21	No data
	Auto flammability	3.12	321°C (IUCLID dataset, 2000)
	Reactivity towards container material	3.18	THF attacks some forms of plastics, rubber and coatings (ICSC, 1998)
	Thermal stability	3.19	No data
	Conversion factor		1 ppm = 0.00299 mg/L (1 ppm = 2.99 mg/m3) 1 mg/L = 334 ppm (1 mg/m3 = 0.334 ppm)

Table 1: Summary of physico- chemical properties

2 MANUFACTURE AND USES

2.1 Identified uses

INDUSTRIAL:

THF is used as a solvent for a variety of plastics, dyes, elastomers, etc., as a glue in joining plastics components (e.g. plumbing fittings), and for synthesis of motor fuels, pharmaceuticals, synthetic perfumes, organometallic compounds, and insecticides …

GENERAL PUBLIC:

THF is used as aerosol paint concentrates, furniture polish and cleaners, laundry starch preparations, lubricating oils, paint and varnish removers, synthetic resin and rubber adhesives …

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

Index n° 603-025-00-0 (19° ATP):

F; R11-19
Xi; R36/37

3.2 Self classification(s)

Not relevant

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Little information is available concerning the toxicokinetics of THF.

Absorption

Absorption is rapid and important by all routes (Bismuth, 2000), particularly through the lungs (alveolar membrane), the gastro-intestinal tract and the skin (Widstrom and Friis, 1989; Droz *et al.*, 1999; Cartigny *et al.*, 2001). THF can also readily penetrate the skin of rats and rabbits and can be lethal via this route (IUCLID dataset, 2000).

Distribution

THF is widely distributed throughout the body of rats (IUCLID dataset, 2000). An administration of THF by gavage (200 mg/kg) in rats produced a peak in levels of THF in blood approximately 1 hour after exposure and a plateau during 1.5 to 2 hours after administration. The levels then gradually declined to negligible concentrations within 24 hours (Hara *et al.*, 1987; Nagata *et al.*, 1983). THF concentrations in adipose tissue and kidneys were ca. 1.3-3 fold higher than in blood and other tissues (Hara *et al.*, 1987; IUCLID dataset, 2000). Exposure of 3000 ppm THF by inhalation conducted to higher concentrations in the thymus glands of rats immediately after exposure and remaining higher than in other tissues during elimination (Kawata and Ito, 1984). In humans exposed to 100 ppm for 20-minute periods, 60% of inhaled THF vapour is retained by the body (Wagner, 1972; Wagner, 1974).

Biotransformation

The biotransformation of THF is not well known. It was hypothesized that THF undergoes an alpha-hydroxylation carried out by an inducible enzyme system (ACGIH, 1991; IUCLID dataset, 2000), followed by a subsequent ring opening similarly to dioxane (Droz *et al.*, 1999), which could give rise to a hepatotoxic aldehyde (butanal). A second pathway could be an oxidation of the hydroxyl group before the ring opening occurs, leading to the formation of a gamma-butyrolactone, a potential neurotoxic (convulsive action), and a gamma-hydroxibutyric acid (Bismuth, 2000).

Incubated in presence of rat S9 mix, THF is capable of inhibiting mixed function oxidases, such as cytochromes P450 which enhance toxicity of a number of compounds (in particular the 2E1 isoform catalysing the alcohol dehydrogenase in the metabolism of ethanol, so that an alcohol-conditioned increase of toxicity can result) and forming peroxides and formaldehyde (formaldehyde dehydrogenase) (IUCLID dataset, 2000). Repeated exposure of rats to THF could also increase specifically the activity of 7-ethoxycoumarin-O-deethylase in liver and kidneys, and lead to a decline of the concentration in tissues after 2 weeks (IUCLID dataset, 2000), by which means animals adapted by either improving the rate of metabolism or elimination of THF, which may also form possible toxic metabolites (BGIA Gestis).

Biochemical effects in the cerebellum were not detected, while gluteal muscle specimens showed increased succinate dehydrogenase activity in a dose-related manner. This points to effects on the energy metabolism. Muscle acetylcholine esterase activity was also increased showing possible effects on the myoneural junctions (IUCLID dataset, 2000).

Elimination

A fraction of the absorbed THF is relatively rapidly eliminated in unchanged form via the kidneys or is exhaled (Bismuth, 2000; BGIA Gestis). In exposed rats to 15000 ppm of THF for 30 minutes, a rapid elimination from brain, thymus, lungs, heart, liver, kidneys, spleen and blood occurs during the first hour after the exposure and concentrations were ranged as following: blood > brain > kidneys > heart > liver > spleen > thymus > lung (200 mg/kg for the lung, 480-600 for the other organs, after 1 h when the concentrations fell 70-80%) (Kawata and Ito, 1984). Lower tissue concentrations were detected immediately after the last inhalation in rats exposed for seven days than rats given a single exposure. During the following 12-13 hours THF was almost completely eliminated. However, repeatedly exposed rats had higher concentrations 1 and 3 hours after the last exposure. The authors suggested that repeated exposure by inhalation causes a decline in the rate of excretion through the lungs.

After an oral administration of 300 mg/kg body weight to rats, the biological half-life of THF in blood was 5 -7.5 hours (Nagata *et al.*, 1983; Hara *et al.*, 1987). A peak was detected 1.5-2 h after administration, then the levels declined gradually to negligible concentrations within 24 h.

In human, the highest excretion is by expiration. The same pattern than in rats was found in healthy volunteers exposed for three hours at 50 ppm. THF exposure resulted in 40% expiration of THF in males with normal breathing and 27% in males with deep breathing. The elimination half-life of THF was 30 minutes. In subjects exposed at 50 ppm THF in air for 6 hours, traces of THF were present at 3 hours after the end of exposure. In individuals exposed at 200 ppm THF for 3 hours, THF blood concentration were higher at 1 hour after the end of exposure than immediately after cessation of exposure (ACGIH, 1991; Droz *et al.*, 1999).

Moreover a milk excretion of THF can occur since it was detected in mother's milk reported in 1 of 12 samples collected in four urban areas in New Jersey, Pennsylvania, and Louisiana (Pellizzari *et al.*, 1982). The actual levels of these contaminants in the breast milk were not determined.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Human data

In a case of fatal poisoning after the ingestion of an unknown quantity of THF, the patient presented initial symptoms of gastric pain, nausea and vomiting followed by coma. The patient died six days after ingestion, having developed jaundice, oliguria and high fever before death. The jaundice was considered to be caused by liver damage. Redness and swelling of the digestive tract mucosa were observed at autopsy (Nagata *et al.*, 1983).

