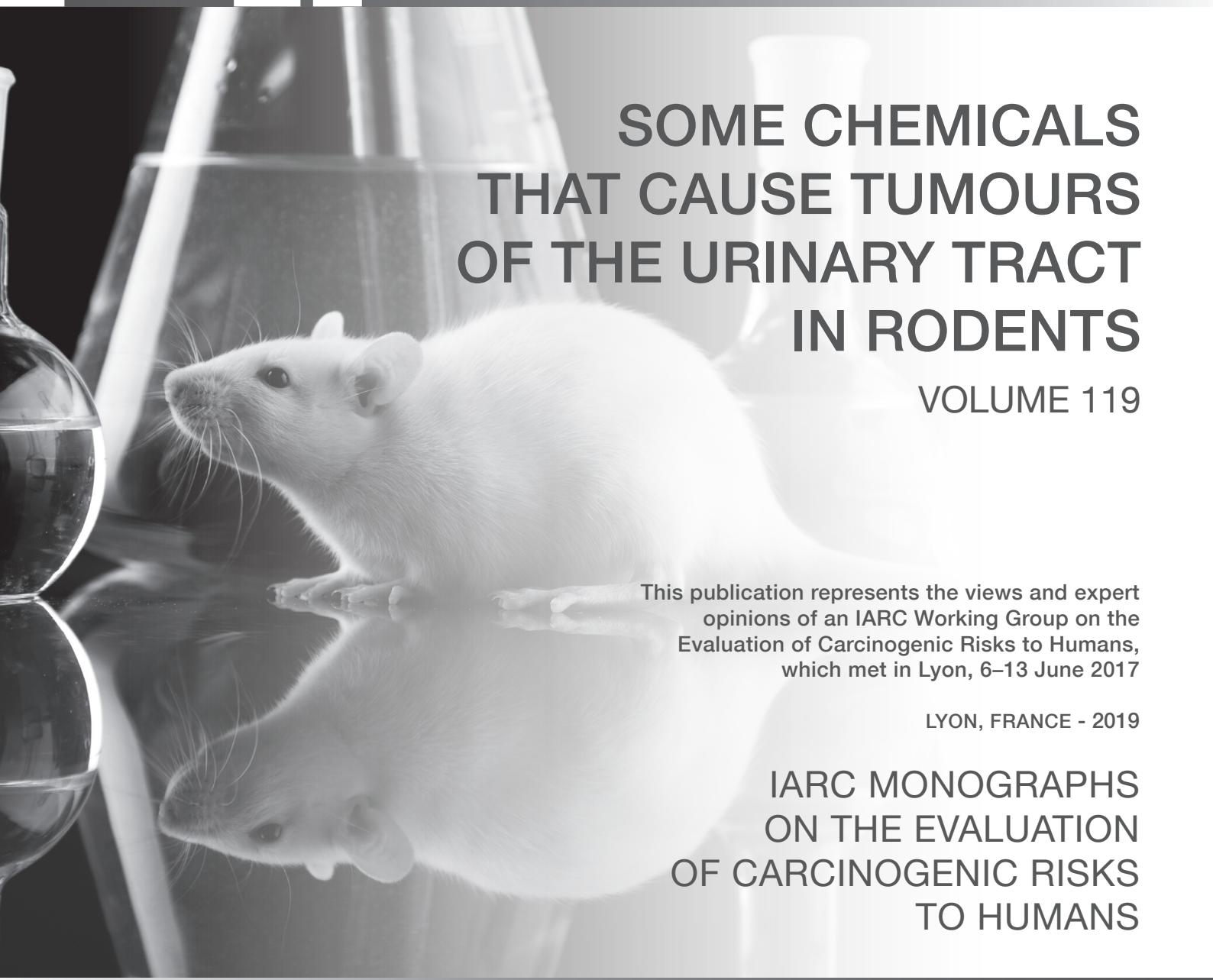
IARC MONOGRAPHS



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

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

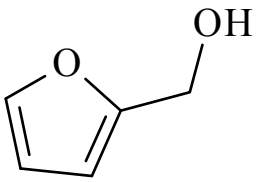
EC name: Furfuryl alcohol

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: $C_5H_6O_2$

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/cm^3 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/m^3 in humans; 50% response at 8 ppm

