A white mouse is shown in profile, facing left, in a laboratory setting. The mouse is standing on a reflective surface, and its reflection is visible below it. In the background, there are various pieces of laboratory glassware, including a large Erlenmeyer flask and a smaller flask, all slightly out of focus. The overall scene is dimly lit, with the mouse being the central focus.

SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

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OF CARCINOGENIC RISKS
TO HUMANS

FURFURYL ALCOHOL

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 98-00-0

Chem. Abstr. Serv. name: Furanmethanol

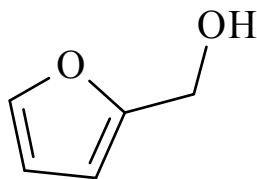
EC name: Furfuryl alcohol

IUPAC systematic name: 2-Furylmethanol

Synonyms: 2-Furanmethanol, furfurol, 2-(hydroxymethyl)furan, 2-furylcarbinol; 2-furancarbinol; α -furylcarbinol; furfuralcohol

From [NTP \(1999\)](#); [European Commission \(2011\)](#)

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: C₅H₆O₂

Relative molecular mass: 98.10 ([NTP, 1999](#))

1.1.3 Chemical and physical properties

Description: Furfuryl alcohol is a colourless or pale yellow liquid with characteristic “burning” odour and bitter taste; it turns red or brown on exposure to light and air

Boiling point: 170 °C

Melting point: -15 °C

Density: 1.1296 g/cm³ at 20 °C

Solubility: Very soluble in ethanol and ethyl ether, soluble in ketone and chloroform; it dissolves cellulose nitrate, some dyes and synthetic resins ([Ellis, 1972](#)); it is miscible with water, forming an azeotrope at atmospheric pressure (water, 80 wt%; boiling point, 98.5 °C).

Volatility: Vapour pressure, 53 kPa at 20 °C

Flash point: 65 °C (tag closed cup)

Explosive limits: 1.8–16.3 vol% in air

Stability: Pure furfuryl alcohol decomposes upon standing for extended periods; it should be stored in a dark bottle in a refrigerator at 0 °C ([NIOSH, 1994](#))

Relative vapour density: 3.4 (air = 1)

Octanol/water partition coefficient (P): log K_{ow}, 0.28

Odour threshold: About 28 mg/m³ in humans; 50% response at 8 ppm

Conversion factor: 1 ppm = 4.01 mg/m³ at normal temperature (25 °C) and pressure (103.5 kPa)

Impurities: No data on impurities were available; overall purity is usually > 98% ([NTP, 1999](#); [Hoydonckx, 2007](#)).

From [NTP \(1999\)](#); [Lide \(2005\)](#); [Hoydonckx \(2007\)](#); [European Commission \(2011\)](#).

1.2 Production and use

1.2.1 Production process

Furfuryl alcohol is produced industrially by the hydrogenation of furfural. Vapour-phase reaction or liquid-phase reaction are both used, although the vapour-phase reaction at atmospheric pressure is currently the most widely employed, except in China ([Chen et al., 2002](#); [Hoydonckx, 2007](#); [ITC, 2012](#)).

Furfural contains two kinds of reactive group – a carbonyl group and carbon–carbon double bonds; hydrogenation of the former gives furfuryl alcohol, and hydrogenation of the latter results in tetrahydrofurfural. The catalytic hydrogenation of the furfural carbonyl group requires the presence of heterogeneous or homogeneous catalysts. The heterogeneous copper chromite catalyst has been used at an industrial scale for more than six decades ([Villaverde et al., 2013](#)); however, the toxicity and carcinogenic potential associated with chromite ([IARC, 1990](#); [Chen et al., 2002](#)), and environmental problems associated with deactivated copper chromite catalyst have prompted the development of other catalysts based on copper ([Vargas-Hernández et al., 2014](#); [Jiménez-Gómez et al., 2016](#)), nickel ([Baijun et al., 1998](#); [Li et al., 2003](#); [Kotbagi et al., 2016](#)), ruthenium ([Tukacs et al., 2017](#)), platinum, and palladium ([O’Driscoll et al., 2017](#)), among others.

Production of furfuryl alcohol from xylose over a dual heterogeneous catalyst system has also been described ([Perez & Fraga, 2014](#); [Cui et al., 2016](#)).

The potential of microbial conversion of furfural for the production of furfuryl alcohol

has been explored as an alternative; however, it is still relatively understudied and not widely applied ([Mandalika et al., 2014](#)).

1.2.2 Production volume

Global production of furfuryl alcohol was estimated at about 300 000 tonnes in 2015 ([Grand View Research, 2015](#)). Furfuryl alcohol is listed by the Organisation for Economic Co-operation and Development (OECD) ([OECD, 2018](#)) and the United States Environmental Protection Agency (EPA) as a chemical with a high production volume, with more than 1 million pounds [more than 453 tonnes] produced annually ([Franko et al., 2012](#)). China is the main global manufacturer and user of furfuryl alcohol, with 80–85% of global capacity and production, and about 60% of global consumption in 2015 ([IHS Markit, 2016](#)). Between 10 000 and 100 000 tonnes are manufactured and/or imported into the European Economic Area each year ([ECHA, 2018a](#)). A single industrial plant in Belgium produced around 40 000 tonnes per year ([IFC, 2016](#)). The database ChemSources-Online lists 31 manufacturing companies worldwide ([Chemical Sources International, 2017](#)).

1.2.3 Use

It has been estimated that the production of furan resins for foundry sand binders in the metal casting industry accounted for about 85–90% of furfuryl alcohol used worldwide ([IHS Markit, 2016](#)). Furfuryl alcohol is also used as a wetting agent and as a solvent for dyes and as corrosion inhibitor in fibre-reinforced plastics, in cements and mortars, and in wood protection. Applications also include use in flavours and fragrances. Moreover, furfuryl alcohol is used as a laboratory reagent and as a chemical building block for drug synthesis ([Sriram & Yogeewari, 2010](#); [European Commission, 2011](#); [IHS Markit, 2016](#)). In addition, the product of

Table 1.1 Representative methods for the analysis of furfuryl alcohol

Sample matrix	Assay procedure	Limit of detection	Reference
Air of workplace	TDS-GC-FID	2.25 mg/m ³ (LOQ)	Tschickardt (2012)
	TDS-GC-FID	NR	ISO (2000, 2001) ; NIOSH (1994)
Dust particles	GC-UV	≤ 0.4 µg/g	Nilsson et al. (2005)
Foundry resins	GC-FID	173 µg/L	Oliva-Teles et al. (2005)
	LC-UV	5.2 mg/L	
Fruit juices	LC-UV	3 mg/L	Yuan & Chen (1999)
Environmental water	GC-MS	0.02 µg/L	Kawata et al. (2001)
Roasted coffee	SPME-GC-MS	NR	Yang & Peppard (1994)
Wine	SPME-GC-MS	7 µg/L	Carrillo et al. (2006)
Coffee	HS-SPME-GC-MS	0.59 mg/L	Petisca et al. (2013a)
Coffee	NMR	3.2 mg/L	Okaru & Lachenmeier (2017)
Deep-fried products	HS-SPME-GC-MS	1.5 mg/kg	Pérez-Palacios et al. (2012)

GC-FID, gas chromatography-flame ionization detector; GC-MS, gas chromatography-mass spectrometry; GC-UV, gas chromatography-ultraviolet spectrometry; HS, headspace; LC-UV, liquid chromatography-ultraviolet spectrometry; LOQ, limit of quantification; NMR, nuclear magnetic resonance; NR, not reported; SPME, solid-phase microextraction; TDS, thermal desorption system

the hydrogenation of furfuryl alcohol, tetrahydrofurfuryl alcohol, is used in plant protection products ([ECHA, 2018b](#)).

1.3 Analytical methods

Representative methods for the analysis of furfuryl alcohol in environmental and food matrices are summarized in [Table 1.1](#). In general, gas chromatography with mass spectrometry (GC-MS) is preferred due to its higher sensitivity.

Thermal desorption combined with GC-MS or with gas chromatography-ultraviolet spectrometry (GC-UV) has been used to analyse furfuryl alcohol adsorbed to indoor dust particles ([Nilsson et al., 2005](#)).

Extraction of furfuryl alcohol from food matrices (before chromatographic analysis) can be performed by different methods, namely solvent extraction, solid-phase extraction, simultaneous distillation extraction, and solid-phase microextraction ([Yang & Peppard, 1994](#); [Cocito et al., 1995](#); [Spillman et al., 1998](#); [Gómez Plaza et al., 1999](#); [Jerković et al., 2007](#)).

Headspace-solid phase microextraction methods are advantageous for the analysis of

volatile compounds like furfuryl alcohol ([Carrillo et al., 2006](#); [Pérez-Palacios et al., 2012](#); [2013](#); [2014](#); [Petisca et al., 2013a, 2013b, 2014](#)). The first reports on analysis indicated headspace incubation and extraction temperatures of 80 °C for at least 30 minutes ([EFSA, 2004](#)), but temperature was later reduced to 60 °C ([FDA, 2005](#)), and even lower ([Pérez-Palacios et al., 2012](#)), to avoid formation of additional amounts of furanic compounds during analysis.

