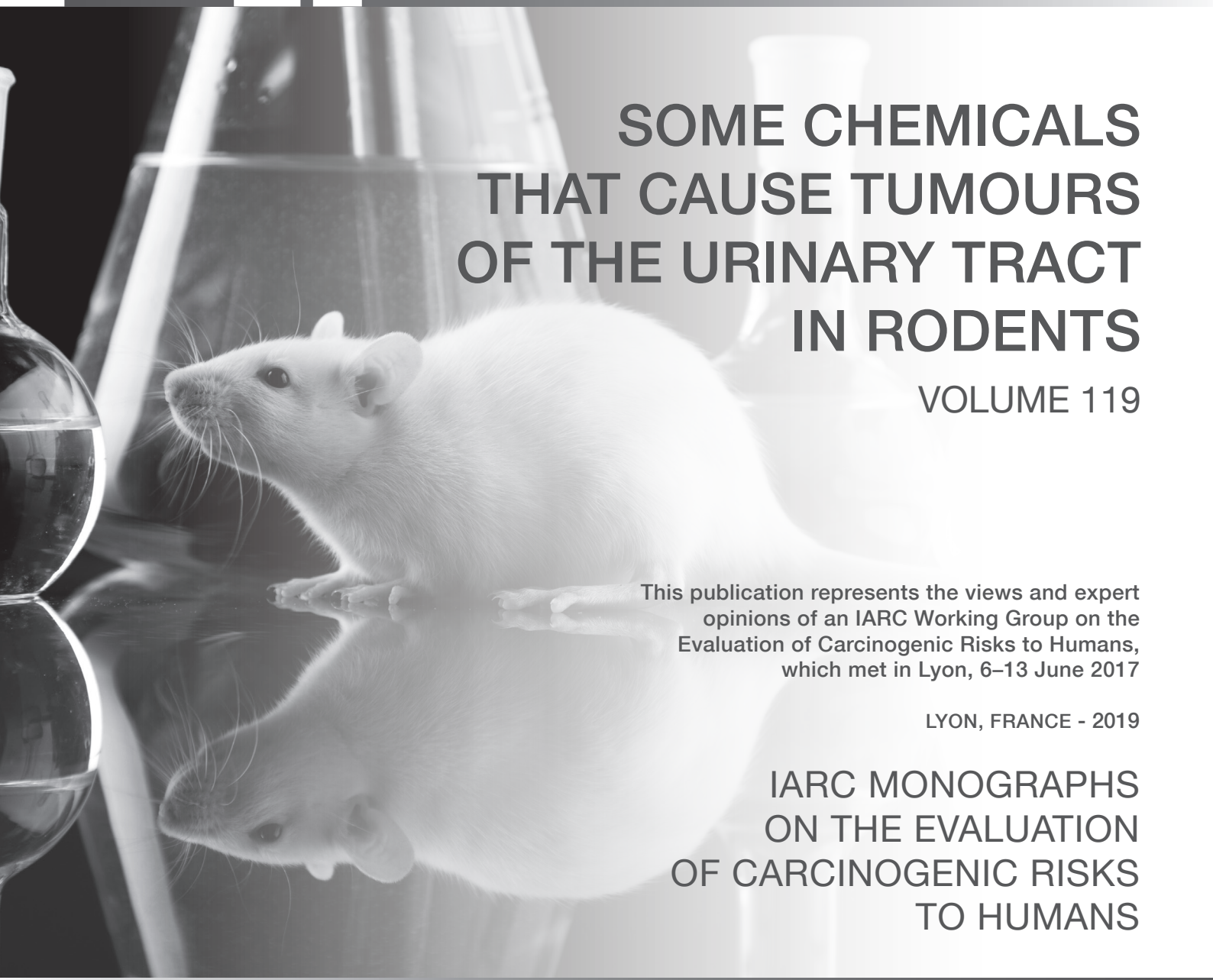
IARC MONOGRAPHS



SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 June 2017

LYON, FRANCE - 2019

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

TETRAHYDROFURAN

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 109-99-9

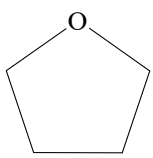
EC/List No.: 203-726-8

Chem. Abstr. Serv. name: Tetrahydrofuran

IUPAC systematic name: Oxolane

Synonyms: Butane alpha,delta-oxide; butane, 1,4-epoxy-; cyclotetramethylene oxide; diethylene oxide; 1,4-epoxybutane; furan, tetrahydro-; furanidine; hydrofuran; oxacyclopentane; tetramethylene oxide; THF

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C_4H_8O

Relative molecular mass: 72.11

1.1.3 Chemical and physical properties

Description: Tetrahydrofuran is a colourless, volatile liquid with an ethereal or acetone-like odour (EPA, 2012)

Boiling point: 65–66 °C (EPA, 2012)

Melting point: –108.44 °C (ECHA, 2018)

Relative density: 0.883 at 25 °C (water, 1) (ECHA, 2018)

Solubility: Miscible in water (ECHA, 2018)

Volatility: Vapour pressure, 19.3 kPa at 20 °C (IPCS, 1997)

Relative vapour density: 2.5 (air = 1); relative density of the vapour/air mixture at 20 °C (air = 1): 1.28 (IPCS, 1997)

Stability: Tetrahydrofuran is prone to oxidation to peroxides, butyric acid, butyraldehyde, and related compounds, mainly on ageing and in the presence of light, heat, and moisture. The formation of peroxides can be retarded by adding stabilizers such as hydroquinone or 2,6-di-*tert*-butyl-*p*-cresol at 250 mg/kg (Coetzee & Chang, 1985; Müller, 2012).

Flash point: –14.5 °C (IPCS, 1997)

Explosive limits: 2.0–11.8 vol% in air (IPCS, 1997)

Auto-ignition temperature: 321 °C (NIOSH, 2014)

Octanol/water partition coefficient (P): log K_{ow}, 0.45 at 25 °C (ECHA, 2018)

Odour threshold: 2–7.4 ppm; 60–150 mg/m^3 (EPA, 2012)

Conversion factor: 1 ppm = 2.95 mg/m^3 (EPA, 2012)

1.2 Production and use

1.2.1 Production process

A process developed by Reppe in the 1930s was for many years the preferred synthetic route to 1,4-butanediol and tetrahydrofuran, and is still the most common approach in Europe and the USA. The Reppe process involves a reaction between acetylene and formaldehyde to give 2-butyne-1,4-diol, with subsequent hydrogenation to 1,4-butanediol, which is further dehydrated and cyclized by acid catalysis at temperatures above 100 °C to tetrahydrofuran (Müller, 2012). This and other industrial routes to produce tetrahydrofuran (e.g. butadiene acetoxylation, propylene oxide process, maleic anhydride hydrogenation, *n*-butane–maleic anhydride process, and pentosan/furfural processes) are described in more detail by Müller (2012).

1.2.2 Production volume

Tetrahydrofuran appears in the Organisation of Economic Co-operation and Development (OECD) 2007 list of high production volume chemicals (OECD, 2009), which contains those chemicals which are produced or imported at quantities greater than 1000 tonnes/year in at least one member country or region.

According to the European Chemicals Agency (ECHA) database, more than 100 000 tonnes of tetrahydrofuran are manufactured and/or imported in the European Economic Area per year (ECHA, 2018).

World consumption of tetrahydrofuran was approximately 439 000 tonnes in 2006 (Müller, 2012). It grew by about 40% during 2012–2015 (IHS Markit, 2016) and is projected to exceed 1 million tonnes in 2020 (Global Industry Analysts, 2018).