Animal data

Species	LD50 (mg/kg)	Observations and Remarks	Method guideline	Ref.
Rat	1650	No other details	No information	Sax's Dangerous Properties of Industrial Materials, 2004
Rat	3300 (Male)	No details	No information	IUCLID dataset, 2000

(Wistar)	3400 (Female)			
Rat	_	Clinical symptoms (somnolence, bradypnea, cyanosis) appeared 3-5 min after application of the substance. Histological results were necrosis of gastric mucosa, enteritis, cerebral oedema, hyperaemia, haemorrhagia and necrotic foci in liver, kidneys and spleen. LDLo = 3000 mg/kg LD100 = 5000 mg/kg	No	Stasenkova and Kochetkova, 1963
Mouse	2000-2500	Effect: general anaesthetic	No	Stasenkova and Kochetkova, 1968
Guinea pig	2300-2600	No details	No	IUCLID dataset, 2000

5.2.2 Inhalation

Not evaluated for this dossier

5.2.3 Summary and discussion of acute toxicity

The lowest oral DL50 was observed in rats (i.e. 1650 mg/kg bw). This value is cited in BASF MSDS, in the Sax's Dangerous Properties of Industrial Materials, 2004 and in the RTECS. However, based on the lack of information on this study and on the results of the other acute toxicity studies, no classification is proposed.

5.3 Irritation

5.3.1 Skin

Human data

THF produced irritating effect to human skin even after a short exposure (Engel *et al*., 1938; Hofmann and Oettel, 1954; IUCLID Dataset, 2000).

Number of persons	Exposure time (h/day)	conc. (wt/wt)	Dressing: Occlusive semi-occlusive open	Observations and remarks (specify the experimental conditions, score and evaluation method)	Method guideline	Ref.

6	24 h	20% aqueous solution of THF	Occlusive, soaked cotton swab, upper arm	5 persons displayed no symptoms 1 out of 6 persons displayed a very slight reddening. and itching, which was normal after 3 days. THF was not considered as irritating	No	Engel *et al*., 1938 (BASF in IUCLID)
6	_	Different concentrations of technical THF	Occlusive and non occlusive	Varied irritating effects depending on the concentrations of technical THF Irritation more severe when THF was allowed to evaporate. The authors concluded that THF itself was non-irritating and they assumed that the irritation was caused by impurities that remained after THF had evaporated away (i.e. peroxides). No additional information was provided to evaluate the adequacy of this study.	No	Lehmann and Flury, 1943 Hofmann and Oettel, 1954
196	Guidelines from the "Office of dermatoses" U.S. Public Health Service	No data	No details	Not irritating	No	BASF AG, 1953

Animal data

Species	N° of animals	Exposure time (h/day)	conc. (wt/wt)	Dressing: Occlusive semi-occlusive open	Observations and remarks (specify the experimental conditions, score and evaluation method)	Method guideline	Ref.
Guinea pig	10	_	50% 100%	_	50% THF: strong irritation on intact and scratched skin 100%: mild (on scratched skin) to moderate (scratched and intact skin) irritation when tested on the intact skin.	No	IUCLID dataset, 2000
Rabbit	6	24 h	0.5 mL	Occlusive wrapping to the abraded and intact skin	Based on reactions noted at 24 and 72 hours, a Primary Irritation Index of 1.93 was calculated. THF was judged mildly irritating to rabbit skin.	No	IUCLID dataset, 2000

Rabbit			1 mL		Considerable redness of the skin with subsequent thickening and scaling. Complete recovery in 7-8 days.	No	Stasenkova and Kochetkova, 1963
Rabbit			20% solution of THF		Irritation of the skin	No	Lehmann and Flury, 1943

5.3.2 Summary and discussion of irritation

THF is found irritating (moderately to strongly) in skin irritation studies using mice, Guinea pigs and rabbits. However, these studies are old and poorly reported, making them difficult to evaluate. Human data show some cases of skin irritation. But this could be attributed to the formation of peroxides when THF exposed to air. Therefore, a classification for skin irritation is no longer supported. In the light of the contradictory and limited data available here, we recommend that skin irritation is not harmonised and producers need to evaluate relevance of skin irritation classification with regards to their substance impurity profile and other relevant information that may be available to them. Therefore, we propose a note H, which is used to indicate that it may be necessary to complement the harmonised classification for some endpoints.

5.4 Sensitisation

Not evaluated for this dossier

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Species	Dose mg/kg/body weight	Duration of treatment	Observations and Remarks	Method guideline	Ref.
Rat (Fischer 344)	0, 125 or 2 000 (gavage)	> 14 days	Male and female F344 rats were exposed to THF by gavage. Results: - body weight loss (20% in high-dose males and 13% in females), mortality in high dose males (90% in females). - Histopathology: acute inflammation of the trachea and serofibrious exudates in the tracheal lumen (result of THF aspiration), increased lung weights (result of repeated THF aspiration or viral infection), and hyperplasia, hyperkeratosis and inflammation of the epithelium and mucosa of the forestomach, in all	No (Study considered as inadequate by the NTP, terminated without complete processing or reporting)	IUCLID dataset, 2000)

			treated groups.		
Rat	1 780, 2 225, 2 670 (2.0, 2.5, 3.0 mL/kg) (gavage)	2-4 weeks	5 animals per group received a 20% aqueous solution. Results: at 1 780 mg/kg and above, there were no special macroscopic pathological changes, but frequent and significant dilated stomach, often containing THF. Six animals from the 3 groups examined histopathologically showed liver lesions (vacuole-like changes of the liver cells, diffuse single or focal hepatic cells necrosis, proliferation of the Kupffer cells) and nephrosis.	No information	IUCLID dataset, 2000
Mouse (B6C3F1)	63, 125, 250, 500, or 1 000 (gavage)	> 49 days	One high-dose female died on day 49. No observable compound-related changes. The only effect was a decreased liver weight in all treatment groups, which was not dose-related but significant at 200 and 500 mg/kg.	No information	IUCLID dataset, 2000

5.5.2 Repeated dose toxicity: inhalation

Species	Conc. mg/L	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Method guideline	Ref.
Rat (Male Wistar)	45	0.5 h/day 7 days/week	7 days	29 animals per group (control: 5 animals) Results: irritation symptoms of the skin and the mucosa (tears, mucus, bloody nasal secretions), no histopathological effect (brain, thymus, lung, heart, liver, kidneys, spleen). The dopamine content of the cerebrum was reduced 48 h after the last inhalation.	No information	IUCLID dataset, 2000
Rat	10 - 193	2-6 h/day	1-30 days	Narcosis and irritation of the mucosa (severity of the symptoms concentration- and exposure time-dependant). No macro- or microscopic liver lesions; no clinical or histopathological indication of renal lesions.	No information	Hofmann and Oettel, 1954