1.4 Occurrence and exposure

1.4.1 Occurrence

Due to its high production volume and large number of industrial and consumer uses, furfuryl alcohol is ubiquitous in the environment.

Should furfuryl alcohol be released to the soil, it is expected to have very high mobility based upon an estimated soil adsorption coefficient, K_{oc} , of 34. If released into water, furfuryl alcohol is not expected to adsorb to suspended solids and sediment, based upon an observed degradation of 75–79% in 2 weeks. If released to air, furfuryl alcohol will exist solely as a vapour

in the atmosphere (on the basis of its vapour pressure), and will be degraded by reaction with photochemically produced hydroxyl radicals. The half-life for this reaction is estimated to be 3.7 hours. Furfuryl alcohol may also be susceptible to direct photolysis by sunlight, on the basis of its absorption of ultraviolet light at wavelengths > 290 nm ([National Library of Medicine, 2018](#)).

Furfuryl alcohol has been identified as a side product in Maillard reactions ([Schirle-Keller & Reineccius, 1992](#); [Chen & Ho, 1999](#)). Its formation from glucose in aqueous systems has been described. The mechanism involves the oxidation of glucose to gluconic acid, which is decarboxylated to a pentitol and followed by dehydration and cyclization to furfuryl alcohol ([Wnorowski & Yaylayan, 2000](#); [Yaylayan & Keyhani, 2000](#)). Likewise, sugar degradation, or hydrolysis and heating of polysaccharides containing hexoses or pentoses, can result in the formation of furfuryl alcohol. Glucose or fructose can undergo isomerization reactions at high temperatures. The intermediate compounds formed will react further by cyclization and aromatization, forming furfuryl alcohol ([Brands & van Boekel, 2001](#); [Murkovic & Swasti, 2013](#)).

Furfuryl alcohol occurs naturally in some types of fruit, and in tea, coffee, and cocoa ([European Commission, 2011](#)), and in many foods, mainly due to food processing, storage or ageing, or its addition in flavouring agents. These flavouring agents have low taste thresholds and deliver a characteristic cocoa, butter, or fruity odour. Thermal processing (e.g. roasting, baking, or deep-frying) to obtain a desirable flavour increases the formation of furfuryl alcohol ([Pérez-Palacios et al., 2012, 2013, 2014](#); [Petisca et al., 2013a, b](#)). Dried ([Giannetti et al., 2014](#); [Pasqualone et al., 2014](#)), cured or smoked ([Yu et al., 2008](#)), fermented, stored, or aged products ([Spillman et al., 1998](#); [Karagül-Yüceer et al., 2002](#); [Qian & Reineccius, 2002](#); [Morales et al., 2004](#); [Vanderhaegen et al., 2004](#); [Giri et al., 2010](#); [Lidums, et al., 2015](#), [Liang et al., 2016](#), [Harada](#)

[et al., 2017](#); [Pico et al., 2017](#)) also contain furfuryl alcohol.

Among the many heterocyclic compounds reported to be present in roasted coffee, furans were found to be abundant ([Flament & Bessiere-Thomas, 2002](#); [Petisca et al., 2013a](#)). The formation of furanic compounds in roasted coffee has been attributed to Maillard reactions; however, degradation of less volatile coffee constituents, such as quinic, caffeic, and chlorogenic acids can also result in the formation of furfuryl alcohol ([Moon & Shibamoto, 2010](#)).

During wine ageing, furfuryl alcohol is formed by microbiological reduction of the furfuryl aldehydes ([Spillman et al., 1998](#)). The concentration of furfuryl alcohol in wine in all of the sampled oak barrels was reported to be low during the first 180 days of maturation, but increased rapidly from day 180 to day 270, coinciding with spring and summer, when high temperature favours microfloral growth and enzyme activity ([Pérez-Prieto et al., 2003](#)).

Furfuryl alcohol is also found in beer. In pale beers, the concentration of furfuryl alcohol is essentially determined by the “thermal load” on wort (from heating and boiling) during brewing operations, while in dark beers a considerable fraction of furfuryl alcohol may come from the dark malts used ([Vanderhaegen et al., 2004](#)).

Products that are prepared using processes involving a short, rapid cooking method at quite high temperatures are associated with a relatively high content of furfuryl alcohol, as in the case of rice cakes and deep-fried products ([Buttery et al., 1999](#); [Pérez-Palacios et al., 2014](#)). The influence of cooking and handling conditions on the quantity of furfuryl alcohol and other furanic compounds in deep-fried breaded fish products has been studied ([Pérez-Palacios et al., 2013](#)). The content of furanic compounds in these products was lower after oven-baking or reheating in a microwave oven than after deep-frying. The content of furfuryl alcohol (and generation of furanic compounds) decreased with decreasing

temperature and duration of deep-frying, and also when there was a delay after deep-frying and before sampling. Adjusting the cooking method and conditions by using an electric oven, deep-frying in sunflower oil at 160 °C for 4 minutes, or waiting 10 minutes after cooking are strategies that could be applied to reduce the furfuryl alcohol content of breaded fish products ([Pérez-Palacios et al., 2013](#)).

1.4.2 Exposure in the general population

The general population is exposed to furfuryl alcohol mainly in food and beverages, but exposure can also occur via inhalation and the dermal route ([NIOSH, 2015](#); [IFA, 2017](#)). [The Working Group noted that there may be potential inhalation exposure from cigarette smoke or electronic cigarette aerosols, but no studies were available.]

Most reported individual foods contained low or trace amounts of furfuryl alcohol, but the cumulative amount ingested could contribute significantly to exposure. The major source of furfuryl alcohol in foods is thermal processing and ageing of alcoholic beverages ([Okaru & Lachenmeier, 2017](#)). The concentrations of furfuryl alcohol in certain items can reach several thousands of micrograms per litre or per kilogram, as summarized in [Table 1.2](#). Coffee, bread, baked goods, deep-fried fish, and some spirits may contain furfuryl alcohol at high levels; however, there is great variability according to the degree of roasting or the preparation procedure used.

Since furfuryl alcohol is an approved food flavouring additive, exposure will increase with the consumption of foods that contain added furfuryl alcohol. Daily intake of flavouring substances was evaluated by two different methods: maximized survey-derived daily intake (MSDI) estimated from annual production data for flavours, and possible average daily intake (PADI). The latter calculates an exaggerated intake, since it makes the assumption that the

flavouring agent is used at the average use level in all foods within a category of foods in which the flavour was anticipated to be used by industry. As expected, the two methods give different results, because PADI provides a substantial overestimation of the actual intake. However, this higher estimation of intake is useful to determine whether margins of safety are still adequate in a worst-case scenario ([Munro & Danielewska-Nikiel, 2006](#)). The estimated furfuryl alcohol intake was 4 µg/kg bw per day when calculated by MSDI, and 130 µg/kg bw per day by PADI ([Munro & Danielewska-Nikiel, 2006](#)).

[The Working Group estimated that, based on a furfuryl alcohol concentration of 70 mg/L, one cup of 30 mL of espresso coffee represents an intake of 2 mg of furfuryl alcohol, or about 0.03 mg/kg bw (body weight, 70 kg). Based on a consumption of 4 kg of roasted coffee for European Union inhabitants per year and average content of 250 mg/kg in roasted coffee, per capita intake would be 3 mg/day, assuming the worst-case scenario of complete extraction of furfuryl alcohol into the liquid.]

[The Working Group noted that current exposure estimates (MSDI and PADI) that are based only on added flavouring agents underestimate total intake because of the additional contribution from foods and beverages that contain furfuryl alcohol as a result of cooking or preparation processes (e.g. coffee).]

1.4.3 Occupational exposure

See [Table 1.3](#)

Workplace exposure to furfuryl alcohol can occur in the chemical industry when furfuryl alcohol is used in the manufacture of other products, and in a variety of end-user situations when furfuryl alcohol is emitted as a process-generated substance.