1.2.3 Use

Tetrahydrofuran has two primary industrial uses. Its main use is as a monomer in the production of polytetramethylene ether glycol (PTMEG), a component of cast and thermoplastic urethane elastomers, polyurethane stretch fibres, and high-performance copolyester-polyether elastomers. In 2015, the production of PTMEG accounted for almost 90% and about 80% of total use in Asia and in the USA, respectively. A smaller amount of tetrahydrofuran is used as a solvent in polyvinyl chloride (PVC) cements, pharmaceuticals and coatings, precision magnetic tape manufacture, and as a reaction solvent (IHS Markit, 2016). The National Industrial Chemicals Notification and Assessment Scheme of the Australian Government assessed tetrahydrofuran (NICNAS, 2016) and, similarly to the ECHA assessment, identified many domestic and industrial uses of tetrahydrofuran. Domestic uses include as: polish and cleaning agents; adhesives; stain, paint, and varnish removers; sealants; lubricating oils; coating products; and pharmaceuticals. Industrial uses include as solvent in the production of polymers (e.g. PTMEG); reagent for chemical reactions; bulk pharmaceutical manufacturing; synthetic perfumes; insecticides; printing inks, dyes, adhesives, lacquers, and other coatings; synthesis of motor fuels; PVC cement; fabrication of articles for packaging, transporting, or storing food (if residual amount does not exceed 1.5% of the film); and metalworking fluids (ECHA, 2009, 2018; NICNAS, 2016).

1.3 Analytical methods

All methods used to analyse tetrahydrofuran in ambient air are derived from the United States Environmental Protection Agency (EPA) method 8260B, which is a general method used to determine tens of different volatile organic compounds in nearly all types of samples using

Table 1.1 Analytical methods for measurement of tetrahydrofuran in the workplace

Method	Technique	Target concentration	Remarks
IRSST 179-1 (IRSST, 1996)	GC-FID	Precision, 0.8 Minimum reported value, 53 µg	Flow rate, maximum 0.2 L/min TWA sampling volume, 9 L
IRSST 369 (IRSST, 1996)	GC-MS	Analytical uncertainty (CVa), 5.4%	
NIOSH 1609 (NIOSH, 1994)	GC-FID	Estimated LOD, 50 µg/sample Range studied, 323–1240 mg/m³ Overall precision, 0.055 Accuracy, ±12.6%	Flow rate: minimum 0.01 L/min; maximum 0.2 L/min Sampling volume, 1–9 L Working range, 100–2600 mg/m³ for a 5-L air sample This is also the primary method used by OSHA
MTA/MA-049/A01 (2001) GESTIS (2004)	GC-FID	Working range, 13–275 mg/m³	Flow rate, 0.2 L/min Recommended sampling time, 60 min Recommended air volume, 12 L Validated according to INSHT protocol

CVa, coefficient of variation; FID, flame ionization detection; GC, gas chromatography; INSHT, Instituto Nacional de Seguridad e Higiene en el Trabajo; IRSST, Institut de recherche Robert-Sauvé en santé et en sécurité du travail; LOD, limit of detection; min, minute(s); MS, mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; TWA, time-weighted average

gas chromatography in combination with mass spectrometry (GC-MS) (EPA, 1996). Analytical methods for tetrahydrofuran measurement in the workplace are reported in Table 1.1.

There are also European Union guidelines on testing conditions for articles in contact with foodstuffs, with a focus on kitchenware (European Commission, 2009). United States EPA method 524.2 is a general-purpose method to evaluate the concentration of tetrahydrofuran and other volatile organic compounds in water (EPA, 1995).

Finally, there is at least one method to evaluate the concentration of residual solvents in pharmaceutical products. Li et al. (1998) described a capillary gas chromatographic procedure for the analysis of nine common residual solvents, including tetrahydrofuran, in water-insoluble bulk pharmaceuticals.

1.3.1 *Exposure assessment and biological markers*

In 1991, it was demonstrated that the associations between occupational exposure to tetrahydrofuran and its concentrations in exhaled air, in blood, and in urine had correlation coefficients of r = 0.61, 0.68, and 0.88, respectively (Ong et al., 1991). Laboratory methodological considerations, together with the good correlation between the concentration of tetrahydrofuran in the environment and urinary tetrahydrofuran concentration, suggest that urinary tetrahydrofuran concentration is a useful biological marker of occupational exposure to tetrahydrofuran (Ong et al., 1991).

According to the American Conference of Governmental Industrial Hygienists (ACGIH), there is inadequate information to set biological exposure indices (BEI) for tetrahydrofuran in venous blood and in exhaled air (ACGIH, 2008).

Using a headspace GC-MS technique, Prado et al. (2010) demonstrated a detection limit low enough to quantify tetrahydrofuran in urine at occupational exposure levels. The established occupational exposure limit value, measured at the end of the working day, was 2 mg/L (INSHT, 2011).

1.4 Occurrence and exposure

Exposure to tetrahydrofuran may occur as a result of its release into the environment or its potential occurrence in some foods and consumer products.

1.4.1 Environmental occurrence

Tetrahydrofuran is a synthesized organic compound that is not found in the natural environment (ACGIH, 2001). Release to the environment from the manufacture of PTMEG is no more than 1% of the tetrahydrofuran produced or handled. Other environmental exposures during regular use are also low (OECD, 2000).

Fugacity models, distribution-based models incorporating all environmental compartments and based on steady-state fluxes of pollutants across compartment interfaces, suggest that tetrahydrofuran will be found in the environmental compartment in which it was released. Photodegradation by hydroxyl radicals in air is estimated to be rapid; hydroxyl radical reaction half-life is estimated to be 7.3 hours. Tetrahydrofuran released to the environment could partition to the water compartment where it is readily biodegradable, but it would not degrade through hydrolysis. Bioaccumulation of tetrahydrofuran is not expected because of its very low octanol/water partition coefficient. Based upon its physical and chemical properties, production, use patterns, and low levels in the environment at a magnitude of parts per billion, the potential of environmental exposure is expected to be low (OECD, 2000).

Release of tetrahydrofuran to the environment is likely to occur from industrial use, for example, in processing aids at industrial sites and in the manufacturing of the substance in closed systems with minimal release. For example, total production of tetrahydrofuran in 1999 was 551 million pounds [250 000 tonnes], of which 78% was used for the synthesis of PTMEG in closed systems (OECD, 2000). Other release to the environment of this substance is likely to occur from outdoor and indoor use (e.g. machine wash liquids and/or detergents, automotive care products, paints and coatings, adhesives, fragrances, and air fresheners) (ECHA, 2018).

1.4.2 Occurrence in food

According to the United States Hazardous Substances Data Bank (HSDB, 2011), tetrahydrofuran was detected in some natural materials such as roasted coffee (Heins et al., 1966; Stoffelsma & Pypker, 1968; Stoffelsma et al., 1968; Walter & Weidemann, 1969; Furia & Bellanca, 1975; Ross, 2005), floured chickpea (*Cicer arietinum* L.) seed (Rembold et al., 1989), and chicken breast muscle (Grey & Shrimpton, 1967; Shahidi et al., 1986).

[The Working Group noted that the literature on potential occurrence of tetrahydrofuran in food is extremely limited, dated, and most likely erroneous. Tetrahydrofuran is commonly used in typical laboratory environments, so contamination during analysis may occur. It is also possible that the occurrences in food were from environmental contamination of samples. None of the studies included quantification. For all these reasons, there is currently insufficient evidence to assume a natural occurrence of tetrahydrofuran.]

1.4.3 Exposure in the general population

Non-occupational exposure to tetrahydrofuran has been described as uncommon (EPA, 2011), but the general population may be exposed to it by various media. Tetrahydrofuran often occurs in effluent from the production of synthetic textiles, and at solvent recycling facilities (Isaacson et al., 2006). It has been detected in ambient air, groundwater, drinking-water, and landfill sludge, and in some common household products. In groundwater, it has been measured

at concentrations that exceed the water quality criteria and guidelines set by different states of the USA (50–1300 µg/L) (Isaacson et al., 2006). Tetrahydrofuran may migrate into foods when present in the contact surface of materials intended for use in food processing (NTP, 1998).

Qualitative data have indicated that the general population may be exposed to tetrahydrofuran via the inhalation of ambient air, the ingestion of food and drinking-water, and by dermal contact with products containing tetrahydrofuran (HSDB, 2011).

In four urban areas of the USA, tetrahydrofuran was qualitatively detected in one out of eight samples of breast milk (Pellizzari et al., 1982). The United States Consumer Product Information Database lists 56 liquid or paste products for home maintenance that contain tetrahydrofuran in concentrations of 10–75% (National Library of Medicine, 2017).

[No quantitative exposure data in the general population were available to the Working Group.]