Rat (Male Wistar)	9	1 h/day 5 days/week	12 weeks	29 male rats per group (5 animals in the control group) were studied. They showed irritation symptoms of the skin and the mucous membrane (tears, mucus, bloody nasal secretions). From the 4th week, a more significant decreased body weight was noted. Histopathology revealed lung bronchial epithelium showing papillar hyperplasia and partial catarrhal changes, renal lesions (albumin cylindrical structures in the renal tubules; hyaline-droplets degeneration); changes of the content noradrenalin and dopamine in the cerebrum. No changes in serum GOT, GPT, and AP were detected.	No information	(IUCLID dataset, 2000)
Rat (Sprague-Dawley)	0, 0.3, 0.6, 3, or 15	4 h/day 5 days/week	12 weeks	10 male rats per group were studied. - 0.3 mg/L: no significant effects compared to control, except for slight local irritation of the mucosa. - 0.6 mg/L: nasal mucus: lesions of goblet and ciliar cells; vacuoles between the epithelial cells; reduced number of cilia tracheal mucosa: increased volume of mucus in the cilia; tumefaction of the cilia membrane, disorder of the ciliary movements - 3 and 15 mg/L: affected liver function as indicated by serum chemistry tests (GOT, cholinesterase, and blood sugar values increased); effects on central nervous system. - 15 mg/L: decreased body weight gain and significant changes of the relative organ weights; marked local irritation symptoms and morphological damage of the mucous membrane in the respiratory tract (nasal mucosa: partial destruction and pyknosis of the epithelial cells, damage of the goblet and ciliar cells; tracheal mucosa: disorder of the ciliary erection, occurrence of compound cells with tumefaction of the cellular walls), significant differences compared to control for the number of leukocyte, the glycaemia, and the liver values in haematological and clinical, chemical tests. NOAEL = 0.3 mg/L (100 ppm)	≈ OECD 413 Deficiencies: Only males studied Weight measurements for: brain, lung, heart, liver, spleen, and kidney Histological observation of lung tissues only, apparently	Katahira *et al*., 1982a

Rat	0.0002, 0.002, or 0.02	24 h/day 7 days/week	3 months	15 animals per group were exposed. Results: - 0.0002 mg/L: no effect. - 0.002 mg/L: muscular chronaxy reduced; liver damage detected by the sulfobromein test. Histopathology: reversible, morphological changes in different organs. - 0.02 mg/L: muscular chronaxy significantly reduced after a 6-week exposure; coproporphyrin content in urine increased from the 7th week of exposure (indication on the state of CNS); reduced cholinesterase activity in blood, liver lesions by bromosulfur test. Histopathology revealed dystrophic changes in different tissues. NOAEL = 0.0002 mg/L (0.07 ppm)	No information	IUCLID dataset, 2000
Rat (Fischer 344 / N)	0, 0.2, 0.6, 1.8, 5.4, or 15	6 h/day 5 days/week	13 weeks	Groups of 10 male and female rats were exposed to THF with 99% purity. Results: - ≤ 5.4 mg/L: 1 animal with nasal and ocular secretions, without special results. - 15 mg/L: symptoms of toxic effect on the CNS: ataxis (male and female), reduction with persistence of the period exposure (acclimatisation effect); significant reduced thymus and spleen weight (male and female), significant increased liver weight (female); increased number of erythrocytes and larger haematological changes; 5/20 males and 8/10 females showed acanthosis in (very) slight grades characterised by (multi)focal increase of the no-keratinised layer of the Schuppel epithelium; 2/10 males and 4/10 females had purulent inflammation of the forestomach. NOAEL = 5.4 mg/L (1800 ppm)	≈ OECD 413	Chhabra *et al.*, 1990
Rat (Sprague-Dawley)	0, 1.5, 4.5, or 9	6 h/day 5 days/week	14 weeks	At 4.5 or 9 mg/L, they showed diminished startle responses to an auditory alerting stimulus, transient and rapidly reversible supported by the lack of neurological effects, but no additional neurobehavioral or pathological effects. The demonstrated NOEL level of THF was 1.5 mg/L (500 ppm).	≈ OECD 413 Only clinical and neurotoxicological findings were reported.	Malley *et al.*, 2001

Rat (Wistar)	0.6, 3, or 6	6 h/day 5 days/week	2-18 weeks	20 males per group were treated. Sections were carried out at 2, 5, 13, and 18 weeks showed an increase in different enzymatic systems (oxidative) in the liver and the kidneys without induction of cytochrome P450, but no effect on the brain.	No information	IUCLID dataset, 2000
Rat	9	8 h/day 5 days/week	20 months	50 animals per sex and per group showed a significant increase of the relative liver weight in females compared to control (also found with the satellite group receiving 3000 ppm acetone). There were no toxicological symptoms, no macroscopic and histopathologic changes in the liver and the kidneys compared to controls.	No information	IUCLID dataset, 2000
Mouse (B6C3F1)	0, 0.2, 0.6, 1.8, 5.4, or 15	6 h/day 5 days/week	13 weeks	10 animals per sex and per group were exposed to THF with 99% purity. Results: ≤ 0.6 mg/L: one animal with nasal and ocular secretions, no other findings. 1.8 mg/L: significantly reduced thymus weight and significantly enhanced liver weight (male). 5.4 mg/L: toxic effect in the CNS (male/female), significantly reduced thymus weight (male) and significantly enhanced liver weight (male/ and female); minimal to mild centrilobular hepatocytomegaly (1 of 10 males). 15 mg/L: 3 of 10 male mice found dead within the exposure, thereof 2 with inflammation of the urinary tract; toxic effect on the CNS (male/female); torpidity stopped up to 2 h after the end of exposure with an adaptation effect; significantly reduced weight gain and reduced thymus weight (male),reduced spleen weight (male and female) and enhanced liver weight (male and female); minimal to mild centrilobular hepatocytomegaly (7 of 10 males and 10 of 10 females); atrophy of the uterus and degeneration of the X-zone (inner cortex of the adrenal cortex): absence of fatty vacuolar change normally present in young female mice, X-zone markedly thinner and erythrocyte congestion in the capillaries. NOAEL = 0.2 mg/L	≈ OECD 413	Chhabra *et al*., 1990

5.5.3 Repeated dose toxicity: dermal

Not evaluated for this dossier

5.5.4 Other relevant information

Human data

A distal sensitivo-motor peripheral neuropathy occurred in a 55-year man exposed for 2 years at THF and at 2-butanone, with insufficient protections. He presented neither alcoholism nor drugs consumption. Neuropathy recovered in 3 months after cessation of exposure. THF is likely involved (Viader *et al.*, 1975).

THF is a central nervous system depressant in humans; based on effects seen in animals, it may also cause irritation of the mucous membranes and upper respiratory tract, and liver and kidney damage. There are no reports of chronic effects in humans (Hathaway *et al.*, 1991).

Investigators exposed to unknown concentrations while testing THF's pharmacological properties developed severe occipital headaches. Researchers engaged in the experimental spinning of synthetic fibers showed a marked decrease in white blood cell count that is believed to have been caused by exposure to THF, which was used as a solvent; these individuals recovered after 2 years of treatment (Gosselin *et al.*, 1984).

Animal data via other routes

Species	Dose mg/kg/day	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Method guideline	Ref.
Rat	220, 1110 (0.25, 1.25 mL/kg)	Daily	4 months	11-15 animals per group were exposed to 20% THF in soya bean oil by i.p. Results: 220 mg/kg: narcotic symptoms, which were persistent when repeated application; death after 2-4 months; in 5 of 6 animals examined: liver damage (vacuole-like transformation of the liver cells, diffuse necrosis of single and focal cells, proliferation of the Kupffer cells), nephrosis; all animals found dead during the study. 1110 mg/kg: narcotic symptoms, which were slightest when repeated application; death after 1-2 months, all animals found dead during the study; similar but more severe effects than at 220 mg/kg. In the two dosed groups, 1-2 weeks before death, the authors observed marked weight loss, cachectic aspect, and in macroscopy: diffuse peritonitis, severe fibrinous	No information	Jochman, 1961

				purulent fusion of the loop of small intestine, compared to liver, spleen and kidneys; liver sometimes enlarged; haemorrhagia intestinal tissue.		