Furfuryl alcohol is used in polymers, laboratory chemicals, and coating products, and in the manufacture of chemicals and plastic

Table 1.2 Occurrence of furfuryl alcohol in food and beverages

Food item	Furfuryl alcohol content	Reference
<i>Liquids</i>		
Turkish coffee	14 691 µg/L	Amanpour & Selli (2016)
French press coffee	13 799 µg/L	Amanpour & Selli (2016)
Espresso coffee	31 000–70 000 µg/L	Petisca et al. (2014)
Aged wines	350–850 µg/L	Pérez-Prieto et al. (2003)
Aged wines	3500–9600 µg/L	Spillman et al. (1998)
Beer	1800–4000 µg/L	Vanderhaegen et al. (2004)
Wine vinegar	ND–594 µg/L	Tesfaye et al. (2004)
Cereal vinegar	35–40 µg/L	Liang et al. (2016)
<i>Solids</i>		
Instant coffee	267 000 µg/kg	Golubkova (2011)
Filter coffee	1 430 000 µg/kg	Golubkova (2011)
Roasted coffee	158 000–1 340 000 µg/kg	Golubkova (2011)
Roasted coffee	251 000 µg/kg	Okaru & Lachenmeier (2017)
Baked goods	110 000 µg/kg	Okaru & Lachenmeier (2017)
Bread	187 000 µg/kg	Okaru & Lachenmeier (2017)
Deep-fried coated fish	4580–22 280 µg/kg	Pérez-Palacios et al. (2012, 2013, 2014)
Toasted almonds	4400–8880 µg/kg	Vázquez-Araújo et al. (2008)
Fish miso	612–40 761 µg/kg	Giri et al. (2010)
Soy miso	4366 µg/kg	Giri et al. (2010)
Rice miso	1290 µg/kg	Giri et al. (2010)
Non-fat dried milk (stored 3 months)	14 500 µg/kg	Karagül-Yüceer et al. (2002)
Rice cake	2000–2300 µg/kg	Buttery et al. (1999)
Corn tortilla chips	540 µg/kg	Buttery & Ling (1998)
Popcorn	38.2–82.1 µg/kg	Park & Maga (2006)
Sweet potatoes	14 µg/kg	Wang & Kays (2000)
Honey	1550 µg/kg	Vazquez et al. (2007)
Citrus honeys	44–61 µg/kg	Escriche et al. (2011)
Citrus honeys	5.5–23.5 µg/kg	Castro-Vázquez et al. (2007)
Roasted cocoa powder	0–69 µg/kg	Bonvehí (2005)
Wheat bread	0.187–0.613 µg/kg	Jensen et al. (2011)

ND, not detected

products. Chemical manufacturing is carried out in enclosed process systems, which minimize potential workplace exposure. [NIOSH \(1979\)](#) described measurements made in the 1970s at two plants manufacturing furfuryl alcohol in the USA; these were mostly < 0.4 mg/m³. No recent published exposure measurements for the use of furfuryl alcohol in manufacturing industry were available to the Working Group. Occupational exposure may occur by inhalation and skin contact.

Around 85–90% of furfuryl alcohol is used to produce furan resins for use in the foundry industry ([IHS Markit, 2016](#)), and the available exposure data for this substance were mostly from foundry operations. These resins have been increasingly used in foundry operations since the 1960s. Furan binders are copolymers of furfuryl alcohol in urea–formaldehyde and phenol–formaldehyde resins ([Kim et al., 1998](#)). Unhardened resin contains free furfuryl alcohol, small amounts of free formaldehyde, and other

Table 1.3 Occupational exposure to furfuryl alcohol

Reference	Location, collection date	Description of occupation or work task	Sampling matrix; approach; N; duration	Agent, exposure level ^a	Exposure range	Comments
Low & Mitchell (1985)	Australia, around 1984	Foundry Furan mould process: mixing machine	Air; personal; N = NR; NR	Furfuryl alcohol NR	3–8 ppm [12–32 mg/m ³]	
Low & Mitchell (1985)	Australia, around 1984	Foundry Furan mould process: general foundry	Air; personal; N = NR; NR	Furfuryl alcohol NR	10–50 ppm [40–200 mg/m ³]	
Virtamo & Tossavainen (1976)	Finland, around 1976	Foundry Furan mould process	Air; personal; N = 36; 1–2 h	Furfuryl alcohol 4.6 ppm [18.4 mg/m ³]	0.2–40 ppm [0.8–160 mg/m ³]	Measurements made in the core-making areas of 10 iron and steel foundries; 22% of results exceeded 5 ppm [20 mg/m ³] (the TLV)
Pfafli et al. (1985)	Finland, around 1984	Foundry	Urine; biological; N = 6; NR	Furoic acid in urine NR	20–1300 µmol/ mmol creatinine	Data extracted from Fig. 4 of Pfafli et al. (1985)
Landberg et al. (2015)	Sweden, around 2015	Foundry Core-making	Air; personal; N = 3; 2 h	Furfuryl alcohol 40 mg/m ³	30–54 mg/m ³	In core-making, a core of about 0.3–1 m ³ was made by pouring sand mixed with furfuryl alcohol into a mould. This scenario was carried out for about 2 h per day, every day of the week. There were no other sources. No control measures or personal protection were used, and the work was performed in a large work room with general ventilation
Ahman et al. (1991)	Sweden, around 1991	Foundry Furan mould and core-makers	Air; personal; N = 40; 8 h	Furfuryl alcohol 7 mg/m ³	< 1–15 mg/m ³	Over short periods of time (sampling time in general, 15–30 min), the mean concentrations in six subjects exceeded the present short-term exposure limit recommended in Sweden (STEL, 40 mg/m ³). During manual filling and packing of big moulding boxes, occasional peak concentrations of up to 100 mg/m ³ were recorded on a direct-reading instrument In general, exposure concentrations of furfuryl alcohol observed in the moulding group were higher than those measured in the core-making group

Table 1.3 (continued)

Reference	Location, collection date	Description of occupation or work task	Sampling matrix; approach; N; duration	Agent, exposure level ^a	Exposure range	Comments
Westberg et al. (2001)	Sweden, 1992–1995	Foundry Furan moulds in an aluminium foundry	Air; personal; N = 3; 8 h	Furfuryl alcohol 2.4 mg/m ³ Geometric mean	0.8–23 mg/m ³	
NIOSH (1979)	USA, 1976	All Furfuryl alcohol manufacture	Air; personal; N = 24; NR	Furfuryl alcohol < 0.1 ppm [< 0.4 mg/m ³]	< 0.1–0.2 ppm [< 0.4–0.8 mg/m ³]	
NIOSH (1979)	USA, 1978	All Furfuryl alcohol manufacture	Air; personal; N = 4; NR	Furfuryl alcohol 0.3 ppm [1.2 mg/m ³]	0.2–0.4 ppm [0.8–1.6 mg/m ³]	
NIOSH (1972)	USA, 1972	Foundry Core-maker, assistant and apprentice	Air; personal; N = 3; 8 h	Furfuryl alcohol < 20 mg/m ³ Median	< 20–25 mg/m ³	
NIOSH (1973)	USA, 1973	Foundry Core-making	Air; environmental; N = 1; 8 h	Furfuryl alcohol 2.2 ppm [8.8 mg/m ³]	NA	Furfuryl alcohol was measured at: 2.2 ppm [8.8 mg/m ³] during normal conditions that day and collected over a complete core production cycle (1 h); 8.6 ppm [34.4 mg/m ³] under normal conditions and during the core preparation time only (15 min); 10.8 ppm [43.2 mg/m ³] during the core preparation when the sand was heated to a warm condition (15 min); and 15.8 ppm [63.2 mg/m ³] during the core preparation when the sand was hot (15 min)
OSHA (2018)	USA, 1984–2013	Various	Air; personal; N = 204; Various	Furfuryl alcohol 0.26 mg/m ³ Median	ND–20 mg/m ³	
INRS (2018)	France, 1987–2017	Various	Air; personal; N = 123; 61–149 min	Furfuryl alcohol 2.0 mg/m ³ Median	< 0.01–176 mg/m ³	Data from industrial manufacturing; measurement duration, > 60 min

^a Arithmetic mean unless otherwise reported
min, minute; NA, not applicable; ND, not detected; STEL, short-term exposure limit; TLV, threshold limit value

volatile agents. In foundries, furfuryl alcohol is emitted during sand mixing, moulding or core making, mould assembly, casting, knockout, shot-blasting and manual welding ([HSE, 2017](#)). Exposure levels vary according to the specific tasks being carried out. Early measurement data sets (1970s and 1980s) from foundries in Australia ([Low & Mitchell, 1985](#)) and Finland ([Virtamo & Tossavainen, 1976](#)) showed that workers could be exposed to peak concentrations of furfuryl alcohol of between 100 and 200 mg/m³, with a mean exposure of 17.2 mg/m³ reported by [Virtamo & Tossavainen \(1976\)](#). Average exposure levels were generally below 18 mg/m³. There may be coexposure to low air concentrations of formaldehyde and other volatile organic substances for core makers, with higher concentrations of these substances possibly occurring in general foundry operations. In a foundry, there could be more than one core-making process being used, and so coexposure to other volatile agents is possible.

In the United States Occupational Safety and Health Administration (OSHA) database of compliance exposure measurements, 204 measurements of exposure to furfuryl alcohol were collected between 1984 and 2014 from a variety of industries; 45% of the data were below the limit of detection and more than 95% were less than 20 mg/m³. The highest measurements were from iron foundries ([OSHA, 2018](#)). Similar data were available from France, and showed a similar pattern of general low exposure in the industrial manufacturing sector (123 measurements of more than 60 minutes duration, with 95% of the measured values being less than 35 mg/m³ ([INRS, 2018](#)).

The Finnish Institute of Occupational Health exposure database contained 16 measurements for inhalation exposure to furfuryl alcohol collected between 2012 and 2016. The measurements ranged from < 0.1 to 27 mg/m³, with the eight highest results from workers involved in

manufacturing paper and paperboard (arithmetic mean, 13 mg/m³) ([FIOH, 2018](#)).

1.5 Regulations and guidelines

For chemical use, the [ECHA \(2018a\)](#) requires the following warning: “Danger!”. According to the harmonized classification and labelling (ATP01) approved by the European Union, this substance is toxic if inhaled, harmful if swallowed, harmful in contact with skin, causes serious eye irritation, is suspected of causing cancer, may cause damage to organs through prolonged or repeated exposure, and may cause respiratory irritation.