1.4.4 Occupational exposure

Exposure to tetrahydrofuran is most likely to occur in occupational settings through inhalation or by dermal contact. In an initial assessment profile, the OECD reported in 2000 that worker exposure at production and use facilities were well below any designated exposure limits, with average concentrations in air less than 10 ppm. Plumbers who use plastic pipe solvent cements can be exposed to tetrahydrofuran; however, workplace exposure monitoring is well below United States standards/guidelines of 200 ppm 8-hour daily values, and the short-term exposure limit (STEL; 15 minutes) of 250 ppm. Monitoring of the plumbing workplace during the use of plastic pipe solvent cements revealed that exposure to tetrahydrofuran did not exceed the above values (OECD, 2000).

In Germany, a report compiled data from 357 measurements made at approximately 120 companies from the year 1990 onwards. Exposure levels per shift were measured as: 166 mg/m^3 (95% value) in the manufacture of plastics adhesives (20 measurements from 7 companies); 89 mg/m^3 (95% value) in the manufacture of plastics and plastic foams (19 measurements from 13 companies); and 182 mg/m^3 and 290 mg/m^3 in plastic coating with ventilation (149 measurements from 47 companies) and without ventilation (140 measurements from 50 companies), respectively (BGAA, 1999).

Twenty measurements of workplace exposure from the Finnish Institute of Occupational Health, collected between 2012 and 2016, range between 0.01 and 14 mg/m^3 with a mean of 1 mg/m^3. The highest measurements were from gluing plastic products (FIOH, 2017).

In a study of 78 plumbers installing plastic pipe, 4 of 29 workers who had significant skin contact with primer and cement had urinary tetrahydrofuran concentrations 1.4–6.7-fold higher than the maximum measured among plumbers with little skin contact but with similar airborne exposures, suggesting the likelihood of significant skin contribution (ACGIH, 2005).

1.5 Regulations and guidelines

The Committee of Experts on the Transport of Dangerous Goods and the Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations Economic Commission for Europe identified tetrahydrofuran as: United Nations No. 2056, Hazard Class 3, United Nations Packing Group II (UNECE, 2015).

Tetrahydrofuran 8-hour (140–590 mg/m^3) and short-term (15 minutes, 280–737 mg/m^3) limit values for different countries, from the GESTIS international limit values database, are presented in Table 1.2 (GESTIS, 2017).

For the ACGIH, the time-weighted average (TWA) threshold limit value (TLV) was 200 ppm during 1957–2004. A TLV-STEL value of

Table 1.2 Eight-hour and short-term limit values for occupational exposure to tetrahydrofuran in different countries or regions

Country or region	8-hour limit value		Short-term limit value	
	ppm	mg/m³	ppm	mg/m³
Australia	100	295		
Austria	50	150	100	300
Belgium	50	150	100	300
Canada (Ontario)	50		100	
Canada (Quebec)	100	300		
China		300		
Denmark	50	148	100	296
European Union	50	150	100	300
Finland	50	150	100[a]	300[a]
France	50[b]	150[b]	100[b]	300[b]
Germany (AGS)	50	150	100[a]	300[a]
Germany (DFG)	50	150	100[a]	300[a]
Hungary		150		300
Ireland	50	150	100[c]	300[c]
Italy	50[d]	150[d]	100[d]	300[d]
Japan	50			
Japan (JSOH)	50	148		
Latvia	50	150	100[a]	300[a]
Netherlands		300		600
New Zealand	100	295		
Poland		150		300
Republic of Korea	50	140	100	280
Romania	50	150	100[a]	300[a]
Singapore	200	590	250	737
Spain	50[d]	150[d]	100[d]	300[d]
Sweden	50	150	80[a]	250[a]
Switzerland	50	150	100	300
Turkey	50	150	100[a]	300[a]
United Kingdom	50	150	100	300
USA (NIOSH)	200	590	250[a]	735[a]
USA (OSHA)	200	590		

AGS, Ausschuff für Gefahrstoffe; DFG, Deutsche Forschungsgemeinschaft; JSOH, Japan Society for Occupational Health; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; ppm, parts per million

[a] 15-minute average value

[b] Restrictive statutory limit values

[c] 15-minute reference period

[d] Dermal exposure

Source: GESTIS (2017)

250 ppm was added in 1976. In 2005, the ACGIH committee approved a TLV-TWA of 50 ppm and a TLV-STEL of 100 ppm (ACGIH, 2005).

The United States National Institute for Occupational Safety and Health proposed an immediately dangerous for life and health limit of 2000 ppm, based on 10% of the lower explosive limit (NIOSH, 2014).

The American Industrial Hygiene Association published Emergency Response Planning Guidelines (ERPGs) for various chemicals, including tetrahydrofuran. Values for ERPG-1, 2, and 3 are 100, 500, and 5000 ppm, respectively, where the maximum 1-hour airborne exposure limit concentration classifications are: ERPG-1 for mild, transient adverse health effects or clearly objectionable odour; ERPG-2 for irreversible or other serious health effects; and ERPG-3 for life-threatening health effects (25% of the lower explosion limit) (AIHA, 2008).

For use in pharmaceutical products, tetrahydrofuran is classified in class 2 of table 2 of the United States Food and Drug Administration Guidance for Industry. Based on chronic toxicity and/or carcinogenicity data, the permitted daily exposure (PDE) to tetrahydrofuran as a residual solvent is 7.2 mg/day and the concentration limit is 720 ppm (FDA, 2017).

In 1993, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area set the biological tolerance value (BAT) of 8 mg tetrahydrofuran per litre of urine for samples collected at the end of exposure or shift. In 2001, for exposure to a tetrahydrofuran concentration of 50 mg/m^3 (the maximum permissible concentration in the workplace (MAK) value), the BAT value was re-evaluated and lowered to 2.0 mg tetrahydrofuran per litre of urine (DFG, 2016).

In 2000, the ACGIH adopted a BEI value of 8 mg tetrahydrofuran per litre of urine at the end of shift (ACGIH, 2005).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 7 weeks) were exposed to tetrahydrofuran (purity, ~99%; no impurities > 0.1%) by whole-body inhalation at 0 (control), 200, 600, or 1800 ppm for 6 hours plus T_{90} (time to achieve 90% of the target concentration after the beginning of vapour generation; 12 minutes) per day, 5 days per week, for 105 weeks (Chhabra et al., 1998; NTP, 1998). After week 36, the survival of the males exposed at 1800 ppm was significantly less than that of controls. The survival of males exposed at 200 or 600 ppm, and of all exposed females, was similar to that of controls. Mean body weights of males and females exposed to tetrahydrofuran were similar to those of controls throughout the study. Necropsies were performed on all mice and major organs were investigated by light microscopy.

Increased incidences of hepatocellular adenoma and carcinoma were reported in exposed female mice relative to controls. The incidences of hepatocellular adenoma or carcinoma (combined) were 17/50, 24/50, 26/50, and 41/48, and the incidences of hepatocellular carcinoma were 6/50, 10/50, 10/50, and 16/48 for groups exposed to tetrahydrofuran at 0, 200, 600, and 1800 ppm, respectively. The increases in the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were statistically significant by the trend test ($P < 0.001$), and statistically significant ($P < 0.001$) by pairwise comparison