5.5.5 Summary and discussion of repeated dose toxicity:

Mortality and body weight loss at high dose, lesions of stomach and liver, and nephrosis are observed in rats exposed orally to THF (125 to 2670 mg/kg bw/d) for 2-4 weeks. Mice appear less sensitive since only liver weight is decreased.

By inhalation, only signs of narcosis and irritation of skin and mucosa are observed in rats when exposed up to 30 days. When exposed to 12-13 weeks, decreased body weight and body weight gain, marked local irritation symptoms and morphological damage of the mucous membrane in the nasal and tracheal mucosa, histopathologic lesions in lung (papillar hyperplasia), liver and respiratory tract, renal lesions, significant changes of the relative organ weights, muscular chronaxy, symptoms of toxic effect on the CNS: ataxis (male and female). The NOAEL for repeated dose toxicity is 5.4 mg/L (1800 ppm).

In a neurotoxicity study, rats exposed for 14 weeks to 4.5 or 9 mg/L showed decreased startle responses to an auditory alerting stimulus, transient and rapidly reversible supported by the lack of neurological effects, but no additional neurobehavioral or pathological effects.

When mice are exposed by inhalation to THF for 13 weeks up to 15 mg/L. At the highest dose, death, inflammation of the urinary tract, toxic effect on the CNS (male/female); significantly reduced weight gain and reduced thymus weight (male), reduced spleen weight (male and female) and enhanced liver weight (male and female); minimal to mild centrilobular hepatocytomegaly (7 of 10 males and 10 of 10 females); atrophy of the uterus and degeneration of the X-zone (inner cortex of the adrenal cortex): absence of fatty vacuolar change normally present in young female mice, X-zone markedly thinner and erythrocyte congestion in the capillaries. Toxic effect in the CNS (male/female) are also observed at 5.4 mg/L. Significantly reduced thymus weight and significantly enhanced liver weight are observed from 1.8 mg/L. The NOAEL is set at 0.6 mg/L.

Overall, according to the available repeated dose toxicity studies in rats and mice, target organs for THF appear to be the upper respiratory tract, the kidneys, the liver, and the central nervous system. According to Annex VI to directive 648/67/EC, THF should not be classified for repeated dose toxicity.

5.6 Mutagenicity

5.6.1 In vitro data

Test	Cell type	Conc.	Metabolic Activity	Observations and Remarks	Method guideline	Ref.
	BACTERIAL TESTS					
Ames test	S. *typhimurium* D 3052 TA 1538 TA 98 C 3076 TA 1537 G 46 TA 1535 TA 100	2.5, 5, 10, 20 mg/L	With (S9 from Rat or Hamster) / Without	Negative	No	IUCLID Dataset, 2000
Ames test	TA 98 TA 100 TA 1535 TA 1537	Up to 10 000 µg/plate	With (Rat Liver S9) / Without	Negative	OECD 471	Mortelmans *et al*., 1986
E. *coli* reverse mutation assay	WP 2 uvr A	100-10000 µg/plate (Solvent: Water)	With (Rat Liver S9) / Without	Negative (Preincubation method)	≈ OECD 471	IUCLID dataset, 2000
E. *coli* reverse mutation assay	WP 2 uvr A	1 µmol / L	With (S9) / Without	Positive (without S9) 10% mutagenicity compared to epibromohydrin (positive control)	No information	Chemminke *et al*., 1982 (Russian article)
	IN VITRO MAMMALIAN CELL TESTS					
Transformation Assay	A-31-1- 13 Balb/c-3T3	13.9 - 351 mM	Without	Negative Non-cytotoxic to the BALB/c-3T3 cells (LD50 = 90.3 mM) Tetrahydrofuran was evaluated as inactive in the transformation assay.	No current guideline	Matthews *et al*., 1993
Cytogenetic assay Sister Chromatide Exchange assay	CHO-W-B1 cells	500 to 5000 mg/L	With (Aroclor-induced rat or hamster liver S9) / Without	Negative Incubation times: 26 h (without S9) and 2 h (with S9)	OECD 479	NTP, 1998

<table>
<tr><td>Unscheduled DNA synthesis</td><td>Rat hepatocytes</td><td>–</td><td>–</td><td>Negative</td><td>No information</td><td>Mirsalis et al., 1983

(abstract)</td></tr>
<tr><td>Enhancement of viral DNA transformation</td><td>Syrian hamsters embryo cells</td><td>–</td><td>–</td><td>Positive

Cultivated cells were exposed to THF in sealed chambers (2 or 20 hours); then determination of the survival rate and analysis for elevated sensitivity to SA 7-virus transformation</td><td>No current guideline</td><td>Hatch et al., 1983

(abstract)</td></tr>
<tr><td>Cytogenetic assay

Chromosomal aberration</td><td>CHO-W-B1 cells</td><td>500 to 5000 mg/L</td><td>With (Aroclor-induced rat or hamster liver S9) / Without</td><td>Equivocal

Incubation time: 14 h (without S9) and 2 h + 12 h (with S9)

In the second trial conducted with S9, the middle-level dose of 3000 mg/L produced a positive response.

Trial 1: without S9
<table>
<tr><th>Dose (µg/mL)</th><th>Total cells scored</th><th>N) of Abs</th><th>Abs/cell</th><th>Cells with Abs (%)</th></tr>
<tr><td>Distilled water</td><td>100</td><td>7</td><td>0.07</td><td>7.0</td></tr>
<tr><td>Mytomycin-C 0.15</td><td>50</td><td>23</td><td>0.46</td><td>30.0</td></tr>
<tr><td>THF 500</td><td>100</td><td>8</td><td>0.08</td><td>8.0</td></tr>
<tr><td>1600</td><td>100</td><td>17</td><td>0.17</td><td>16.0</td></tr>
<tr><td>5000</td><td>100</td><td>8</td><td>0.08</td><td>8.0</td></tr>
</table>
Trial 1: with S9
<table>
<tr><th>Dose (µg/mL)</th><th>Total cells scored</th><th>N) of Abs</th><th>Abs/cell</th><th>Cells with Abs (%)</th></tr>
<tr><td>Distilled water</td><td>100</td><td>8</td><td>0.08</td><td>8.0</td></tr>
<tr><td>Cyclophosphamide 15</td><td>100</td><td>28</td><td>0.28</td><td>23.0</td></tr>
</table></td><td>OECD 473</td><td>NTP, 1998</td></tr>
</table>

				THF 500	100	11	0.11	7.0
				1600	100	11	0.11	10.0
				5000	100	13	0.13	13.0

Trial 2: without S9

Dose (µg/mL)	Total cells scored	N) of Abs	Abs/cell	Cells with Abs (%)
Distilled water	100	4	0.04	4.0
Mytomycin-C 0.15	50	26	0.52	40.0
THF 3000	100	7	0.07	7.0
4000	100	9	0.09	7.0
5000	100	9	0.09	6.0