Furfuryl alcohol is included in the most recent register of approved flavouring substances in Europe according to Regulation (EU) No 872/2012 ([European Commission, 2012](#)). However, if furfuryl alcohol is formed as a contaminant due to food processing, food legislation in Europe (Council Regulation 315/93) would demand that its content be reduced to as low as reasonably achievable (ALARA principle) ([Okaru & Lachenmeier, 2017](#)).

According to the regulations of the United States Food and Drug Administration (FDA), furfuryl alcohol is an “indirect food additive” for use only as a component of adhesives in packaging, transporting, or holding food in accordance with prescribed conditions ([FDA, 2017](#)). [According to the FDA, indirect food additives are substances that may come into contact with food as part of packaging or processing equipment, but are not intended to be added directly to food.]

In 1996, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) began a programme to evaluate the safety of food flavouring agents. To perform these evaluations, flavouring substances are first compiled into groups of structurally related materials, which are expected to present similar routes of metabolism and toxicity. JECFA has established a group

Table 1.4 Occupational exposure limits values for furfuryl alcohol as an air contaminant

Country or region	Limit value – 8 hours		Limit value – short-term		Comments
	ppm	mg/m ³	ppm	mg/m ³	
Australia	10	40	15	60	
Austria	5	20			
Belgium	10	41	15	61	
Canada (Ontario)	10	[40]	15	[60]	
Canada (Quebec)	10	40	15	60	
China		40		60*	*15 min average value
Denmark	5	20	10	40	
Finland	2	8.1	10*	41*	*15 min average value
France	10	40			
Hungary		40		40	
Ireland	5	20	15*	60*	*15 min reference period
Japan – JSOH	5	20			
New Zealand	10	40	15	60	
Poland		30		60	
Republic of Korea	10	40	15	60	
Singapore	10	40	15	60	
Spain	5	20	15	61	Skin
Sweden	5	20	10*	40*	*15 min average value
Switzerland	10	40	10	40	
United Kingdom	(5)	(20)	(15)	(61)	The United Kingdom Advisory Committee on Toxic Substances has expressed concern that, for the OELs shown in parentheses, health may not be adequately protected because of doubts that the limit was not soundly based. These OELs were included in the published United Kingdom 2002 list and its 2003 supplement, but are omitted from the published 2005 list
USA – NIOSH	10	40	15*	60*	*15 min average value
USA – OSHA	50	200			

From GESTIS international limit values ([IFA, 2017](#))

JSOH, Japanese Society for Occupational Health; NIOSH, National Institute for Occupational Safety and Health; OEL, occupational exposure level; OSHA, Occupational Safety and Health Administration

acceptable daily intake (ADI) of 0.5 mg/kg bw for furfuryl alcohol, furfural, furfuryl acetate, and methyl 2-furoate. For all animal species, the European Food Safety Authority (EFSA) has established a maximum proposed use level of furfuryl alcohol in complete feed of 5 mg/kg ([EFSA, 2016](#)).

The exposure limits for furfuryl alcohol as an air contaminant are summarized in [Table 1.4](#). In the USA, the National Institute for Occupational Safety and Health (NIOSH) has recommended a time-weighted average threshold limit value

(TLV–TWA) of 10 ppm (40 mg/m³) and a short-term exposure limit (TLV–STEL) of 15 ppm (60 mg/m³) for occupational exposure to furfuryl alcohol, to minimize the potential for eye and respiratory passageways irritation ([NIOSH, 2016](#)). In Germany in a 1992 reassessment, a “MAK” (TLV–TWA) value of 40 mg/m³ (10 mL/m³) was established because of data showing irritation of the respiratory tract ([MAK Commission, 2008](#)). However, in 2007, furfuryl alcohol was classified as “Carcinogen Category 3B”. In addition, workplace experience showed that irritation

of the respiratory tract and eyes occurred after exposure to furfuryl alcohol at concentrations of 1.75 mL/m³ and above, with peak concentrations of more than 10 mL/m³. Consequently, the previous MAK value of 10 mL/m³ was withdrawn ([MAK, 2016](#)).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See [Table 3.1](#)

3.1 Mouse

3.1.1 Inhalation

Groups of 50 male and 50 female B6C3F₁ mice (age, 6 weeks) were exposed to test atmospheres of furfuryl alcohol at 0 (control), 2, 8, or 32 ppm (purity, > 98%, impurities not characterized) by whole-body inhalation for 6 hours plus T₉₀ (12 minutes) per day, 5 days per week, for 105 weeks ([NTP, 1999](#)). Survival of exposed male and female mice was similar to that of the controls. Mean body weights of exposed male mice were similar to those of controls throughout the study. Mean body weights of exposed female mice were 7–14% lower than those of controls beginning at week 39 for mice at the highest dose and at week 59 for mice at the lowest and intermediate dose. Furfuryl alcohol was irritating and toxic to the nasal cavity in males and females. Nephropathy was observed in all groups of males and females. The severity of nephropathy increased with increasing exposure concentration in male mice. In male mice at the highest dose, there was an increase in the incidence of renal tubule adenoma (single section: 0/50, 0/49, 0/49, 2/50 (4%)), renal tubule carcinoma

(single section: 0/50, 0/49, 0/49, 2/50 (4%)), and renal tubule adenoma or carcinoma (combined) (single section: 0/50, 0/49, 0/49, 4/50 (8%)) that all exceeded historical control ranges for inhalation studies; there was a significant positive trend ($P = 0.002$, poly-3 test) in the incidence of renal tubule adenoma or carcinoma (combined). [Renal tubule neoplasms are uncommon in male B6C3F₁ mice.] In 2-year inhalation studies with untreated chamber controls carried out by the National Toxicology program (NTP), historical incidence (mean ± standard deviation) was: renal tubule adenoma (single section), 3/1093 (0.3% ± 0.6%); range, 0–2%; renal tubule carcinoma (single section), 1/1093 (0.1% ± 0.4%); range, 0–2%; and renal tubule adenoma or carcinoma (combined) (single section), 4/1093 (0.4% ± 1.0%); range, 0–4%. Additional analyses performed by step sectioning of the kidneys revealed an additional adenoma in males at the highest dose; the revised incidence for each group was thus 0/50 ($P = 0.009$, trend by poly-3 test), 0/49, 0/49, and 3/50 (6%). The incidence of renal tubule adenoma or carcinoma (combined) – standard (single section) evaluation and extended evaluation (step sections) combined – became 0/50 ($P < 0.001$, trend), 0/49, 0/49, 5/50 (10%), with the incidence in the group at the highest dose being significantly greater ($P = 0.036$, poly-3 test) than in the control group. There was no significant increase in the incidence of any tumours including those of the kidney in treated female mice. [The Working Group noted that this was a well-conducted study that complied with good laboratory practice (GLP), and was carried out in males and females.]

3.2 Rat

3.2.1 Inhalation

Groups of 50 male and 50 female F344/N rats (age, 6 weeks) were exposed to furfuryl alcohol at test atmospheres of 0 (control), 2, 8, or 32 ppm