Table 3.1 Studies of carcinogenicity with tetrahydrofuran in rodents

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 7 wk 105 wk NTP (1998)	Inhalation (whole-body exposure) Tetrahydrofuran, ~99% Clean air 0, 200, 600, 1800 ppm for 6 h + T_{90} (12 min) per d, 5 d/wk for 105 wk 50, 50, 50, 50 32, 31, 28, 12	*Liver* Hepatocellular adenoma: 24/50, 19/50, 16/50, 14/50 Hepatocellular carcinoma: 14/50, 13/50, 14/50, 9/50 Hepatocellular adenoma or carcinoma (combined): 35/50, 31/50, 30/50, 18/50	 NS NS NS	Principal strengths: GLP study in both males and females Overall historical control incidence in chamber controls for hepatocellular adenoma or carcinoma (combined), 358/947 (37.8 ± 12.5%); range, 11–60% Statistical test: logistic regression
Full carcinogenicity Mouse, B6C3F$_1$ (F) 7 wk 105 wk NTP (1998)	Inhalation (whole-body exposure) Tetrahydrofuran, ~99% Clean air 0, 200, 600, 1800 ppm for 6 h + T_{90} (12 min) per d, 5 d/wk for 105 wk 50, 50, 50, 50 29, 33, 26, 32	*Liver* Hepatocellular adenoma: 12/50*, 17/50, 18/50, 31/48** Hepatocellular carcinoma: 6/50*, 10/50, 10/50, 16/48** Hepatocellular adenoma or carcinoma (combined): 17/50*, 24/50, 26/50, 41/48**	 *$P < 0.001$ (trend), **$P < 0.001$ *$P = 0.012$ (trend), **$P = 0.014$ *$P < 0.001$ (trend), **$P < 0.001$	Principal strengths: GLP study in both males and females Statistical test: logistic regression
Full carcinogenicity Rat, F344/N (M) 7 wk 105 wk NTP (1998)	Inhalation (whole-body exposure) Tetrahydrofuran, ~99% Clean air 0, 200, 600, 1800 ppm for 6 h + T_{90} (12 min) per d, 5 d/wk for 105 wk 50, 50, 50, 50 12, 6, 5, 6	*Kidney* Renal tubule adenoma: 1/50, 1/50, 4/50, 3/50 Renal tubule carcinoma: 0/50, 0/50, 0/50, 2/50 Renal tubule adenoma or carcinoma (combined): 1/50*, 1/50, 4/50, 5/50	 NS NS *$P = 0.037$ (trend)	Principal strengths: GLP study in both males and females Historical incidence for 2-yr NTP inhalation studies in chamber controls: renal tubule adenoma or carcinoma (combined), 6/652 (0.9 ± 1.3%) [range, 0–4%]; renal tubule carcinoma, 0/652 Statistical test: logistic regression The NTP (1998) original slides were reviewed by Bruner et al. (2010)

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Full carcinogenicity Rat, F344/N (F) 7 wk 105 wk NTP (1998)	Inhalation (whole-body exposure) Tetrahydrofuran, ~99% Clean air 0, 200, 600, 1800 ppm for 6 h + T_{90} (12 min) per d, 5 d/wk for 105 wk 50, 50, 50, 50 25, 25, 26, 26	*Mammary gland* Fibroadenoma: 23/50*, 22/50, 29/50, 31/50	*P = 0.031 (trend)	Principal strengths: GLP study in both males and females Historical incidence for 2-yr NTP inhalation studies in chamber controls: mammary gland fibroadenoma, 180/653 (27.6 ± 7.7%) [range, 16–42%] Statistical test: logistic regression

d, day(s); F, female; GLP, good laboratory practice; h, hour(s); M, male; min, minute(s); NS, not significant; NTP, National Toxicology Program; ppm, parts per million; T_{90}, time to achieve 90% of the target concentration after the beginning of vapour generation; wk, week(s); yr, year(s)

between the controls and the group exposed to the highest dose. The incidences of hepatocellular adenoma or carcinoma (combined) in male mice were 35/50 (70%), 31/50 (62%), 30/50 (60%), and 18/50 (36%) for groups exposed to tetrahydrofuran at 0, 200, 600, and 1800 ppm, respectively. No statistically significant increase in the incidences of hepatocellular adenoma, carcinoma, or adenoma or carcinoma (combined) were observed in treated males compared with the control group; however, the incidence of hepatocellular adenoma or carcinoma (combined) for the control group (70%) was above the maximum value for historical controls (37.8 ± 12.5%, with a range of 11–60%). In addition, the rates of incidence for the groups given the middle dose (60%) and low dose (62%) were at the high end or slightly above the range for historical controls. The low tumour incidence in the group given the highest dose was attributed to lower survival in this group; the survival-adjusted incidence was comparable between the group given the highest dose (73.4%) and the control group (77.2%) (NTP, 1998). [The Working Group noted this was a well-conducted good laboratory practice (GLP) study and that both sexes were used.]

3.2 Rat

Groups of 50 male and 50 female F344 rats (age, 7 weeks) were exposed to tetrahydrofuran (purity, 99%; no impurities > 0.1%) by whole-body inhalation at 0 (control), 200, 600, or 1800 ppm for 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 105 weeks (Chhabra et al., 1998; NTP, 1998). The survival of males and females exposed to tetrahydrofuran was similar to that of controls. Mean body weights of exposed groups of males and females were similar to those of controls throughout the study. Necropsies were performed on all rats and major organs were investigated by light microscopy.

In males, NTP (1998) reported slight (but non-significant) increases in renal tubular epithelial tumours at exposure concentrations of 600 ppm (adenoma, 4/50) and 1800 ppm (adenoma, 3/50; carcinoma, 2/50) compared with controls (adenoma, 1/50; carcinoma, 0/50). The incidences of renal tubule adenoma or carcinoma (combined) were 1/50, 1/50, 4/50, and 5/50 at 0, 200, 600, and 1800 ppm, respectively; statistical analysis revealed a significant positive trend (P = 0.037). The original slides from the NTP (1998) study were subsequently reviewed by an additional group of experts, who examined the slides for which kidney proliferative lesions had been reported (Bruner et al., 2010). This re-evaluation confirmed the presence of treatment-related renal tubule proliferative lesions, but failed to reproduce the results of the original NTP (1998) study; two carcinomas were downgraded to adenomas in the re-evaluation (Bruner et al., 2010). [The Working Group analysed the three relevant articles cited above, critically reviewed the results, and weighed the interpretations; in consideration of all data, the Working Group agreed with the conclusions of the original NTP (1998) study.] In females, there was a small but significant positive trend (P = 0.031) in the incidence of mammary gland fibroadenoma (23/50, 22/50, 29/50, and 31/50) (Chhabra et al., 1998; NTP, 1998). [The Working Group noted this was a well-conducted GLP study and that both sexes were used.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Absorption, distribution, and excretion

(a) Humans

Tetrahydrofuran is extensively absorbed following inhalation (Ong et al., 1991); it rapidly appears in the blood, demonstrating rapid systemic absorption from the lungs of exposed workers. Although dermal uptake does occur, the degree of absorption through the skin was negligible compared with inhalation (Brooke et al., 1998).

The half-life of tetrahydrofuran in humans is estimated to be approximately 30 minutes. Analysis of hepatic blood flow and clearance values suggests that tetrahydrofuran is extensively metabolized in human liver during first-pass metabolism (Fowles et al., 2013).

Several studies of workers exposed to tetrahydrofuran by inhalation were summarized by Droz et al. (1999) and were used to develop a physiologically based pharmacokinetic model for the biomonitoring of exposed workers.

(b) Experimental systems

Chronic exposure of rats to tetrahydrofuran vapour (at 200, 1000, or 2000 ppm) initially resulted in a dose-dependent increase in tetrahydrofuran content in brain and perirenal fat; exposure for up to 18 weeks showed a decrease with time in tetrahydrofuran content in the body, consistent with rapid metabolism and the low potential for bioaccumulation (Elovaara et al., 1984). In a study in which rats and mice were exposed to [^{14}C]-labelled tetrahydrofuran by gavage and monitored for up to 168 hours after dosing (Fowles et al., 2013), rapid absorption and metabolism of tetrahydrofuran, with the majority recovered as carbon dioxide, were observed in rats. Generally similar kinetics were observed for mice; the main difference between observed results for rats and mice was that the maximal plasma concentration in rats of both sexes was achieved at about 4 hours, whereas that in male and female mice was achieved at 0.8 and 1 hour, respectively, consistent with faster overall pharmacokinetics in mice compared with rats.

Tissue distribution of tetrahydrofuran after oral dosing was analysed in male and female Fischer 344 rats or B6C3F$_1$ mice given [^{14}C]-labelled tetrahydrofuran by single gavage at target concentrations of 50 or 500 mg/kg body weight (bw) (DuPont Haskell Laboratory, 1998). The liver exhibited the highest concentrations of radioactivity, followed by fat and adrenal glands. Relatively high amounts of tetrahydrofuran were detected in the spleen, suggesting distribution through the lymphatic circulation. Differences in distribution between the sexes were not evident.