Trial 2: with S9

Dose (µg/mL)	Total cells scored	N) of Abs	Abs/cell	Cells with Abs (%)
Distilled water	100	3	0.03	3.0
Cyclophosphamide 15	50	21		18.0
THF 1000	100	4	0.04	4.0
2000	100	6	0.06	6.0
3000	100	12	0.12	12.0*
4000	100	8	0.08	7.0
5000	100	12	0.12	12.0

5.6.2 In vivo data

Somatic cells

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Method guideline	Ref
Cytogenetic assay In vivo mammalian bone marrow chromosome aberration test	Male Mouse B6C3F1 (10/group)	Bone marrow cells	i.p. Single injection Harvest time: 17 h and 36 h post-exposure	Negative 50 first division metaphase cells scored from each of 8 animals / dose Concentrations: 500, 1000, and 2000 mg/kg bw/d Signs of toxicity observed at the highest dose	OECD 475	NTP, 1998
Cytogenetic assay SCE assay	Male Mouse B6C3F1 (5/group)	Bone marrow cells	1/4, 1/2, 1/1 MTD (0, 500, 1 000, 2 000 mg/kg) killed 23 to 42 h after application research of SCE, 25 cells from each of 4 animals	Equivocal The initial test at 23 h was positive. A repeated test was negative and the results of the single trial performed with a 42-hour sample time were also negative. Doses (mg/kg) Mean SCEs/cell I 23 h: mitomycin: 0.5 7.04 THF 0 3.79 500 3.91 2000 6.27* II 23 h: mitomycin: 0.5 10.48 THF 0 5.70 500 6.02 2000 5.62 2500 - (lethal) I 42 h: acrylamide: 160 9.37 THF 0 5.05 500 5.86 2000 4.05 2500 4.29	No current guideline	NTP, 1998
Micronucleus assay	Male Mouse B6C3F1	Total bone marrow erythrocytes	i.p., 3 injections at 24 h intervals	Negative 24h after the final injection, femur bone marrow smears were prepared from 5 or more animals; 2000 PCE per animal scored . percentage of PCEs among the total bone marrow erythrocytes scored as a measure of toxicity	OECD 474	Shelby and Witt, 1995

Micronucleus assay	Mouse B6C3F1 (10 male and 10 female /group)	Peripheral blood	Inhalation 6 h/day 4 days/week 14 weeks 0.2, 0.6, 1.8, 5.4, or 15 mg/L = 600, 1800, 5000 ppm	Equivocal Females were negative and males displayed a marginal response in a trend test, but the highest effect observed was within historical control levels. Micronucleated cells/1000 cells PCEs NCEs Male Chamber control 1.50 1.18 THF 600 1.69 1.27 THF 1800 1.79 1.58* THF 5000 1.47 1.41 Female Chamber control 1.85 1.43 THF 600 1.01 1.16 THF 1800 1.34 1.15 THF 5000 1.29 1.18 (10 mice for erythrocyte scoring per group, except 7 mice in the 5000 ppm male mice group)	OECD 474	NTP, 1998
Unscheduled DNA synthesis in rat hepatocytes	Male Rat Fischer 344	Hepatocytes	*In vivo* treatment gavage	Negative No other details (poster abstract)	No information	Mirsalis *et al.*, 1983 (abstract)

Germ cells

Test	Species	Tissue	Exposure route & Harvest time	Observations and remarks	Method guideline	Ref
Drosophila SLRL test (sex-linked recessive lethal assay	Male D. *melanogaster* Wildtype Canton S	10 000, 40 000, and 125 000 ppm	Oral feed 72 h exposure (with regeneration food after 24 and 48 h)	Negative	OECD 477	NTP, 1998

5.6.3 Human data

No data

5.6.4 Summary and discussion of mutagenicity

Bacterial tests were all negative except a E. *coli* reverse mutation assay. In addition, results from *in vitro* genotoxicity tests in mammalian cells were overall negative, but structural changes in calf thymus DNA and viral DNA transformation in Syrian hamsters embryonic cells were observed. However, *in vivo* mammalian assays do not allow to conclude about the genotoxic potential of THF since negative and equivocal responses occurred. Therefore, classification for mutagenic effects is not warranted.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

No data

5.7.2 Carcinogenicity: inhalation

Species	Conc. mg/L	Exposure time (h/day)	Duration of treatment	Observations and Remarks	Method guideline	Ref.
Rat	9 mg/L	8 h/day 5 days/week	20 months	50 animals per sex and per group were exposed to THF. No differences were observed compared to controls (liver function test, haematological test, clinical test, chemical test, relative liver and kidneys weight after a 12- and a 20-month exposure, histopathological analysis). THF was found not carcinogenic.	No informati on	IUCLID dataset, 2000

Rat (Fischer 344)	0, 0.6, 1.8, or 5.4 mg/L (0, 200, 600, or 1800 ppm)	6 h/day 5 days/week	105 weeks	Fifty male and 50 female rats were exposed to THF for 105 weeks. Survival, body weight, and clinical findings were similar to those of chamber controls (number of survivors in the chamber control: 12/50, and 1 800 ppm group: 6/50). Results for male rats; Positive trend (P=0.037) for combined occurrence of renal tubule epithelial adenoma and carcinoma (although pairwise comparisons between control and experimental groups were not significant). The incidence was as follows: historical control range: 0-4%, current control: 1/50 (2%), 200 ppm: 1/50 (2%), 600 ppm: 4/50 (8%), and 1 800 ppm: 5/50 (10%). Slightly higher incidence of mammary gland fibroadenoma in high-dose male rats, but not significant. The incidence was as follows: historical incidence: 4.2 ± 3.5%, current controls: 0/50 (0%), 200 ppm: 2/50 (4%), 600 ppm: 3/50 (6%), and 1800 ppm: 4/50 (8%). Higher incidence of testes adenoma in treated rats (but within the historical control range). The incidence was as follows: historical control: 46-83%, current controls: 23/50 (46%), 200 ppm: 31/50 (62%), 600 ppm: 31/50 (62%) and 1800 ppm: 31/50 (68%) Increased incidence of epithelium hyperplasia in the prostate. The incidence was as follows: current controls: 2/50 (4%), 200 ppm: 1/50 (2%), 600 ppm: 0/50 (0%) and 1800 ppm:	OECD 451	NTP, 1998