Table 3.1 Studies of carcinogenicity in rodents treated with furfuryl alcohol by inhalation (whole-body exposure)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments	
Mouse, B6C3F ₁ (M) 6 wk 105 wk NTP (1999)	Purity, > 98% 0, 2, 8, 32 ppm 6 h plus T ₉₀ (12 min) per d, 5 d/wk, for 105 wk 50, 50, 50, 50 34, 36, 30, 38	<i>Kidney, standard (single section) evaluation</i>		Principal strengths: GLP study; study in males and females	
		Renal tubule adenoma: 0/50, 0/49, 0/49, 2/50 ^a	NS	^a Exceeded historical control ranges for inhalation studies Historical incidence: 3/1093 (0.3% ± 0.6%); range, 0–2%	
		Renal tubule carcinoma 0/50, 0/49, 0/49, 2/50 ^b	NS	^b Exceeded historical control ranges for inhalation studies Historical incidence: 1/1093 (0.1% ± 0.4%); range, 0–2%	
		Renal tubule adenoma or carcinoma (combined): 0/50*, 0/49, 0/49, 4/50 ^c	*P = 0.002 (poly-3 trend test)	^c Exceeded historical control ranges for inhalation studies Historical incidence: 4/1093 (0.4% ± 1.0%); range, 0–4%	
		<i>Kidney, standard (single section) evaluation and extended evaluation (step sections) (combined)</i>			
		Renal tubule adenoma: 0/50*, 0/49, 0/49, 3/50	*P = 0.009 (poly-3 trend test)		
Renal tubule carcinoma: 0/50, 0/49, 0/49, 2/50	NS				
Renal tubule adenoma or carcinoma (combined): 0/50*, 0/49, 0/49, 5/50**	*P < 0.001 (poly-3 trend test) **Significantly greater (P = 0.036) than the control group; poly-3 test				
Mouse, B6C3F ₁ (F) 6 wk 105 wk NTP (1999)	Purity, > 98% 0, 2, 8, 32 ppm 6 h plus T ₉₀ (12 min) per d, 5 d/wk, for 105 wk 50, 50, 50, 50 34, 33, 32, 40	Any tumour type: no significant increase		Principal strengths: GLP study; study in males and females	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Rat, F344/N (M) 6 wk 105 wk NTP (1999)	Purity, > 98%	<i>Nose</i>		Principal strengths: GLP study; study in males and females
	0, 2, 8, 32 ppm	Lateral wall adenoma:		
	6 h plus T ₉₀ (12 min)	0/50, 1/50, 0/50, 0/50	NS	
	per d, 5 d/wk, for	Respiratory epithelium adenoma:		
	105 wk			
	50, 50, 50, 50	0/50, 0/50, 1/50 ^a , 0/50	NS	^a Historical control incidence for inhalation studies: 1/897 (0.1% ± 0.5%); range, 0–2%
8, 5, 9, 0	Respiratory epithelium carcinoma:			
	0/50, 0/50, 0/50, 1/50 ^b	NS	^b Exceeded historical control incidence for inhalation studies: 0/897	
	Respiratory epithelium, squamous cell carcinoma:			
	0/50*, 0/50, 0/50, 3/50 ^b	*P = 0.006 (trend, poly-3 test)		
	Respiratory epithelium adenoma, carcinoma, or squamous cell carcinoma (combined):			
	0/50*, 1/50, 1/50, 4/50**	*P = 0.013 (trend) **P = 0.044 (poly-3 test)		
	<i>Kidney, standard (single section) evaluation</i>			
	Renal tubule adenoma:			
	1/50, 1/50, 2/50 ^c , 0/50	NS	^c Historical control incidence for inhalation studies: 9/902 (1.0% ± 1.2%); range, 0–4%	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Rat, F344/N (F) 6 wk 105 wk NTP (1999)	Purity, > 98% 0, 2, 8, 32 ppm 6 h plus T ₉₀ (12 min) per d, 5 d/wk, for 105 wk 50, 50, 50, 50 26, 26, 22, 16	<i>Kidney, standard (single section) evaluation</i>		Principal strengths: GLP study; study in males and females
		Renal tubule adenoma:	NS	^a Exceeded historical control incidence for inhalation studies Historical incidence: 1/898 (0.1% ± 0.5%); range, 0–2%
		0/50, 0/49, 0/49, 2/50 ^a		
		Renal tubule carcinoma:	NS	^b Historical control incidence for inhalation studies: 4/898 (0.5% ± 0.9%); range, 0–2%
		0/50, 1/49 ^b , 0/49, 0/50		
		Renal tubule adenoma or carcinoma (combined):	NS	^c Historical control incidence for inhalation studies: 5/898 (0.6% ± 0.9%); range, 0–2%
0/50, 1/49, 0/49, 2/50 ^c				
<i>Nose</i>				
Lateral wall adenoma:	NS			
0/49, 0/50, 1/48, 0/49				
Respiratory epithelium adenoma:	NS		^d Historical control incidence for inhalation studies: 1/892 (0.1 ± 0.5%); range, 0–2%	
0/49, 0/50, 0/48, 1/49 ^d				
Adenoma (lateral wall or respiratory epithelium, combined):	NS			
0/49, 0/50, 1/48, 1/49				

d, day; F, female; GLP, good laboratory practice; M, male; NS, not significant; T₉₀, time to achieve 90% of the target concentration after the beginning of vapour generation; wk, week

(purity, > 98%, impurities not characterized) by whole-body inhalation for 6 hours plus T₉₀ (12 minutes) per day, 5 days per week, for 105 weeks (NTP, 1999). All male rats exposed at 32 ppm died by week 99. Survival of all other exposed groups of male and female rats was similar to that of the control groups. Mean body weights of males at 32 ppm were less than those of the controls beginning week 19; mean body weights of males at 2 and 8 ppm, and of all exposed females were similar to those of the control groups throughout the study. Furfuryl alcohol was irritating and toxic to the nasal cavity in males and females. All groups of exposed males and females had significantly increased incidences of non-neoplastic lesions in the nose. In the nose, one (2%) lateral wall adenoma was observed in a male at 2 ppm, and one (2%) in a female at 8 ppm; one (2%) adenoma of the respiratory epithelium was observed in a male at 8 ppm (historical incidence, 1/897; range, 0–2%) and one (2%) female at 32 ppm (historical incidence, 1/892; range, 0–2%); one male at 32 ppm (2%) developed a carcinoma of the respiratory epithelium, and three other males at 32 ppm (6%) developed squamous cell carcinomas of the respiratory epithelium. Individually, the incidence per group was not significantly greater than that in the control groups. However, in males there was a significant positive trend in the incidence of squamous cell carcinoma of the respiratory epithelium ($P = 0.006$, poly-3 test), and the incidence of adenoma, carcinoma or squamous cell carcinoma (combined) of the respiratory epithelium was significantly increased in the group at the highest dose (4/50, 8%; $P = 0.044$ by poly-3 test) with a significant positive trend ($P = 0.013$, poly-3 test). Carcinomas and squamous cell carcinomas of the respiratory epithelium were not observed in males in historical controls (0/897) in previous NTP inhalation studies.

The incidence of renal tubule hyperplasia (single section) in exposed male and female rats was not significantly different from that of

controls. Renal tubule adenomas (single section) were observed in one (2%) male in the control group, one male (2%) at 2 ppm, two males (4%) at 8 ppm, and two females (4%) at 32 ppm (historical incidence (single section) in females: 1/898 (range, 0–2%); and one female (2%) at 2 ppm had a renal tubule carcinoma. The incidence was within the historical control range for male rats, but exceeded the historical control range for female rats. Additional analyses were performed by step sectioning of the kidneys, which revealed one additional renal tubule adenoma in each group of males for the controls, at 2 ppm, and at 8 ppm, and four additional adenomas in males at 32 ppm. The incidence of renal tubule adenoma or carcinoma (combined) – standard (single section) and extended evaluation (step sections) – in males became 2/50 (4%), 2/50 (4%), 3/50 (6%), 4/50 (8%). After step sectioning, two renal tubule adenomas were observed in females at 8 ppm and one in a female at 32 ppm, and a carcinoma was observed in a female at 2 ppm. The incidence of renal tubule adenoma or carcinoma (combined) – standard (single section) and extended evaluation (step sections) – in females became 0/50, 2/50 (4%), 2/50 (4%), 3/50 (6%); [the Working Group noted that incidence was incorrectly reported (typing error) in Table 10 of NTP (1999)]. [The Working Group noted this was a well-conducted GLP study in males and females.]

3.3 Transgenic animals

3.3.1 Skin application

Spalding et al. (2000) tested the tumorigenic activity of furfuryl alcohol using the Tg.AC transgenic mouse model (Tennant et al., 1996). Groups of 15–20 hemizygous female Tg.AC transgenic mice (age, 14 weeks) were treated with furfuryl alcohol (purity, > 98%) at a dose of 0, 0.25, 0.75, or 1.5 mg per mouse in 200 mL of acetone, by skin application, five times per week for 20 weeks. 12-*O*-Tetradecanoylphorbol-13-acetate (TPA)

(1.25 µg, three times per week) was used as a positive control. At 20 weeks, survival of the mice at the highest dose (90%) was lower than in the other treated groups and negative controls (100% in all groups). No information on body weights was provided. At 26 weeks, full histopathology was performed. No significant increase in the incidence of skin tumours (papillomas) was observed in mice exposed to furfuryl alcohol. Only one mouse at the intermediate dose developed a skin papilloma, while all mice treated with TPA had skin papillomas (100%). [The Working Group noted that this was a short-term, gene-specific assay in transgenic mice, and did not provide critical information that can be obtained in longer-term bioassays (e.g. effects on multiple target organs, interactions of time and age) ([Pritchard et al., 2003](#)).]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

The absorption, distribution, metabolism, and excretion of furfuryl alcohol and some related compounds were discussed in WHO Food Additive Series No. 46 ([WHO, 2001](#)). These chemicals were also briefly addressed in WHO Technical Report Series No. 974 ([WHO, 2012](#)).