Conversion factor: 1 ppm = 4.01 mg/m^3 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 & Yogeeswari, 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/m³ (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 expresso 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
Liquids		
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)
Solids		
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/m^3. 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/m³]	
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/m³]	
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/m³]	0.2–40 ppm [0.8–160 mg/m³]	Measurements made in the core-making areas of 10 iron and steel foundries; 22% of results exceeded 5 ppm [20 mg/m³] (the TLV)
Pfaffli 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 Pfaffli et al. (1985)
Landberg et al. (2015)	Sweden, around 2015	Foundry Core-making	Air; personal; *N* = 3; 2 h	Furfuryl alcohol 40 mg/m³	30–54 mg/m³	In core-making, a core of about 0.3–1 m³ 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/m³	< 1–15 mg/m³	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/m³). During manual filling and packing of big moulding boxes, occasional peak concentrations of up to 100 mg/m³ 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/m³ Geometric mean	0.8–23 mg/m³	
NIOSH (1979)	USA, 1976	All Furfuryl alcohol manufacture	Air; personal; *N* = 24; NR	Furfuryl alcohol < 0.1 ppm [< 0.4 mg/m³]	< 0.1–0.2 ppm [< 0.4–0.8 mg/m³]	
NIOSH (1979)	USA, 1978	All Furfuryl alcohol manufacture	Air; personal; *N* = 4; NR	Furfuryl alcohol 0.3 ppm [1.2 mg/m³]	0.2–0.4 ppm [0.8–1.6 mg/m³]	
NIOSH (1972)	USA, 1972	Foundry Core-maker, assistant and apprentice	Air; personal; *N* = 3; 8 h	Furfuryl alcohol < 20 mg/m³ Median	< 20–25 mg/m³	
NIOSH (1973)	USA, 1973	Foundry Core-making	Air; environmental; *N* = 1; 8 h	Furfuryl alcohol 2.2 ppm [8.8 mg/m³]	NA	Furfuryl alcohol was measured at: 2.2 ppm [8.8 mg/m³] during normal conditions that day and collected over a complete core production cycle (1 h); 8.6 ppm [34.4 mg/m³] under normal conditions and during the core preparation time only (15 min); 10.8 ppm [43.2 mg/m³] during the core preparation when the sand was heated to a warm condition (15 min); and 15.8 ppm [63.2 mg/m³] 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/m³ Median	ND–20 mg/m³	
INRS (2018)	France, 1987–2017	Various	Air; personal; *N* = 123; 61–149 min	Furfuryl alcohol 2.0 mg/m³ Median	< 0.01–176 mg/m³	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/m^3, with a mean exposure of 17.2 mg/m^3 reported by Virtamo & Tossavainen (1976). Average exposure levels were generally below 18 mg/m^3. 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/m^3. 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/m^3 (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/m^3, with the eight highest results from workers involved in manufacturing paper and paperboard (arithmetic mean, 13 mg/m^3) (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/m³	ppm	mg/m³	
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 B6C3F_1 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 T_{90} (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 B6C3F_1 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	*Kidney, standard (single section) evaluation* Renal tubule adenoma:		Principal strengths: GLP study; study in males and females
		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%
		Kidney, standard (single section) evaluation and extended evaluation (step sections) (combined) 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% 0, 2, 8, 32 ppm 6 h plus T_{90} (12 min) per d, 5 d/wk, for 105 wk 50, 50, 50, 50 8, 5, 9, 0	*Nose* Lateral wall adenoma: 0/50, 1/50, 0/50, 0/50	NS	Principal strengths: GLP study; study in males and females
		Respiratory epithelium adenoma: 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%
		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)	
		Kidney, standard (single section) evaluation 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	*Kidney, standard (single section) evaluation* Renal tubule adenoma: 0/50, 0/49, 0/49, 2/50[a]	NS	Principal strengths: GLP study; study in males and females [a]Exceeded historical control incidence for inhalation studies Historical incidence: 1/898 (0.1% ± 0.5%); range, 0–2%
		Renal tubule carcinoma: 0/50, 1/49[b], 0/49, 0/50	NS	[b]Historical control incidence for inhalation studies: 4/898 (0.5% ± 0.9%); range, 0–2%
		Renal tubule adenoma or carcinoma (combined): 0/50, 1/49, 0/49, 2/50[c]	NS	[c]Historical control incidence for inhalation studies: 5/898 (0.6% ± 0.9%); range, 0–2%
		Nose Lateral wall adenoma: 0/49, 0/50, 1/48, 0/49	NS	
		Respiratory epithelium adenoma: 0/49, 0/50, 0/48, 1/49[d]	NS	[d]Historical control incidence for inhalation studies: 1/892 (0.1 ± 0.5%); range, 0–2%
		Adenoma (lateral wall or respiratory epithelium, combined): 0/49, 0/50, 1/48, 1/49	NS	