				5/50 (10%) Results for female rats: Slightly greater incidence of mammary gland fibroadenoma in the high-dose group with a trend marginally significant (P=0.031) (but the pairwise comparisons were not). The incidence was as follows: historical control: 16-42%, controls: 23/50 (46%), 200 ppm: 22/50 (44%), 600 ppm: 29/50 (58%), and 1800 ppm: 31/50 (62%). The NTP concluded that THF exhibited some evidence of carcinogenic activity in male rats for renal tubule epithelial adenoma and carcinoma but no evidence of carcinogenic activity in female. Overall, increased incidences of tumours are seen in several tissues: renal tubule epithelial adenoma and carcinoma (males, significant), testes adenoma (males), and mammary gland fibroadenoma (males and females, significant in females).		
Mouse (B6C3F1)	0, 0.6, 1.8, or 5.4 mg/L (0, 200, 600, or 1800 ppm)	6 h/day 5 days/week	105 weeks	50 animals per sex and per group were used. Survival and lifespan (of high-dose males were significantly lower than the survival and lifespan (456 days versus 689 days for controls). Mean body weight of exposed male and female mice were not affected. The highest exposure concentration (1800 ppm) selected for male mice in this study exceeded the MTD (state of narcosis during and up to 1 h after the exposure periods). High-dose males had significantly greater incidences of nonneoplastic lesions of the urogenital tract than those in the chamber controls. The	OECD 451	NTP, 1998

				authors explained this by the inflammatory character of these lesions, which occurred primarily among the animal dying the first 52 weeks of the study, suggested an ascending bacterial infection (due likely to prolonged wetting of the preputial fur). In high-dose females, there were an increase of incidence of hepatocellular neoplasms (adenoma and carcinoma) [85% versus 34% in controls (significant)], and of multiple hepatocellular neoplasms and liver necrosis. The increases in the incidences of liver neoplasms in the 200 and 600 ppm exposure groups were not statistically significant, but the trend test was positive. There was no indication of an increase in the incidences of hepatocellular neoplasms in male mice. The incidence of nonneoplasic effects in males was increased: iliac hyperplasia in the lymph node is 75% in low and mid-dose groups and 100 % in high dose group (0% in controls), hematopoietic cell proliferation in the spleen was increased (19% in controls; 27% in 200 ppm group; 30% in 600 ppm group; 37% in 1200 ppm group), and the incidence of thymus atrophy was enhanced (6% in controls; 5% in 200 ppm group; 12% in 600 ppm group; 25% in 1200 ppm group). The NTP concluded that THF exhibited no evidence of carcinogenic activity in male mice but showed clear evidence of carcinogenic activity in female mice.		

5.7.3 Carcinogenicity: dermal

Species	Dose mg/kg/bw	Exposure time	Duration of treatment	Observations and Remarks	GLP	Ref.
Mouse	89 mg/animal	25 weeks Post-observation period: 11.5 months	Twice a week	11 of 25 animals survived after 17.5 months. Mice showed four benign tumours (non specified).	No information	IUCLID dataset, 2000

5.7.4 Carcinogenicity: human data

Neither experiences in humans nor epidemiological studies are available.

5.7.5 Summary and discussion of carcinogenicity

The NTP considers THF as reasonably anticipated to be a carcinogen (NTP, 1998). The ACGIH classified THF as A3 Confirmed Animal Carcinogen with Unknown Relevance to Humans (ACGIH, 2004). In addition, the DFG placed THF in category 4 (i.e. Substances with carcinogenic potential for which genotoxicity plays no, or at most a minor role) (DFG website).

The NTP conducted a carcinogenesis study in rats exposed to THF by inhalation. It concluded that THF exhibited some evidence of carcinogenic activity in male rats for renal tubule epithelial adenoma and carcinoma but no evidence of carcinogenic activity in female.
Therefore, an α 2u-globulin mechanism could be hypothesised. However, according to the IARC Working Group, the production of renal-cell tumours in male rats by agents that fulfil all defined criteria for an α 2u-globulin-associated response is not predictive of carcinogenic hazard to humans (Swenberg and Lehman-McKeeman, 1999). These criteria are discussed with respect to the effects of THF observed in the literature:

1. Lack of genotoxic activity (agent and/or metabolites) based on an overall evaluation of in-vitro and in-vivo data

Overall bacterial tests but one E. *coli* reverse mutation assay were negative. *In vitro* and *in vivo* mammalian cell tests were also negative with the exception of a SCE assay carried out in SHE cells and a chromosome aberration test in CHO cells showing an equivocal result. In addition, some *in vivo* assays were also equivocal: one SCE in bone marrow cells from a male mouse exposed by gavage, which was positive in the initial test, then negative, and a micronucleus assay from peripheral blood from male mice exposed by inhalation.

2. Male rat specificity for nephropathy and renal tumorigenicity

Nephrosis was observed in male rats in a gavage study conducted over 14 days and 4 months (Jochman, 1961) but not in other inhalation repeated studies (Katahira *et al.*, 1982a; Kawata and Ito, 1986; Chhabra *et al.*, 1990; IUCLID dataset, 2000). In addition, the NTP carcinogenesis study did

not demonstrate the presence of additional aspects of the pathological sequence of lesions associated with α 2u globulin nephropathy. Indeed, there is no compound-related increase in the incidence of:

- chronic progressive nephropathy in males (controls: 96% - 200 ppm: 100% - 600 ppm: 100% - 1800 ppm: 100%) and even in female rats (controls: 96% - 200 ppm: 88% - 600 ppm: 86% - 1800 ppm: 84%). These values demonstrate that the incidence of nephropathy is not specific to the male rats.

- linear mineralization of papillary tubules [renal tubule mineralization = controls: 16% - 200 ppm: 14% - 600 ppm: 4% - 1800 ppm: 10% (female rats: controls: 94% - 200 ppm: 92% - 600 ppm: 100% - 1800 ppm: 92%]

- renal tubule hyperplasia (male rats: controls: 14% - 200 ppm: 10% - 600 ppm: 12% - 1800 ppm: 14 %) (Lock and Ward, 2004). Regenerative proliferation of epithelial cells in the P2 segment in response to the cell loss constitutes the tumorigenic response in the male rat kidney regarding to α 2u-globulin mechanism (Melnick *et al.*, 1996). Consequently, the non-increase in the incidence of this effect does not support an α 2u-globulin mechanism for the THF-mediated renal tumor formation in male rats.

In the NTP carcinogenesis study, the evaluation of a single section of each rat's kidney demonstrated an increase in the incidence of renal tubule adenomas or carcinomas only in male rats (controls: 2% - 200 ppm: 2% - 600 ppm: 8% - 1800 ppm: 10%), which exceeds the historical values for inhalation studies (range, 0-4%; rate, 0.9 ± 1.3%).

The authors of the NTP study concluded that there was a lack of a chemical-related increase in the incidence and/or severity of age-related degenerative renal diseases (chronic progressive nephropathy) in exposed male rats (Chhabra *et al*., 1998).

3. Induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory

Gamer *et al.* demonstrated a slightly increased amount of hyaline droplets (but not granular casts) in proximal tubular cells in 5/6 male rats after 20 exposures at 5.4 mg/L (1800 ppm), 6 h per day, for 4 weeks (Gamer *et al.*, 2002) and Kawata and Ito observed hyaline-droplets in male rats exposed to 9 mg/L ethanol, one hour a day, for 12 weeks (Kawata and Ito, 1984). In contrast, Chhabra *et al.* found in a 13-week study [included in the NTP Toxicity and Carcinogenesis study of THF (NTP, 1998)] in rats exposed to THF 6 h per day of THF that protein droplets in control rats were finer and more densely and diffusely distributed in the cytoplasm of tubular epithelial cells in the outer cortex, whereas in 1800 ppm rats the droplets were more coarse and concentrated in scattered foci in the outer cortex. However, the average severity grades (based on the amount of positively staining protein droplet (α 2u-globulin) accumulated in the cytoplasm of renal tubules and the character of the droplet aggregates for droplet accumulation did not differ significantly between the controls (2.6) and 1800 ppm group (2.8) (Chaabra *et al*. 1998).