4.1.2 Metabolism

Few data were available on the metabolism of tetrahydrofuran in human or other mammalian systems. The initial step is oxidative metabolism by cytochrome P450 (CYP) enzymes with further hydrolysis by paraoxonase 1 and further action of cytoplasmic dehydrogenases. The specific CYPs have not been clearly identified. One reaction results in hydroxylation of the ring structure, whereas the other results in ring-opening to form a hydroxylated butanal. A major metabolite that is detected is gamma-hydroxybutyrate (GHB; 4-hydroxybutyrate), a neurotoxicant that can arise either from 4-hydroxyl-butanal or from γ-butyrolactone (GBL; 4-butyrolactone) (ECHA, 2010). GHB is oxidized to succinic semialdehyde, which is then converted to succinate and processed through the citric acid cycle to yield carbon dioxide (Fowles et al., 2013).

Both GHB and carbon dioxide have been recovered (Fowles et al., 2013), consistent with

the pathway. In a tetrahydrofuran poisoning case (Cartigny et al., 2001; Imbenotte et al., 2003), analysis of urine and serum samples by ^{1}H-nuclear magnetic resonance spectroscopy showed very high concentrations of GHB in urine and serum. Urinary and serum concentrations of tetrahydrofuran were 850 and 813 mg/L (11.8 and 11.3 mM), respectively, and those of GHB were 2977 and 239 mg/L (28.6 and 2.3 mM), respectively.

4.1.3 Modulation of metabolic enzymes

As reviewed by Moody (1991), the effects of tetrahydrofuran on mixed-function oxidation were observed to range from increased, decreased, or no change in activities or processes in studies in vivo. Male Sprague-Dawley rats were exposed to tetrahydrofuran for 16 hours, resulting in the induction of activities dependent upon CYP (CYP2E1). Total CYP content and ethoxycoumarin deethylase (ECOD) activity (marker for CYP1A1) increased in liver microsomes isolated from male Wistar rats exposed by inhalation to tetrahydrofuran for 18 weeks (Moody, 1991). Increased total CYP content and activities of ethoxyresorufin-*O*-deethylase and pentoxyresorufin-*O*-dependentylase, suggesting induction of CYP1A1 and CYP2B1, respectively, was reported in the liver of female B6C3F$_1$ mice 5 days after exposure by inhalation to tetrahydrofuran at 5400 mg/m^3 (1800 ppm) (Gamer et al., 2002). Tetrahydrofuran both stimulates and inhibits other enzyme systems in rats, including inhibition of hepatic alcohol and formaldehyde dehydrogenase activities (Elovaara et al., 1984), and also both stimulates and inhibits rat and rabbit phosphorylase activity (Moody, 1991).

In female B6C3F$_1$ mice, exposure to a high concentration of tetrahydrofuran (15 000 mg/m^3) by inhalation markedly induced hepatic microsomal enzymes (van Ravenzwaay et al., 2003). Choi et al. (2017) reported a 1.6-fold increase in total CYP content and a 1.4–1.7-fold increase in mRNA expression of *Cyp1a1/1a2* and *Cyp2b10* in wildtype [C57BL/6] female mice exposed orally to tetrahydrofuran at 1500 mg/kg bw. The oral exposure of constitutive androstane receptor/pregnane X receptor (*Car/Pxr*) knockout female mice to tetrahydrofuran at 1500 mg/kg bw had no effect on CYP expression.

In vitro studies, as reviewed by Moody (1991), showed varying degrees of inhibition, primarily in rat but also in pig liver microsomes. In particular, tetrahydrofuran inhibited benzo[*a*]pyrene metabolism in liver microsomes from phenobarbital-induced rats, and markedly inhibited glutathione *S*-transferase activity in rat liver cytosol with benzo[*a*]pyrene, styrene, or 1,2-dichloro-4-nitrobenzene as substrates. Liver microsomes from female rats were notably more sensitive to the inhibition of ECOD by tetrahydrofuran than those from male rats.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

No change was seen in micronucleated polychromatic and normochromatic erythrocytes in female B6C3F$_1$ mice and in polychromatic erythrocytes in male mice exposed to tetrahydrofuran by inhalation at up to 5000 ppm for 14 weeks. However, an increase in the frequency of micronucleated normochromatic erythrocytes was observed in male mice at the end of the 14-week exposure period: a significant increase (P = 0.004) was observed in male mice exposed at 1800 ppm relative to the control group, but the trend test was not significant (P = 0.074) (NTP, 1998).

Although induction of sister-chromatid exchange (SCE) was seen in the bone marrow of male B6C3F$_1$ mice 23 hours (but not 42 hours) after exposure to tetrahydrofuran by intraperitoneal injection at 2000 mg/kg bw, this was not reproduced in a second trial at doses up to 2500 mg/kg bw (lethal dose) (NTP, 1998). No increase in chromosomal aberrations was induced in the bone marrow of male B6C3F$_1$ mice by exposure to tetrahydrofuran by intraperitoneal injection in phosphate-buffered saline or corn oil [the Working Group noted that the vehicle was not clearly reported] at up to 2000 mg/kg bw (NTP, 1998).

(ii) Non-human mammalian cells in vitro

[The Working Group noted that, due to its volatility, the concentration of tetrahydrofuran in the cell culture medium may decline rapidly in the absence of specific controls for volatility. Tetrahydrofuran concentrations in the cell culture medium at different time points from the beginning of the incubations were not assessed in the in vitro studies cited below.]

Tetrahydrofuran (at up to 5000 μg/mL) was negative in the assays for SCE and chromosomal aberrations in Chinese hamster ovary cells (Galloway et al., 1987; NTP, 1998). No increase in micronuclei was seen in metabolically active Syrian hamster embryo cells exposed to tetrahydrofuran (at 3000, 3500, and 4000 μg/mL) for 24 hours (Gibson et al., 1997).

(iii) Non-mammalian systems

Assays for the mutagenicity of tetrahydrofuran (oral exposure at 125 000 ppm in feed or exposure by injections at 40 000 ppm) were negative in *Drosophila melanogaster* (Valencia et al., 1985; NTP, 1998) and in different strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) (Mortelmans et al., 1986; NTP, 1998).

Tetrahydrofuran is a solvent prone to oxidation to peroxides, butyric acid, butyraldehyde, and related compounds, mainly on ageing and in the presence of light, heat, and moisture (Coetzee & Chang, 1985). Tetrahydrofuran containing 2-hydroxy-tetrahydrofuran as a result of its natural oxidation reacted with DNA bases, giving four adducts as products of the reaction of 4-hydroxy-butanal with the DNA bases (Hermida et al., 2006). The adducts were also detected in calf thymus DNA samples after in vitro reactions with oxidized tetrahydrofuran. Rat liver microsomes oxidized tetrahydrofuran to the reactive 4-hydroxy-butanal, assessed by the formation of the dGuo-THF 1 adduct (Hermida et al., 2006).

4.2.2 Altered cell proliferation or death

(a) Humans

No data in exposed humans were available to the Working Group.

In one study using human embryonic lung fibroblasts, tetrahydrofuran (at 0.2% for 24 hours, used to dissolve β-carotene) reduced the percentage of cells in S-phase (Stivala et al., 1996).

(b) Experimental systems

Marginal increased incidences of hyperplasia of the bone marrow in male B6C3F$_1$ mice during the 2-year inhalation study of tetrahydrofuran were reported by NTP (1998).

In the NTP 13-week study (Chhabra et al., 1990; NTP, 1998), inhalation exposure to tetrahydrofuran increased liver weight in male (at 600, 1800, and 5000 ppm) and female (at 1800 and 5000 ppm) B6C3F$_1$ mice, and in female F344 rats (at 5000 ppm). Minimal to mild hepatic centrilobular hypertrophy occurred in male and female mice (at 5000 ppm).

Absolute and relative liver weights increased in female mice exposed to tetrahydrofuran at 1800 ppm (5400 mg/m^3) for 20 days (Gamer et al., 2002). Cell proliferation, assessed by the number of cells in S-phase, increased mainly in the subcapsular region of the renal cortex in male

rats exposed to tetrahydrofuran at 1800 ppm for 5 days and at 600 and 1800 ppm for 20 days. The number of apoptotic cells increased in the renal cortex of male rats exposed to 1800 ppm for 20 days and also for 5 days (the latter evaluated 21 recovery days later).

Cell proliferation in liver was increased in female $B6C3F_1$ mice exposed to tetrahydrofuran by inhalation at 5000 ppm for 6 hours per day, for 5 days (van Ravenzwaay et al., 2003).