d, day; F, female; GLP, good laboratory practice; M, male; NS, not significant; T_{90}, 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 T_{90} (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.

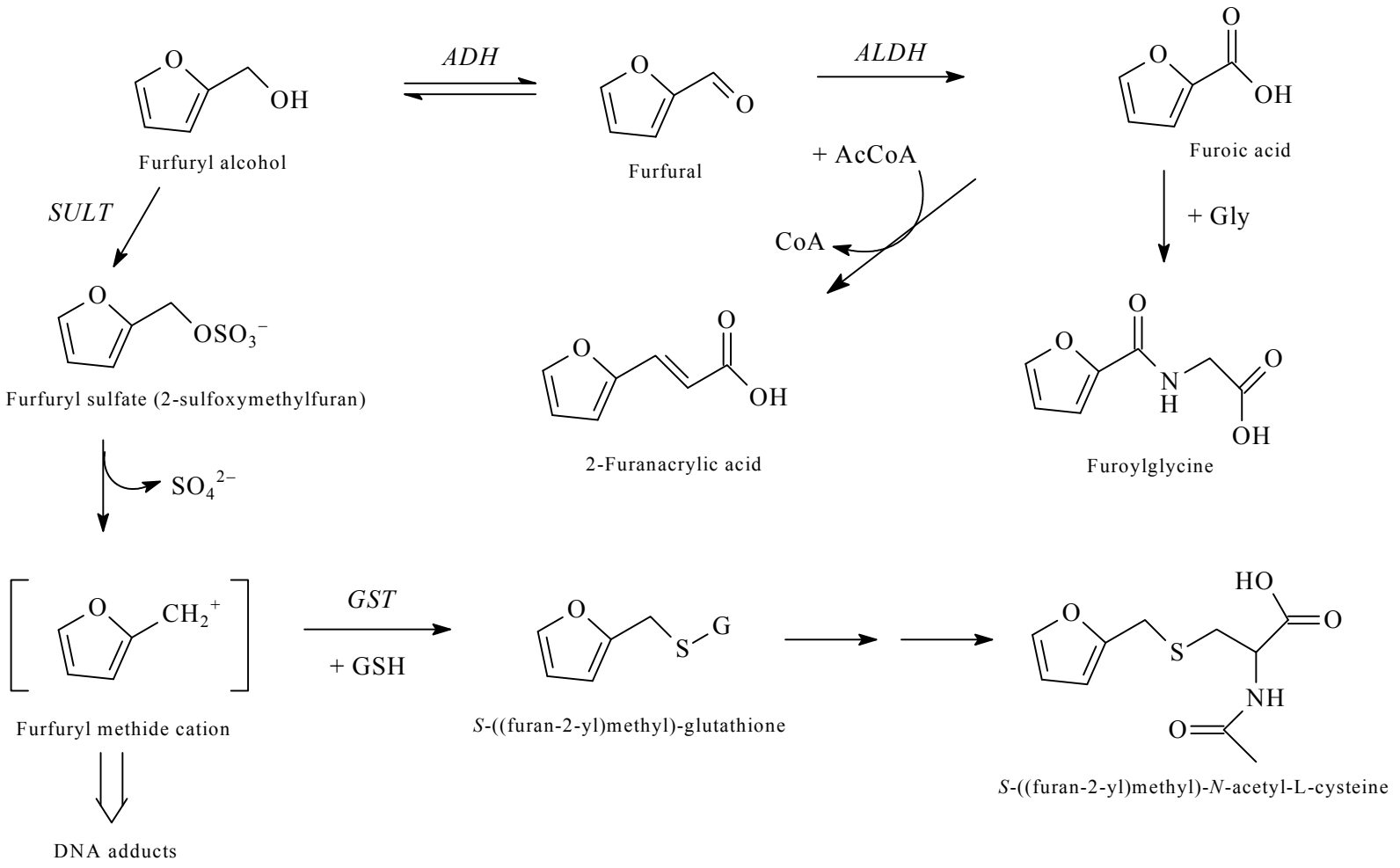
In humans exposed by inhalation to furfural (the primary oxidation product of furfuryl alcohol) (see Fig. 4.1), absorption was rapid and extensive. In male volunteers exposed by inhalation to furfural at vapour concentrations of 7–30 mg/m^3 for 7.5 hours over an 8-hour period, pulmonary retention averaged ~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 ^{14}C-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-furanacrylic 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
N^6-MFdA, N^6-((furan-2-yl)methyl)-2′-deoxyadenosine; N^2-MFdG, N^2-((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	Tisue, 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 N^2-((furan-2-yl)methyl)-2′-deoxyguanosine (N^2-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 $B6C3F_1$ 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 *hSULT1A1/1A2* transgenic)[b]	Colon, liver (wt); small intestine, colon, liver (*hSULT1A1/1A2* 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, *hSULT1A1/1A2* 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 *hSULT1A1/1A2* 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; N^6-MFdA, N^6-((furan-2-yl)methyl)-2′-deoxyadenosine; N^2-MFdG, N^2-((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-*hCYP2E1-hSULT1A1* 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	*Drosophila melanogaster,* germ-line cells	–	NA	1300 ppm		Rodriguez-Arnaiz et al. (1989)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	(–)	(–)	3 µmol/plate	Only one dose tested	Florin et al. (1980)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	–	–	10 000 µg/plate		NTP (1999)
Reverse mutation	*Salmonella typhimurium* TA100	–	NT	10 µmol/plate		Glatt et al. (2012); Monien et al. (2011)