4.1.1 Absorption, distribution, and excretion

(a) Humans

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

In humans exposed by inhalation to furfural (the primary oxidation product of furfuryl alcohol) (see [Fig. 4.1](#)), absorption was rapid and extensive. In male volunteers exposed by inhalation to furfural at vapour concentrations of

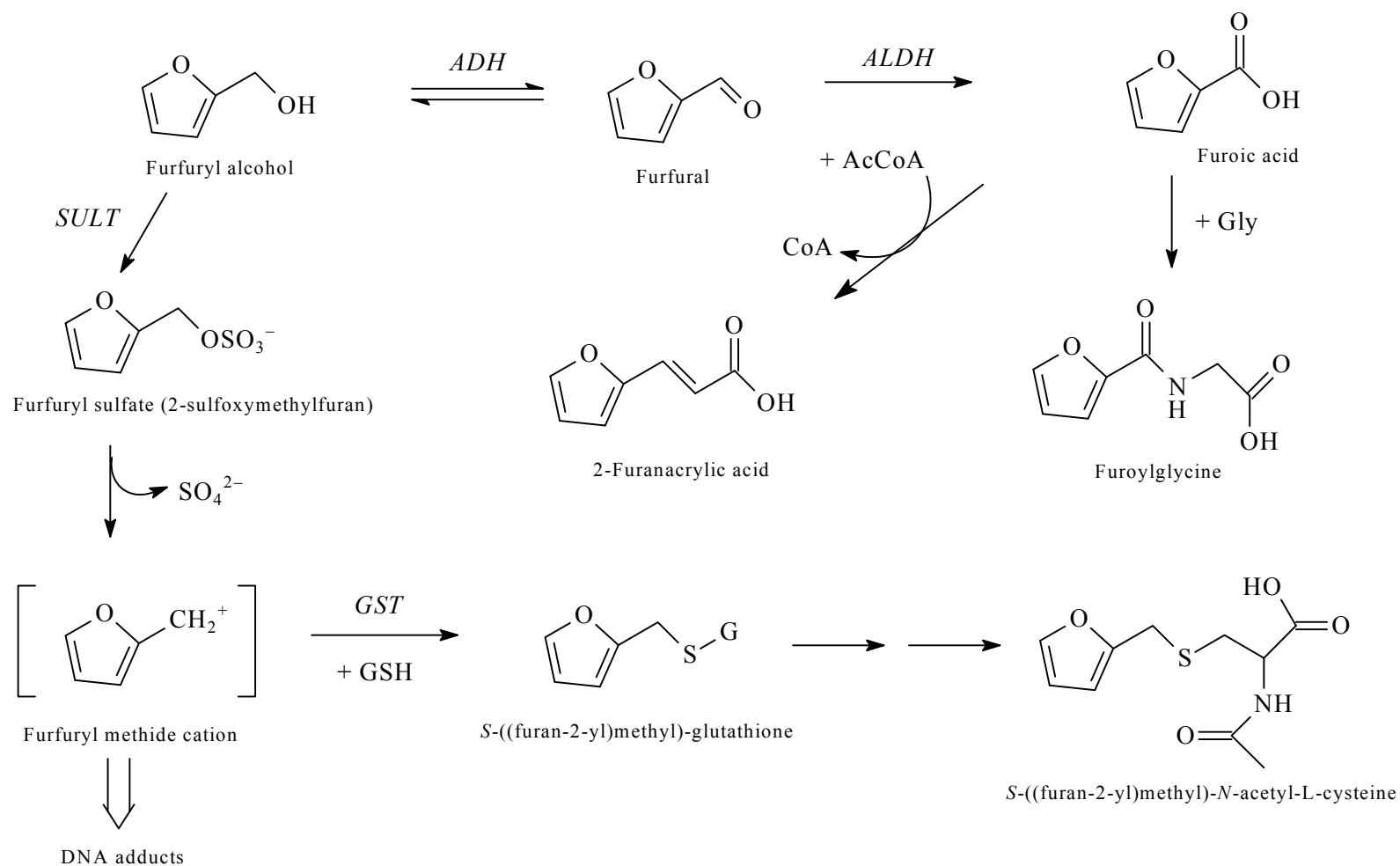
7–30 mg/m³ for 7.5 hours over an 8-hour period, pulmonary retention averaged ~78% regardless of vapour level or duration, and furfural quickly disappeared from the subjects' expired air after exposure ([Flek & Sedivec, 1978](#)). [Flek & Sedivec \(1978\)](#) also reported substantial percutaneous absorption of furfural vapour by male volunteers, particularly under warm and humid conditions.

(b) Experimental systems

Few data were available on the absorption, distribution, metabolism, and excretion of furfuryl alcohol in rodents.

Furfuryl alcohol and furfural are rapidly and extensively absorbed from the gastrointestinal tract in rodents. Furfural is converted to furfuryl alcohol by enteric bacteria under both aerobic and anaerobic conditions ([Boopathy et al., 1993](#)). In male rats treated by gavage with radiolabelled furfuryl alcohol (0.275, 2.75, or 27.5 mg/kg bw) or furfural (0.127, 1.15, or 12.5 mg/kg bw) in corn oil, an average of 86–89% of the administered dose of each compound was absorbed systemically ([Nomeir et al., 1992](#)). The liver and kidneys contained the highest levels of radiolabel at 72 hours after exposure. Both furfuryl alcohol and furfural were extensively metabolized, with 83–88% of the administered doses excreted in the urine within 72 hours. Furoylglycine, the glycine conjugate of furoic acid, was the major urinary metabolite (73–80% of the administered dose). In male and female F344 rats and CD-1 mice given a single oral dose of ¹⁴C-labelled furfural at a wide range of dose levels, the chemical was extensively absorbed and metabolized to furoylglycine and furanacryloyl-glycine, which were primarily excreted in the urine ([Parkash & Caldwell, 1994](#)). There were only minor metabolic differences according to dosage, species, and sex.

Fig. 4.1 Metabolism of furfuryl alcohol in humans and experimental animals



The predominant flux, based on recovery of urinary metabolites, is through the action of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) with conjugation to glycine to form furoylglycine. Small amounts of furfuryl alcohol can undergo sulfate conjugation with spontaneous removal of the sulfate moiety to generate a reactive and unstable intermediate (shown in brackets). Other abbreviations: AcCoA, acetyl-CoA; CoA, coenzyme A; Gly, glycine; G, glutathionyl moiety; GSH, glutathione; GST, GSH S-transferase; SULT, sulfotransferase. Adapted from [Sachse et al. \(2014\)](#). The effect of knockout of sulfotransferases 1a1 and 1d1 and of transgenic human sulfotransferases 1A1/1A2 on the formation of DNA adducts from furfuryl alcohol in mouse models, *Carcinogenesis*, 2014, volume 35, issue 10, p. 2339-2345, with permission of Oxford University Press

4.1.2 Metabolism

(a) Humans

Furfuryl alcohol appears to be rapidly and extensively metabolized by humans. The major metabolite detected in male volunteers who were treated by inhalation with furfural, as in mice and rats, was furoylglycine. A secondary urinary metabolite in humans and rodents was 2-furana-crylic acid (Flek & Sedivec, 1978). An alternate metabolic pathway involved formation of a mutagenic metabolite via sulfate conjugation. Human sulfotransferase 1A1 (SULT1A1) was efficient in catalysing the formation of 2-sulfoxymethylfuran, a reactive intermediate (Sachse et al., 2016a). SULT1A1 is found at high levels in many human tissues, including liver, lung, gastrointestinal tract, brain, and kidney (Glatt & Meinl, 2004).

(b) Experimental systems

Furfuryl alcohol is metabolized by mice and rats in much the same way as in humans. The major metabolic pathway involves the oxidation of furfuryl alcohol by alcohol dehydrogenase to furfural, which is subsequently oxidized to furoic acid. Furoic acid is excreted in the urine of mice and rats, as is its glycine conjugate (Parkash & Caldwell, 1994). Sulfate conjugation of furfuryl alcohol appears to be a minor pathway, quantitatively. In FVB/N mice given drinking-water containing furfuryl alcohol (~390 mg/kg bw) for 28 days, renal, pulmonary, and hepatic DNA adducts were detected by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MSMS) (Monien et al., 2011). Nucleoside adducts were also found in porcine liver DNA incubated with 2-sulfoxymethylfuran and also in DNA from furfuryl alcohol-exposed *Salmonella typhimurium* expressing the human sulfotransferase isoform SULT1A1 (Monien et al., 2011). In *Sult1a1* null mice given a single dose of furfuryl alcohol, levels of DNA adducts in the liver, kidney, lung, colon, and small intestine

were substantially lower than in wildtype mice (Sachse et al., 2014) (see Section 4.2.1). Sachse et al. (2016a) assessed the catalytic efficiencies of 30 sulfotransferase isoforms from mice and rats in metabolically activating furfuryl alcohol. Human SULT1A1 and mouse *Sult1a1* were considerably more efficient than the other isoforms in mediating formation of 2-sulfoxymethylfuran, a reactive DNA electrophile (Sachse et al., 2016a).

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Furfuryl alcohol has been studied in a variety of assays for genetic and related effects. Table 4.1, Table 4.2, Table 4.3, Table 4.4, and Table 4.5 summarize the results of studies carried out in exposed humans, in human cells in vitro, in non-human mammals, in non-human mammalian cells in vitro, and in non-mammalian systems, respectively.

(a) Humans

(i) Exposed humans

See Table 4.1

Furfuryl alcohol–DNA adducts were detected in non-tumour lung tissue of patients with cancer of the lung (Monien et al., 2015).

No effect on sister-chromatid exchange was observed in workers occupationally exposed to furfuryl alcohol and furfural. Exposure levels were not described, but duration of employment, age, and possible confounding factors such as smoking, X-ray during the 2 months before blood sampling, and recent viral infections were reported (Gomez-Arroyo & Souza, 1985).