In $B6C3F_1$ and C57BL/6 female mice given tetrahydrofuran by oral gavage at 300, 1000, or 1500 mg/kg bw per day for 7 days, hepatocellular proliferation was observed, assessed by 5-bromo-2′-deoxyuridine staining. The same effect was not observed in constitutive androstane receptor/pregnane X receptor (*Car/Pxr*) double-knockout C57BL/6 mice that received tetrahydrofuran by oral gavage at 1500 mg/kg bw per day, for 7 days (Choi et al., 2017).

In a study in vitro, tetrahydrofuran at 30–100 µL per 5 mL culture medium inhibited metabolic cooperation, an indication of gap-junctional intercellular communication inhibition, in Chinese hamster V79 lung fibroblast cells (Chen et al., 1984).

4.2.3 Other mechanisms

Tetrahydrofuran was negative when tested for induction of cell transformation in cultured Syrian hamster embryo cells (Kerckaert et al., 1996) and mouse fibroblast BALB/c-3T3 cells (Matthews et al., 1993).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013; EPA, 2016a, b; Filer et al., 2017), see Section 4.3 of the *Monograph* on 1-*tert*-butoxypropan-2-ol in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

The only available data came from case reports of occupational exposure to a glue containing tetrahydrofuran (8 hours per day, for 3 days) during plastic pipe repair in a confined space and without the use of any protective device; reported effects were consistent with liver toxicity (Garnier et al., 1989).

4.5.2 Experimental systems

In the NTP 2-year inhalation study (NTP, 1998), effects observed in male $B6C3F_1$ mice exposed to tetrahydrofuran at 1800 ppm were hyperplasia of the bone marrow and iliac lymph nodes, haematopoietic cell proliferation of the spleen, and thymic atrophy, considered to be consequences of the inflammation of the urinary and urogenital tracts. Liver necrosis was increased in female mice exposed to tetrahydrofuran at 1800 ppm (NTP, 1998). In the NTP 13-week study (Chhabra et al., 1990; NTP, 1998), serum bile acids in female F344 rats were increased. Mild degeneration of the X-zone of the innermost cortex of the adrenal glands and uterine atrophy were observed in the female $B6C3F_1$ mice exposed to tetrahydrofuran at 5000 ppm. Tetrahydrofuran also induced narcosis in mice and ataxia in rats.

A concentration-dependent accumulation of α_{2u}-globulin, assessed by immunohistochemistry, was observed in the renal cortex of male F344 rats exposed to tetrahydrofuran for 5 and 20 days, with no regression in the animals that

were killed 21 recovery days after 5 days of exposure. However, renal cortex α_{2u}-globulin accumulation in the animals that were killed 21 recovery days after 5 days of exposure (concentrations were close to or higher than those observed after 20 days of exposure to tetrahydrofuran) was not accompanied by increased cell proliferation (Gamer et al., 2002).

IARC established seven criteria for the induction of kidney tumours to have occurred by an α_{2u}-globulin-associated response (IARC, 1999). The criterion that was met was the identification of the accumulating protein as α_{2u}-globulin (by immunohistochemical staining, in the short-term studies of Gamer et al., 2002). However, six criteria were not met, specifically: (i) lack of genotoxic activity of the agent and/or metabolite (tetrahydrofuran containing 2-hydroxy-tetrahydrofuran was reactive towards DNA bases in vitro, giving different DNA adducts; see Section 4.2.1); (ii) reversible binding of the chemical or metabolite to α_{2u}-globulin (no data are available); (iii) induction of sustained increases in cell proliferation in the renal cortex (no demonstration of sustained cell proliferation); (iv) induction of the characteristic sequence of histopathological changes associated with α_{2u}-globulin accumulation (the histopathological changes were not detected); (v) male rat specificity for nephropathy and renal tumorigenicity (there was no increase in the incidence or severity of nephropathy in exposed male rats; NTP, 1998); and (vi) similarities in dose–response relationships of the tumour outcome with histopathological end-points associated with α_{2u}-globulin nephropathy (no evidence of histopathological end-points associated with α_{2u}-globulin nephropathy in chronic and subchronic studies; NTP, 1998).

5. Summary of Data Reported

5.1 Exposure data

Tetrahydrofuran is a solvent that is used in a variety of plastics, dyes, elastomers, and glues for joining plastic components. It is also used in the synthesis of motor fuels, and in the manufacture of pharmaceuticals, synthetic perfumes, organometallic compounds, and insecticides. Global consumption is about 650 000 tonnes per year. The general population may be exposed by using household products containing tetrahydrofuran; however, reliable information on the exposure of the general population is unavailable. Workers may be exposed by inhalation and skin contact, particularly in professional use of glues, paints, and other similar products containing tetrahydrofuran.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Tetrahydrofuran was tested by whole-body inhalation in one well-conducted good laboratory practice (GLP) study in male and female mice, and in one well-conducted GLP study in male and female rats.

Tetrahydrofuran caused a significant increase in the incidence of, and a positive trend in the incidence of, hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in female mice. In male rats, tetrahydrofuran caused a significant positive trend in the incidence of renal tubule adenoma or carcinoma (combined). In female rats, tetrahydrofuran caused a significant positive trend in the incidence of fibroadenoma of the mammary gland. There was no

significant increase in the incidence of any tumours in male mice.

5.4 Mechanistic and other relevant data

In humans and experimental animals, tetrahydrofuran is extensively absorbed. Tetrahydrofuran is oxidized by cytochrome P450 (CYP) enzymes with further hydrolysis by paraoxonase 1. Major metabolites include 4-butyrolactone and 4-hydroxybutyrate, which is neurotoxic. Tetrahydrofuran inhibits or induces multiple CYPs. Tetrahydrofuran induces CYPs through activation of constitutive androstane receptor.

Regarding the key characteristics of carcinogens, the evidence is *weak* that tetrahydrofuran is genotoxic. No data are available in humans. Tetrahydrofuran did not induce chromosome damage in mice or in mammalian cells. It also gave negative results in tests in *Drosophila* and in different strains of *Salmonella typhimurium*. However, oxidized metabolites of tetrahydrofuran react with DNA in vitro, yielding DNA adducts; one such adduct was formed in vitro from tetrahydrofuran when activated by rat liver microsomes.

The evidence is *moderate* that tetrahydrofuran alters cell proliferation. Cell proliferation was increased in several studies in female mouse liver and in one study in male rat kidney. One study reported inhibition of gap-junctional intercellular communication in vitro. No induction of cell transformation was reported in vitro.

In the carcinogenicity bioassay, toxic effects were not seen in the kidney of male rats. Only one of the seven criteria established by IARC for the induction of kidney tumours to have occurred by an α_{2u}-globulin-associated response was met.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of tetrahydrofuran.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetrahydrofuran.

6.3 Overall evaluation

Tetrahydrofuran is *possibly carcinogenic to humans (Group 2B)*.

References

ACGIH (2001). Tetrahydrofuran. Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists.

ACGIH (2005). 2005 Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists.

ACGIH (2008). Tetrahydrofuran. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th ed. Cincinnati (OH), USA: American Conference of Governmental Industrial Hygienists.

AIHA (2008). The AIHA 2008 Emergency Response Planning Guidelines (ERPG) and Workplace Environmental Exposure Level (WEEL) handbook. Fairfax (VA), USA: American Industrial Hygiene Association.

BGAA (1999). Altstoffe – Expositionen am Arbeitsplatz. BGAA-Report 1/99. Sankt Augustin, Germany: Hauptverband der gewerblichen Berufsgenossenschaften (HVBG).