4. Identification of the protein accumulating in tubule cells as α 2u-globulin

One study demonstrates an accumulation of α 2u-globulin in the renal cortex, as demonstrated by immunohistochemical evidence, after 5 or 20 exposures and a slightly increased amount of hyaline droplets in proximal tubular cells after 20 exposures (Gamer *et al.*, 2004).

5. Reversible binding of the chemical or metabolite to α 2u-globulin

There is no evidence that THF could bind to α 2u-globulin from the available studies. Chemicals known to bind α 2u-globulin and produce both α 2u-globulin nephropathy and renal tubular tumors

in male rats have a poor solubility in water (from non soluble to 80 g/L) and a high log Pow (from 1.67 to 4.2). In contrast, THF shows a high solubility in water (300 g/L) and a low log Pow (0.46).

6. Induction of sustained increased cell proliferation in renal cortex

After 5 or 20 days of exposure, Gamer *et al.* showed a dose-related (but not exposure period-related) α 2u-globulin accumulation in the renal cortex of male rats associated with "hot spots" of increasing cell proliferation and apoptosis. These authors suggested that tumor formation was consequently through induction of cell proliferation. But the absence of any recorded linear mineralization in the papilla in the 2-year study appears to weaken the argument for α 2u-globulin nephropathy being the pathway underlying the renal tubule tumors with this compound (Lock and Hard, 2004). After a 21-day recovery period, the 5-day study produced no recovery for α 2u-globulin-stained cells but for proliferation, but there are no differences between control and dosed rats for the number of cells in hot spots (cortex).

7. Similarities in dose-response relationship of the tumour outcome with the histopathological end-points (protein droplets, α 2u-globulin accumulation, cell proliferation)

The presence of hyaline droplets is not mentioned in the 2-year NTP carcinogenesis study. In the 13-week study, no differences regarding the severity of hyaline droplet grading were observed between controls and 1800 ppm-treated rats. Consequently no dose-response between hyaline droplet severity and renal tumour incidence can be established.

Conclusion:

No epidemiological studies on THF are available. Therefore, the carcinogenic potential of THF is evaluated on the basis of rodent carcinogenicity studies.
Carcinogenicity studies in rats and mice have been performed by NTP. Results of these studies demonstrate that THF has carcinogenic potential in male rats and female mice. Tumor formation in female mouse liver was not considered to be relevant to human since it was demonstrated that THF induced cell proliferation in female mice liver (Gamer *et al*., 2002, Van Ravenzwaay *et al*., 2003). In male rats, the incidence of renal tubule epithelial adenoma and carcinoma was slightly increased (positive trend P=0.037). Since the criteria established by the IARC Working Group are not fully fulfilled, the α 2u-globulin mechanism should not be deemed as an explanation for the renal tumor formation in male rats. In addition, the incidence of benign tumours is increased in different tissues: mammary gland (fibroadenoma in male and female rats) and testes (adenoma in male, but within the historical control range).

Overall, THF is proposed to be classified as **Carc. cat.3 R40.**

5.8 Toxicity for reproduction

Not evaluated for this dossier

5.9 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not evaluated for this dossier

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated for this dossier.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

New data shows that the substance has CMR properties that justify to revise its harmonised classification and labelling for health.

Relevant acute and repeated toxicity, and mutagenicity data were also reported in this dossier to allow a better understanding of the toxicological profile of THF in relationship with the assessment of its CMR properties. When relevant, potential classifications for endpoints other than CMR are discussed in the proposal to take advantage of having the information available to the competent expert group.

REFERENCES

ACGIH, Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th ed., American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1991, p. 1518.

ACGIH Documentation of the TLVs and BEIs with other worldwide occupational exposure values 2004 CD-ROM. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 2004

BASF AG: Sicherheitsdatenblatt Tetrahydrofuran dest. rein [Safety Data Sheet Pure Distilled Tetrahydrofuran] (June 7, 1993).

BGIA GESTIS website : www.hvbg.de/e/bia/fac/stoffdb/

Bismuth C. Toxicologie Clinique, Médecine-Sciences Flammarion, 5ème édition, 2000, Paris.

Cartigny B, Azaroual N, Imbenotte M, Sadeg N, Testart F, Richecoeur J, Vermeersch G, Lhermitte M. 1H NMR spectroscopic investigation of serum and urine in a case of acute tetrahydrofuran poisoning. Journal of Analytical Toxicology 2001; 25 (4): 270-274.

Chemminke K *et al.*, Gigiena Truda i Professional'nye Zabolevaniya (Labor Hygiene and Occupational Diseases) (Moscow) 1982; 26: 43-44; cited in IUCLID

Chhabra RS, Elwell MR, Chou B, Miller RA, Renne RA. Subchronic toxicity of tetrahydrofuran vapors in rats and mice. Fundamental and Applied Toxicology 1990; 14 (2): 338-345.

Chhabra RS, Herbert RA, Roycroft JH, Chou B, Miller RA and Renne RA. Carcinogenesis Studies Of Tetrahydrofuran Vapors In Rats And Mice. Toxicological Sciences 1998; 41 (2): 183-188

DFG website: http://www.dfg.de/en/news/press_releases/2003/press_release_2003_33.html

Droz PO, Berode M, Jang JY. Biological monitoring of tetrahydrofuran: contribution of a physiologically based pharmacokinetic model. American Industrial Hygiene Association Journal 1999; 60 (2): 243-248.

Engel H *et al.* Toxikologie und Hygiene der technischen Loesungsmittel, Lehman KB and Flury F (Eds), Springer-Verlag; Berlin, Germany p 203-204 (1938)

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Duk S et al. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluation of 108 chemicals. Environmental Mutagenesis 1987; 10 (Suppl 10): 1-175; cited in NTP, 1998

Gamer AO, Jaeckh R, Leibold E, Kaufmann W, Gembardt C, Bahnemann R, van Ravenzwaay B. Investigations on cell proliferation and enzyme induction in male rat kidney and female mouse liver caused by tetrahydrofuran. Toxicological Sciences 2002; 70 (1): 140-149.

Garnier R. Tetrahydrofuran poisoning after occupational exposure. British Journal of Industrial Medecine 1989; 46: 677-678; cited in NOHSC

Gosselin RE, Smith RP, Hodge HC. Clinical Toxicology of Commercial Products. 5th ed. Baltimore: Williams and Wilkins, 1984., p. II-408, in HSDB

Hara K *et al*., "Forensic toxicological analysis of tetrahydrofuran in body material", Zeitschrift fur Rechtsmedizin. Journal of legal medicine 1987; 98: 49-55

Hatch G, Anderson T, Elmore E, et al. Status of enhancement of DNA viral transformation for determination of mutagenic and carcinogenic potential of gaseous and volatile compounds [Abstract]. Environmental Mutagenesis 1983; 5: 422.