(ii) Human cells in vitro

See Table 4.2

No induction of sister-chromatid exchange was observed in cultured human lymphocytes

Table 4.1 Genetic and related effects of furfuryl alcohol in exposed humans

End-point	Tissue or cell type	Description of exposed and controls	Results	Comments	Reference
DNA adducts, N ² -MFdG and N ⁶ -MFdA, UPLC-MS/MS	Lung	Non-tumour lung tissue from 10 (4 female, 6 male) lung cancer patients	+	Smoking status not reported	Monien et al. (2015)
Sister-chromatid exchange	Blood lymphocytes	Six workers occupationally exposed to furfuryl alcohol and furfural; six unexposed workers were used as control; both smokers and non-smokers were included	(-)	Exposure levels were not reported Causative effect of furfuryl alcohol alone could not be demonstrated	Gomez-Arroyo & Souza (1985)

^a +, positive; (-), negative result in a study of limited quality

N⁶-MFdA, N⁶-((furan-2-yl)methyl)-2'-deoxyadenosine; N²-MFdG, N²-((furan-2-yl)methyl)-2'-deoxyguanosine; UPLC-MS/MS, ultra-performance liquid chromatography-tandem mass spectrometry

Table 4.2 Genetic and related effects of furfuryl alcohol in human cells in vitro

End-point	Tissue, cell line	Results ^a	Concentration (LEC or HIC)	Comments	Reference
Sister-chromatid exchange	Cultured lymphocytes	-	9.9 mM [971 µg/mL]	4 donors	Gomez-Arroyo & Souza (1985)
Sister-chromatid exchange	Cultured lymphocytes	(-)	2.0 mM [196 µg/mL]	Number of donors not specified	Jansson et al. (1986)

^a -, negative; (-), negative result in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases
HIC, highest ineffective concentration; LEC, lowest effective concentration

treated with furfuryl alcohol ([Gomez-Arroyo & Souza, 1985](#); [Jansson et al., 1986](#)).

(b) Experimental systems

(i) Non-human mammals

See [Table 4.3](#)

Furfuryl alcohol–DNA adducts were detected in wildtype FVB/N mice and transgenic mice expressing human sulfotransferases SULT1A1 or SULT1A2 ([Monien et al., 2011](#); [Sachse et al., 2014, 2016b](#); [Høie et al., 2015](#)). Transgenic mice expressing human SULTs had a higher level of DNA adduct N²-((furan-2-yl)methyl)-2'-deoxyguanosine (N²-MFdG) compared with wildtype FVB/N mice ([Sachse et al., 2014, 2016b](#)).

Levels of DNA adducts were lower in FVB/N mice lacking functional mouse sulfotransferase

(*mSult1a1* null) than in wildtype mice ([Sachse et al., 2014](#)). The oral administration of ethanol or of 4-methylpyrazole (a competitive substrate and an inhibitor of alcohol dehydrogenase, respectively) before exposure to furfuryl alcohol increased the levels of furfuryl alcohol–DNA adducts in all tissues. Clear sex-specific differences were observed, with adduct levels in female mice being up to fivefold those in male mice ([Sachse et al., 2016b](#)). Negative results were reported in tests for the induction of sister-chromatid exchange, chromosomal aberrations, and micronucleus formation in bone marrow of B6C3F₁ mice treated with furfuryl alcohol ([NTP, 1999](#)).

Table 4.3 Genetic and related effects of furfuryl alcohol in non-human mammals

End-point	Species, strain	Tissue	Results ^a	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
DNA adducts, N ² -MFdG and N ⁶ -MFdA, LC-MS/MS	Mouse, FVB/N	Liver, kidney and lung (but not colon)	+	391 (M) or 393 (F) mg/kg bw	Oral, 28 d	Only one dose tested	Monien et al. (2011)
DNA adducts, N ² -MFdG, UPLC-MS/MS	Mouse, FVB/N (wt and <i>hSULT1A1/1A2</i> transgenic) ^b	Colon, liver (wt); small intestine, colon, liver (<i>hSULT1A1/1A2</i> transgenic)	+	250 mg/kg bw	Oral, 1×		Høie et al. (2015)
DNA adducts, N ² -MFdG and N ⁶ -MFdA, UPLC-MS/MS	Mouse, FVB/N (wt, knockout, <i>hSULT1A1/1A2</i> transgenic) ^c	Liver, lung, kidney, small intestine and colon	+	400 mg/kg bw	Intraperitoneal, 1×	Only one dose tested	Sachse et al. (2014)
DNA adducts, N ² -MFdG (all tissues) and N ⁶ -MFdA (liver only), UPLC-MS/MS	Mouse, FVB/N (wt and <i>hSULT1A1/1A2</i> transgenic) ^d	Liver, lung, kidney, small intestine and colon	+	400 mg/kg bw	Intraperitoneal, 1×	Only one dose tested	Sachse et al. (2016b)
Sister-chromatid exchange, chromosomal aberrations	Mouse, B6C3F ₁	Bone marrow cells	–	300 mg/kg bw	Intraperitoneal, 1×		NTP (1999)
Micronucleus formation	Mouse, B6C3F ₁	Bone marrow cells	–	125 mg/kg bw	Intraperitoneal, 3×		NTP (1999)

^a –, negative; +, positive; the level of significance was set at $P < 0.05$ in all cases

^b Two mouse cell lines: wt, and transgenic expressing human *SULT1A1/1A2*

^c Four mouse cell lines: wt, knockout deficient in either *Sult1a1* or *Sult1d1*, and transgenic expressing human *SULT1A1/1A2* while also being deficient for mouse *Sult1a1/1d1*

^d Two mouse cell lines: wt or transgenic expressing human *SULT1A1/1A2* while also being deficient for mouse *Sult1a1/1d1*

bw, body weight; d, day; F, female; HID, highest ineffective dose; *hSULT1A1/1A2*, human sulfotransferases 1A1/1A2; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LED, lowest effective dose; M, male; N⁶-MFdA, N⁶-((furan-2-yl)methyl)-2'-deoxyadenosine; N²-MFdG, N²-((furan-2-yl)methyl)-2'-deoxyguanosine; *Sult1a1/1d1*, sulfotransferases 1a1/1d1; UPLC-MS/MS, ultra-performance liquid chromatography tandem mass spectrometry; wt, wildtype

Table 4.4 Genetic and related effects of furfuryl alcohol in non-human mammalian cells in vitro

End-point	Species, cell line	Results ^a		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA strand breaks	Chinese hamster, V79 cells	–	NT	15 mM		Huffman et al. (2016)
DNA strand breaks	Chinese hamster, V79- <i>hCYP2E1-hSULT1A1</i> cells ^b	(+)	NT	15 mM	Marginal increase ($P = 0.04$); live cell count, 64%	Huffman et al. (2016)
Chromosomal aberrations	Chinese hamster ovary cells	(+)	(+)	2.5 mM, +S9; 20 mM, –S9	Results poorly reported	Stich et al. (1981)
Chromosomal aberrations	Chinese hamster ovary cells	–	±	500 µg/mL	Aroclor 1254-induced rat liver S9	NTP (1999)
Sister-chromatid exchange	Chinese hamster ovary cells	+	–	500 µg/mL	Aroclor 1254-induced rat liver S9	NTP (1999)

^a +, positive; –, negative; ±, equivocal (variable response in several experiments within an adequate study); (+), positive result in a study that had limitations in reporting or conduct; the level of significance was set at $P < 0.05$ in all cases

^b V79-derived cells co-expressing human cytochrome P450 2E1 (*hCYP2E1*) and human sulfotransferase 1A1 (*hSULT1A1*) genes
HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested; S9, 9000 × g supernatant

(ii) Non-human mammalian cells in vitro

See [Table 4.4](#)

Chromosomal aberrations were induced in Chinese hamster ovary (CHO) cells treated with furfuryl alcohol in the presence and absence of metabolic activation with S9 ([Stich et al., 1981](#)). [The Working Group noted that the results were poorly reported.] In another study, there was no induction of chromosomal aberrations in cultured CHO cells in the absence of metabolic activation; equivocal results were obtained in the presence of metabolic activation based on a positive response in one trial that was not reproduced in a second, follow-up trial ([NTP, 1999](#)). Furfuryl alcohol induced sister-chromatid exchange in cultured CHO cells without but not with metabolic activation ([NTP, 1999](#)). Furfuryl alcohol marginally increased the frequency of DNA damage measured by the comet assay (pH > 13) in Chinese hamster V79 cells expressing human cytochrome P450 2E1 (*hCYP2E1*) and *hSULT1A1*, but not in the parental V79 cell line ([Huffman et al., 2016](#)).

(iii) Non-mammalian systems

See [Table 4.5](#)

In *Drosophila melanogaster*, no mutagenic activity was observed in an assay that measured induction of sex-linked recessive lethal mutations in male germ cells or in a test for sex-chromosome loss ([Rodriguez-Arnaiz et al., 1989](#)).

Furfuryl alcohol was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, without or with metabolic activation ([Florin et al., 1980](#); [NTP, 1999](#); [Monien et al., 2011](#); [Glatt et al., 2012](#)). However, furfuryl alcohol was mutagenic in several TA100-derived strains expressing human and rodent sulfotransferases ([Monien et al., 2011](#); [Glatt et al., 2012](#)). DNA adducts were detected in DNA of furfuryl alcohol-exposed *Salmonella typhimurium* TA100 expressing *hSULT1A1*, but not in the parental strain (TA100) ([Monien et al., 2011](#)). In an acellular system, DNA adducts were detected after incubation of porcine liver DNA with 2-sulfoxymethylfuran ([Monien et al., 2011](#)).