Brooke I, Cocker J, Delic JI, Payne M, Jones K, Gregg NC, et al. (1998). Dermal uptake of solvents from the vapour phase: an experimental study in humans. *Ann Occup Hyg*, 42(8):531–40. doi:10.1016/S0003-4878(98)00064-7 PMID:9838866

Bruner RH, Greaves P, Hard GC, Regan KS, Ward JM, David RM (2010). Histopathologic changes in the kidneys of male F344 rats from a 2-year inhalation carcinogenicity study of tetrahydrofuran: a pathology working group review and re-evaluation. *Regul Toxicol Pharmacol*, 58(1):100–5. doi:10.1016/j.yrtph.2010.04.009 PMID:20447435

Cartigny B, Azaroual N, Imbenotte M, Sadeg N, Testart F, Richecoeur J, et al. (2001). 1H NMR spectroscopic investigation of serum and urine in a case of acute tetrahydrofuran poisoning. *J Anal Toxicol*, 25(4):270–4. doi:10.1093/jat/25.4.270 PMID:11386640

Chen TH, Kavanagh TJ, Chang CC, Trosko JE (1984). Inhibition of metabolic cooperation in Chinese hamster V79 cells by various organic solvents and simple compounds. *Cell Biol Toxicol*, 1(1):155–71. doi:10.1007/BF00125572 PMID:6400921

Chhabra RS, Elwell MR, Chou B, Miller RA, Renne RA (1990). Subchronic toxicity of tetrahydrofuran vapors in rats and mice. *Fundam Appl Toxicol*, 14(2):338–45. doi:10.1016/0272-0590(90)90213-4 PMID:2318358

Chhabra RS, Herbert RA, Roycroft JH, Chou B, Miller RA, Renne RA (1998). Carcinogenesis studies of tetrahydrofuran vapors in rats and mice. *Toxicol Sci*, 41(2):183–8. doi:10.1093/toxsci/41.2.183 PMID:9520354

Choi CJ, Rushton EK, Vardy A, Higgins L, Augello A, Parod RJ (2017). Mode of action and human relevance of THF-induced mouse liver tumors. *Toxicol Lett*, 276:138–43. doi:10.1016/j.toxlet.2017.05.006 PMID:28495613

Coetzee JF, Chang T-H (1985). Purification of solvents for electroanalysis: tetrahydrofuran and dioxane. *Pure Appl Chem*, 57(4):633–8. Available from: https://www.iupac.org/publications/pac-2007/1985/pdf/5704x0633.pdf doi:10.1351/pac198557040633

DFG (2016). List of MAK and BAT values 2016: Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Report 52. Weinheim, Germany: Wiley-VCH. Available from: www.mak-collection.com.

Droz PO, Berode M, Jang JY (1999). Biological monitoring of tetrahydrofuran: contribution of a physiologically based pharmacokinetic model. *Am Ind Hyg Assoc J*, 60(2):243–8. doi:10.1080/00028899908984443 PMID:10222575

DuPont Haskell Laboratory (1998). ^{14}C-Tetrahydrofuran: disposition and pharmacokinetics in rats and mice, with cover letter dated 10/14/1998. HLR-1998-01377. Submitted under TSCA Section 8D; EPA Document No. 86990000002; NTIS No. OTS0573852. Newark (DE), USA: E.I. DuPont de Nemours and Company.

ECHA (2009). Proposal for harmonised classification and labelling. Annex VI Report – Tetrahydrofuran – CAS 109-99-9. Submitted by France. June 2009. Version 2. Helsinki, Finland: European Chemicals Agency.

ECHA (2010). Annex 1: Background Document to the Opinion proposing harmonised classification and labelling at community level of tetrahydrofuran, ECHA/RAC/DOC No. CLH-O-0000000954-69-03/A1. Helsinki, Finland: European Chemicals Agency, Committee for Risk Assessment.

ECHA (2018). Substance information: tetrahydrofuran. Helsinki, Finland: European Chemicals Agency. Available from: https://www.echa.europa.eu/web/guest/regitration-dossier/-/registered-dossier/15474/1, accessed 28 May 2018.

Elovaara E, Pfäffli P, Savolainen H (1984). Burden and biochemical effects of extended tetrahydrofuran vapour inhalation of three concentration levels. *Acta Pharmacol Toxicol (Copenh)*, 54(3):221–6. doi:10.1111/j.1600-0773.1984.tb01921.x PMID:6609523

EPA (1995). Method 524.2. Measurement of purgeable organic compounds in water by capillary column gas chromatography/mass spectrometry. Washington (DC), USA: United States Environmental Protection Agency.

EPA (1996). Method 8260B-3. Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS). Revision 2. Washington (DC), USA: United States Environmental Protection Agency.

EPA (2011). Toxicological review of tetrahydrofuran (CAS No. 109-99-9). Washington (DC), USA: United States Environmental Protection Agency.

EPA (2012). Toxicological review of tetrahydrofuran (CAS No. 109-99-9). In Support of Summary Information on the Integrated Risk Information System (IRIS) EPA/635/R-11/006F. Washington (DC), USA: United States Environmental Protection Agency.

EPA (2016a). iCSS ToxCast Dashboard. Prod_dashboard_v2. Available from: http://actor.epa.gov/dashboard2/, accessed 18 July 2018.

EPA (2016b). Toxicity Forecaster (ToxCast) data. Washington (DC), USA: United States Environmental Protection Agency. Available from: http://www.epa.gov/chemical-research/toxicity-forecaster-toxcasttm-data, accessed 18 July 2018.

European Commission (2009). Guidelines on testing conditions for articles in contact with foodstuffs (with a focus on kitchenware) – A CRL-NRL-FCM Publication, 1st ed. EUR 23814 EN 2009. Brussels, Belgium: European Commission.

FDA (2017). Guidance for industry. Q3C – Tables and list. June 2017 ICH, revision 3. Silver Spring (MD), USA: United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER).

Filer DL, Kothiya P, Setzer RW, Judson RS, Martin MT (2017). tcpl: the ToxCast pipeline for high-throughput screening data. *Bioinformatics*, 33(4):618–20. PMID:27797781

FIOH (2017). Register of exposure measurements, 2012–2016. Helsinki, Finland: Finnish Institute of Occupational Health (FIOH).

Fowles J, Boatman R, Bootman J, Lewis C, Morgott D, Rushton E, et al. (2013). A review of the toxicological and environmental hazards and risks of tetrahydrofuran. *Crit Rev Toxicol*, 43(10):811–28. doi:10.3109/10408444.2013.836155 PMID:24148014

Furia TE, Bellanca N, editors (1975). Fenaroli's handbook of flavor ingredients. 2nd ed. Cleveland (OH), USA: CRC Press.

Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, et al. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ Mol Mutagen*, 10(Suppl 10):1–175. doi:10.1002/em.2850100502 PMID:3319609

Gamer AO, Jaeckh R, Leibold E, Kaufmann W, Gembardt C, Bahnemann R, et al. (2002). Investigations on cell proliferation and enzyme induction in male rat kidney and female mouse liver caused by tetrahydrofuran. *Toxicol Sci*, 70(1):140–9. doi:10.1093/toxsci/70.1.140 PMID:12388842

Garnier R, Rosenberg N, Puissant JM, Chauvet JP, Efthymiou ML (1989). Tetrahydrofuran poisoning after occupational exposure. *Br J Ind Med*, 46(9):677–8. PMID:2675957

GESTIS (2004). Determination of tetrahydrofuran in air. GESTIS – Analytical methods for chemical agents at workplaces. Available from: http://amcaw.ifa.dguv.de/.

GESTIS (2017). GESTIS International Limit Values. Sankt Augustin, Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). Available from: http://limitvalue.ifa.dguv.de, accessed 28 May 2018.

Gibson DP, Brauninger R, Shaffi HS, Kerckaert GA, LeBoeuf RA, Isfort RJ, et al. (1997). Induction of micronuclei in Syrian hamster embryo cells: comparison to results in the SHE cell transformation assay for National Toxicology Program test chemicals. *Mutat Res*, 392(1-2):61–70. doi:10.1016/S0165-1218(97)00045-1 PMID:9269331

Global Industry Analysts (2018). Tetrahydrofuran (THF) market trends. Available from: https://www.strategyr.com/MarketResearch/Tetrahydrofuran_Market_Trends.asp.

Grey TC, Shrimpton DH (1967). Volatile components in the breast muscles of chickens of different ages. *Br Poult Sci*, 8(1):35–41. doi:10.1080/00071666708415647

Heins JT, Maarse H, ten Noever de Brauw MC, Weurman C (1966). Direct food vapour analysis and component identification by a coupled capillary GLC-MS arrangement. *J Chromatogr Sci*, 4(11):395–7. doi:10.1093/chromsci/4.11.395

Hermida SAS, Possari EPM, Souza DB, de Arruda Campos IP, Gomes OF, Di Mascio P, et al. (2006). 2′-deoxyguanosine, 2′-deoxycytidine, and 2′-deoxyadenosine adducts resulting from the reaction of tetrahydrofuran with DNA bases. *Chem Res Toxicol*, 19(7):927–36. doi:10.1021/tx060033d PMID:16841961

HSDB (2011). Tetrahydrofuran. Hazardous Substances Data Bank. Bethesda (MD), USA: National Library of Medicine. Available from: https://householdproducts.nlm.nih.gov.