Hathaway, Proctor, Hughes, and Fischman 1991, p. 537 (http://www.osha.gov/SLTC/healthguidelines/tetrahydrofuran/recognition.html)

Hofmann T, Oettel H. Zur Frage der Toxizitat von Tetrahydrofuran. Naunyn Schmiedebergs Arch Exp Path Pharmak, 222, 233-235, 1954.

Horiguchi S *et al.* Sumitomo Sangyo Eisei 20, 141-157 1984, IUCLID

Ikeoka H et al, "Effects of tetrahydrofuran exposure on the ciliary activity and morphology of tracheal epithelium in rabbits", Osaka City Medical J, 30, 53-67, 1984; cited in IUCLID and in Chhabra *et al*., 1998

ISP Japan website: http://ispjapan.co.jp/toxsum/THF.htm

ICSC. Tetrahydrofuran. NIOSH. Website: http://oshthai.labour.go.th/labourhealth/ipcsneng/neng0578.htm (1998)

IUCLID dataset Tetrahydrofuran (18-feb-2000). ECB - Existing Chemicals, ed.

Katahira T, Teramoto K, Horiguchi S. [Experimental studies on the toxicity of tetrahydrofuran administered to animals by repeated inhalation]. Japanese Journal of Industrial Health Sangyo Igaku 1982a; 24 (4): 379-387.

Katahira T, Teramoto K, Horigushi S. [Experimental studies on the acute toxicity of tetrahydrofuran in animals]. Sangyo Igaku 1982b; 24 (4): 373-378.

Kawata F, Ito A. [Experimental studies of effects on organic solvents in living body, changes of tetrahydrofuran concentration in rats and histological observations after tetrahydrofuran inhalation], Nippon Hoigaku Zasshi 1984; 38 (3): 367-375.

Lehmann KB, Flury F. Toxicology of Industrial Solvents, 269, Williams & Wilkins, Baltimore, 1943.

Malley LA, Christoph GR, Stadler JC, Hansen JF, Biesemeier JA, Jasti SL. Acute and subchronic neurotoxicological evaluation of tetrahydrofuran by inhalation in rats. Drug and chemical toxicology. 2001; 24 (3): 201-219.

Matthews EJ, Spalding JW, Tennant RW. Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays. Environmental Health Perspectives 1993; 101 Suppl 2: 347-482.

Melnick RL, Kohn MC, Portier CJ. Implications for risk assessment of suggested nongenotoxic mechanisms of chemical carcinogenesis. Environmental and Health Perspectives 1996; 104 (1): 123-134.

The Merck Index, Twelfth Edition. Merck Research Laboratories, Susan Budavi, Editor. Division of Merck & Co., Inc. Whitehouse Station, NJ, 1996.

Mirsalis J, Tyson K, Beck J, Loh E, Steimetz K, Contreras C, Austere L, Martin S, Spalding J. Induction of unscheduled DNA synthesis (UDS) in hepatocytes following "in vitro" and "in vivo" treatment. Environmental Mutagenesis 1983; 5: 482.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E. Salmonella Mutagenicity Tests: II. Results From The Testing Of 270 Chemicals; Environmental Mutagenesis 1986; 8 (Suppl. 7):1-119.

Nagata T *et al*. "A fatal case of tetrahydrofuran poisoning", In: Topics in Forensic and Analytical Toxicology, Maes RAA (ed), Elsevier Science Publishers, Amsterdam, Netherlands, 33-37, 1983, cited in NOHSC

National Cancer Institute/National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Tetrahydrofuran (CAS No. 109-99-9) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NCI/NTP Carcinogenesis Technical Report Series 1998; 475: 1-244

NOHSC website: http://www.nohsc.gov.au/OHSInformation/Databases/ExposureStandards/az/Tetrahydrofuran.htm

Pellizzari ED, Hartwell TD, Harris BS 3rd, Waddell RD, Whitaker DA, Erickson MD. Purgeable organic compounds in mother's milk. Bulletin of environmental contamination and toxicology 1982; 28 (3): 322-328

Sax's Dangerous Properties of Industrial Materials (11th Edition) Volumes 1-3. Lewis Richard J. Sr. Wiley Interscience. A John Wiley & Sons, Inc., Publication, 2004.

Shelby MD, Witt KL. Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. Environment and Molecular Mutagenesis 1995; 25 (4): 302-313.

SIDS Initial Assessment Report for 10th SIAM (Japan, March 15-17, 2000)

Stasenkova KP, Kochetkova TA, Toksikol. Novykh. Prom. Khim. Veshchestv, 1963; 5: 21-35.

Stasenkova KP, Kochetkova TA, Toksikol. Nov. Prom. Khim. Vesh. 1968; 10: 35-44.

Valencia R, Mason JM, Woodruff RC, Zimmering S. Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. Environmental and Molecular Mutagenesis 1985; 7 (3): 325-348.

Van Ravenzwaay B, Gamer AO, Leibold E, Kaufmann W. Effect of cytochrome P-450 inhibition on tetrahydrofuran-induced hepatocellular proliferation in female mice. Archives of Toxicology 2003; 77 (8): 459-464.

Viader F, Lechevalier B, Morin P. Polynévrite toxique chez un travailleur du plastique [Toxic polynevritis in a rubber worker]. Nouvelle presse médicale 1975 ; 4 : 1813-1814; In: Fiche toxicologique INRS N°42, 1997.

Walles SA. The influence of some alkylating agents on the structure of DNA in vitro. Chemico-Biological Interactions 1974; 9, 97-103.

Widstrom J, Friis L. DEC and SCG Basis for an Occupational Health Standard - Tetrahydrofuran, Arbete Och Halsa - Vetenskaplig Skriftserie, 27, 1989, cited in NOHSC

ANNEX – LIST OF ABBREVIATIONS

ACGIH, American Conference of Industrial Hygienists

AP, alkaline phosphatase

BAT, Biologische Arbeitsstofftoleranzwerte (Biological Tolerance Value)

BGIA, Berufsgenossenschaftliche Institut für Arbeitsschutz

BRDU, BromoDeoxyUridine

CHO, Cell Hamster Ovary

DFG, Deutsche Forschungsgemeinschaft

GLP, Good Laboratory Practice

GOT, glutamic-oxalacetic transaminase

GPT, glutamic-pyruvate transaminase

IARC, International Agency for Research on Cancer

IUCLID, International Uniform Chemical Information Database

i.p., intra-parenteral

MAK, Maximale Arbeitsplatzkonzentrationen (Maximum Allowable Concentration)

MTD, Maximum Tolerated Dose

NOHSC, National Occupational Health Safety Commission

NTP, National Toxicology Program

PCE, Polychromatic Erythrocyte

s.c, subcutaneous

SCE, Sister Chromatide Exchange

SHE, Syrian Hamster Embryo

STEL, Short Term Exposure Limit

THF, Tetrahydrofuran

TLV, Threshold Limit Value

TWA, Time Weighted Average