Table 4.5 Genetic and related effects of furfuryl alcohol in non-mammalian systems

End-point	Species, strain, tissue	Results ^a		Agent, concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Sex-linked recessive lethal mutations, sex-chromosome loss	<i>Drosophila melanogaster</i> , germ-line cells	–	NA	1300 ppm		Rodriguez-Arnaiz et al. (1989)
Reverse mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537	(–)	(–)	3 µmol/plate	Only one dose tested	Florin et al. (1980)
Reverse mutation	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537	–	–	10 000 µg/plate		NTP (1999)
Reverse mutation	<i>Salmonella typhimurium</i> TA100	–	NT	10 µmol/plate		Glatt et al. (2012) ; Monien et al. (2011)
Reverse mutation	<i>Salmonella typhimurium</i> TA100-derived strains expressing human or rodent sulfotransferases	+	NT	0.1–1 µmol/plate		Glatt et al. (2012)
Reverse mutation	<i>Salmonella typhimurium</i> TA100-derived strains expressing human or rodent sulfotransferases	+	NT	25 nmol/plate		Monien et al. (2011)
DNA adducts, 2-methylfuryl adducts of dAMF, dGMF and dCMF, LC-MS/MS	DNA isolated from porcine liver	+	NT	2-sulfoxymethylfuran (sodium salt), 5 µmol/mL [5 mM]		Monien et al. (2011)
DNA adducts, N ² -MFdG and N ⁶ -MFdA, LC-MS/MS	<i>Salmonella typhimurium</i> TA100	–	NT	167 µM		Monien et al. (2011)
DNA adducts, N ² -MFdG and N ⁶ -MFdA, LC-MS/MS	<i>Salmonella typhimurium</i> TA100-derived strains expressing human sulfotransferases	+	NT	167 µM		Monien et al. (2011)

^a +, positive; –, negative; (–), negative result in a study of limited quality; the level of significance was set at $P < 0.05$ in all cases

dA, 2'-deoxyadenosine; dC, 2'-deoxycytidine; dG, 2'-deoxyguanosine; HIC, highest ineffective concentration; LEC, lowest effective concentration; LM-MS/MS, liquid chromatography-tandem mass spectrometry; N⁶-MFdA, N⁶-((furan-2-yl)methyl)-2'-deoxyadenosine; N²-MFdG, N²-((furan-2-yl)methyl)-2'-deoxyguanosine; NA, not applicable; NT, not tested; ppm, parts per million

4.2.2 Other mechanisms

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

One study reported on the immunotoxic potential of furfuryl alcohol in mice. Furfuryl alcohol was shown to be a sensitizer and an irritant in mice exposed dermally. Enhanced airway hyperreactivity, eosinophilic infiltration into the lungs, and enhanced cytokine production were observed after repeated pulmonary exposure, and the responses were augmented on dermal pre-exposure to furfuryl alcohol ([Franko et al., 2012](#)).

In 14-day and 13-week studies, lesions indicative of altered cell proliferation, cell death, and inflammation were observed in the nose (olfactory epithelium) of F344/N rats and B6C3F₁ mice treated with furfuryl alcohol at all concentrations tested (16–250 ppm for 14 days; 16–32 ppm for 13 weeks) ([Irwin et al., 1997](#); [NTP, 1999](#)). After long-term exposure, the incidence of nasal tumours was significantly increased in male F344/N rats only ([NTP, 1999](#); see Section 3).

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, 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

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

In a 2-year inhalation study of furfuryl alcohol (0, 2, 8, 32 ppm), the severity of nephropathy increased with concentration in male and female F344/N rats and in male B6C3F₁ mice. Furfuryl alcohol was irritating and toxic to the nose and induced non-neoplastic lesions of the nose in all exposed groups of rats and mice. Corneal degeneration occurred in female mice at 32 ppm ([NTP, 1999](#)).

In a 14-week study, furfuryl alcohol induced degeneration and metaplasia of the olfactory epithelium in F344/N rats and B6C3F₁ mice, and hyaline droplets in B6C3F₁ mice ([Irwin et al., 1997](#); [NTP, 1999](#)). In another short-term study in Swiss mice, hepatic and renal toxicity were observed after inhalation of furfuryl alcohol (2000 and 4000 ppm, respectively) ([Sujatha, 2008](#)). [The Working Group noted the high concentrations used in this study relative to those tested in the cancer bioassays.]

5. Summary of Data Reported

5.1 Exposure data

Furfuryl alcohol has several industrial applications, including production of furan resins, wetting agents, and as a solvent. It is listed as a chemical with a high production volume, with between 10 000 and 100 000 tonnes manufactured and/or imported into the European Economic Area each year. China is the main global manufacturer and user with around 85% of the global capacity.

The general population is exposed to furfuryl alcohol mainly in foods and beverages, since it is a contaminant that arises during food processing (such as roasting, drying, baking and deep-frying) to obtain a desirable flavour. Coffee,

deep-fried breaded products, and toasted foods may contain furfuryl alcohol at high levels. Furfuryl alcohol was included in the most recent register of approved flavouring substances by the European Commission, while the United States Food and Drug Administration regulations allow use of furfuryl alcohol only as an indirect food additive due to its occurrence in food contact materials. According to the United States Food and Drug Administration, indirect food additives are substances that may come into contact with food as part of packaging or processing equipment, but are not intended to be added directly to food. Estimates of intake from food additives are well below 0.15 mg/kg bw (body weight) per day. Consuming one cup of espresso coffee leads to an intake of furfuryl alcohol of about 0.03 mg/kg bw. An acceptable daily intake of 0.5 mg/kg bw was established for furfuryl alcohol.

Occupational exposure may occur by inhalation and skin contact. In general, exposure levels registered in the industrial manufacturing sector, both in the USA and in France, have been below 35 mg/m³.

5.2 Human carcinogenicity data

There were no data available to the Working Group.

5.3 Animal carcinogenicity data

Furfuryl alcohol was tested for carcinogenicity in one well-conducted good laboratory practice (GLP) inhalation study in male and female mice, one well-conducted GLP inhalation study in male and female rats, and in a skin application study in a female transgenic mouse model.

In male B6C3F₁ mice, furfuryl alcohol induced a significant positive trend in the incidences of renal tubule adenoma, and renal tubule adenoma or carcinoma (combined); and

a significant increase in the incidence of renal tubule adenoma or carcinoma (combined) occurred at the highest dose. In addition, the incidence of renal tubule adenoma, carcinoma, and adenoma or carcinoma (combined) in male B6C3F₁ mice exposed at the highest dose, in each case exceeded historical control ranges for inhalation studies. Renal tubule neoplasms are rare in male B6C3F₁ mice. There was no significant increase in the incidence of any neoplasm in exposed female B6C3F₁ mice.

In male F344/N rats, furfuryl alcohol induced a significant positive trend in the incidence of adenoma, carcinoma or squamous cell carcinoma (combined) of the nasal respiratory epithelium, and of squamous cell carcinoma of the nasal respiratory epithelium. Furfuryl alcohol also induced a significant increase in the incidence of adenoma, carcinoma or squamous cell carcinoma (combined) of the nasal respiratory epithelium in male rats at the highest dose. Carcinomas and squamous cell carcinomas of the nasal respiratory epithelium have not been observed in male F344/N rats in historical controls. In addition, the incidence of renal tubule adenoma in exposed female F344/N rats exceeded the range for historical controls.

No significant increase in the incidence of tumours of the skin (papillomas) was observed in a study in transgenic female mice treated with furfuryl alcohol by skin application.

5.4 Mechanistic and other relevant data

Furfuryl alcohol is well absorbed by humans and rodents. Few data were available on distribution and elimination in rodents, and no data were available in humans. Furfuryl alcohol is rapidly and extensively metabolized. The predominant metabolic route is via alcohol dehydrogenase and aldehyde dehydrogenase with conjugation to glycine. Furfuryl alcohol can undergo sulfate

conjugation to yield the electrophile 2-sulfoxymethylfuran, leading to DNA adduction.

There is *strong* evidence that furfuryl alcohol is metabolically activated to an electrophile. There were consistent results for the formation of furfuryl alcohol-specific DNA adducts in one study of non-tumorous tissue of patients with cancer of the lung, in several studies in mice, and in an assay in bacteria expressing human sulfotransferase.

There is *moderate* evidence that furfuryl alcohol is genotoxic. Only data on DNA adducts, discussed above, were available from exposed humans. In human cells in vitro, results were negative for sister-chromatid exchange. In mice, results were negative for sister-chromatid exchange, chromosomal aberrations, and micronucleus formation. In mammalian cells in vitro, results were positive for sister-chromatid exchange without (but not with) metabolic activation, but negative for chromosomal aberrations. Results were negative for mutations in *Drosophila melanogaster*. Results were positive for mutation in two studies in *Salmonella typhimurium* transfected with human or rodent sulfotransferase, but negative in the standard Ames test.

In long-term bioassays in mice and rats, renal, nasal and corneal toxicity were reported.

6. Evaluation

6.1 Cancer in humans

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

6.2 Cancer in experimental animals

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

6.3 Overall evaluation

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

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