IARC (1999). Consensus report. In: Capen CC, Dybing E, Rice JM, Wilbourn JD, editors. Species differences in thyroid, kidney, and urinary bladder carcinogenesis. IARC Scientific Publication No. 147. Lyon, France: International Agency for Research on Cancer; pp. 1–14.

IHS Markit (2016). Tetrahydrofuran. Chemical economics handbook. Available from: https://ihsmarkit.com/products/tetrahydrofuran-chemical-economics-handbook.html.

Imbenotte M, Azaroual N, Cartigny B, Vermeersch G, Lhermitte M (2003). Identification and quantitation of xenobiotics by 1H NMR spectroscopy in poisoning cases. *Forensic Sci Int*, 133(1-2):132–5. doi:10.1016/S0379-0738(03)00059-8 PMID:12742700

INSHT (2011). Límites de exposición profesional para agentes químicos en España 2011. N 117/09 Doc. GT/LEP. Madrid, Spain: Instituto Nacional de Seguridad e Higiene en el Trabajo (INSHT).

IPCS (1997). Tetrahydrofuran. International Chemical Safety Cards ICSC: 0578. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. Available from: http://www.inchem.org/documents/icsc/icsc/eics0578.htm.

IRSST (1996). Analyse du tétrahydrofurane. Méthodes analytiques. Montreal, Canada: Institut de recherche Robert-Sauvé en santé et en sécurité du travail. Available from: www.irsst.qc.ca/en/laboratories/references-tools/workplace-air-contaminant/substance/i/103/redirected/1.

Isaacson C, Mohr TKG, Field JA (2006). Quantitative determination of 1,4-dioxane and tetrahydrofuran in groundwater by solid phase extraction GC/MS/MS. *Environ Sci Technol*, 40(23):7305–11. doi:10.1021/es0615270 PMID:17180982

Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N, et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:10.1021/tx3000939 PMID:22519603

Kerckaert GA, Brauninger R, LeBoeuf RA, Isfort RJ (1996). Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. *Environ Health Perspect*,

104(Suppl 5):1075–84. doi:10.1289/ehp.96104s51075 PMID:8933057

Li CQ, Cohen KA, Zhuang G (1998). A capillary gas chromatographic procedure for the analysis of nine common residual solvents in water-insoluble bulk pharmaceuticals. *J Chromatogr Sci*, 36(3):119–24. doi:10.1093/chromsci/36.3.119

Matthews EJ, Spalding JW, Tennant RW (1993). Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in *Salmonella* and carcinogenicity in rodent bioassays. *Environ Health Perspect*, 101(Suppl 2):347–482. doi:10.1289/ehp.93101s2347 PMID:8243403

Moody DE (1991). The effect of tetrahydrofuran on biological systems: does a hepatotoxic potential exist? *Drug Chem Toxicol*, 14(4):319–42. doi:10.3109/01480549109011637 PMID:1811956

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986). *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen*, 8(Suppl 7):1–119. doi:10.1002/em.2860080802 PMID:3516675

Müller H (2012). Tetrahydrofuran. In: Ullmann's encyclopedia of industrial chemistry. Weinheim: Wiley-VCH Verlag GmbH & Co. KgaA.

National Library of Medicine (2017). Household products database. Tetrahydrofuran. Available from: https://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=341.

NICNAS (2016). Furan, tetrahydro-: human health Tier III assessment. Sydney, Australia: National Industrial Chemicals Notification and Assessment Scheme. Available from: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-iii-human-health/furan,-tetrahydro-.

NIOSH (1994). Tetrahydrofuran. Method 1609, issue 2. NIOSH manual of analytical methods (NMAM). 4th ed. Washington (DC), USA: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH).

NIOSH (2014). Tetrahydrofuran. International Chemical Safety Cards (ICSC). Washington (DC), USA: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health (NIOSH). Available from: https://www.cdc.gov/niosh/ipcsneng/neng0578.html.

NTP (1998). NTP toxicology and carcinogenesis studies of tetrahydrofuran (CAS No. 109-99-9) in F344/N rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*, 475:1–244. PMID:12571688

OECD (2000). Screening Information Dataset (SIDS) initial assessment profile for tetrahydrofuran. SIDS initial assessment meeting (SIAM) 10, 15–17 March 2000. Paris, France: Organisation for Economic Co-operation and Development.

OECD (2009). The 2007 OECD list of high production volume chemicals. Series on testing and assessment, No. 112. ENV/JM/MONO(2009)40. Paris, France: Organisation for Economic Co-operation and Development. Available from: www.oecd.org/officialdocuments.

Ong CN, Chia SE, Phoon WH, Tan KT (1991). Biological monitoring of occupational exposure to tetrahydrofuran. *Br J Ind Med*, 48(9):616–21. PMID:1911404

Pellizzari ED, Hartwell TD, Harris BSH 3rd, Waddell RD, Whitaker DA, Erickson MD (1982). Purgeable organic compounds in mother's milk. *Bull Environ Contam Toxicol*, 28(3):322–8. doi:10.1007/BF01608515 PMID:7082873

Prado C, Marin P, Alcaraz J, Periago JF (2010). Determination of tetrahydrofuran and ketones in urine by headspace technique. [Poster]. 28th International Symposium on Chromatography. Valencia, September 2010. Available from: http://www.carm.es/web/pagina?IDCONTENIDO=62286&IDTIPO=60&RASTRO=c911$m6407,3507,3670.

Rembold H, Wallner P, Nitz S, Kollmannsberger H, Drawert F (1989). Volatile components of chickpea (*Cicer arietinum* L.) seed. *J Agric Food Chem*, 37(3):659–62. doi:10.1021/jf00087a018

Ross IA (2005). Coffea arabica. In: Medicinal plants of the world, Volume 3: chemical constituents, traditional and modern medicinal uses. Totowa (NJ), USA: Humana Press; pp. 155–95. doi:10.1007/978-1-59259-887-8_4

Shahidi F, Rubin LJ, D'Souza LA, Teranishi R, Buttery RG (1986). Meat flavor volatiles: a review of the composition, techniques of analysis, and sensory evaluation. *Crit Rev Food Sci Nutr*, 24(2):141–243. doi:10.1080/10408398609527435 PMID:3527563

Stivala LA, Savio M, Cazzalini O, Pizzala R, Rehak L, Bianchi L, et al. (1996). Effect of beta-carotene on cell cycle progression of human fibroblasts. *Carcinogenesis*, 17(11):2395–401. doi:10.1093/carcin/17.11.2395 PMID:8968054

Stoffelsma J, Pypker J (1968). Some new constituents of roasted coffee. *Recl Trav Chim Pays Bas*, 87(3):241–2. doi:10.1002/recl.19680870302

Stoffelsma J, Sipma G, Kettenes DK, Pypker J (1968). New volatile components of roasted coffee. *J Agric Food Chem*, 16(6):1000–4. doi:10.1021/jf60160a010

Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:10.1289/ehp.1205784 PMID:23603828

UNECE (2015). Recommendations on the transport of dangerous goods. Model regulations, Volume I. 19th revised edition. New York (NY), USA, and Geneva, Switzerland: United Nations Economic Commission for Europe.

Valencia R, Mason JM, Woodruff RC, Zimmering S (1985). Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ Mutagen*, 7(3):325–48. doi:10.1002/em.2860070309 PMID:3930234

van Ravenzwaay B, Gamer AO, Leibold E, Kaufmann W (2003). Effect of cytochrome P-450 inhibition on tetrahydrofuran-induced hepatocellular proliferation in female mice. *Arch Toxicol*, 77(8):459–64. doi:10.1007/s00204-003-0474-7 PMID:12802580

Walter W, Weidemann H-L (1969). [Chemical compounds of the coffee aroma]. *Z Ernahrungswiss*, 9(2):123–47. [German] doi:10.1007/BF02021495 PMID:5796636