Reverse mutation	*Salmonella typhimurium* TA100-derived strains expressing human or rodent sulfotransferases	+	NT	0.1–1 µmol/plate		Glatt et al. (2012)
Reverse mutation	*Salmonella typhimurium* TA100-derived strains expressing human or rodent sulfotransferases	+	NT	25 nmol/plate		Monien et al. (2011)
DNA adducts, 2-methylfuramyl 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	*Salmonella typhimurium* TA100	–	NT	167 µM		Monien et al. (2011)
DNA adducts, N^2-MFdG and N^6-MFdA, LC-MS/MS	*Salmonella typhimurium* 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; N^6-MFdA, N^6-((furan-2-yl)methyl)-2′-deoxyadenosine; N^2-MFdG, N^2-((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 B6C3F$_1$ 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 B6C3F$_1$ 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 B6C3F$_1$ mice, and hyaline droplets in B6C3F$_1$ 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/m^3.

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 B6C3F$_1$ 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 B6C3F$_1$ mice exposed at the highest dose, in each case exceeded historical control ranges for inhalation studies. Renal tubule neoplasms are rare in male B6C3F$_1$ mice. There was no significant increase in the incidence of any neoplasm in exposed female B6C3F$_1$ 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)*.

References

Ahman M, Alexandersson R, Ekholm U, Bergström B, Dahlqvist M, Ulfvarson U (1991). Impeded lung function in moulders and coremakers handling furan resin sand. *Int Arch Occup Environ Health*, 63(3):175–80. doi:10.1007/BF00381565 PMID:1917067

Amanpour A, Selli S (2016). Differentiation of volatile profiles and odor activity values of Turkish coffee and French press coffee. *J Food Process Preserv*, 40(5):1116–24. doi:10.1111/jfpp.12692

Baijun L, Lianhai L, Bingchun W, Tianxi C, Iwatani K (1998). Liquid phase selective hydrogenation of furfural on Raney nickel modified by impregnation of salts of heteropolyacids *Appl Catal A Gen*, 171(1):117–22. doi:10.1016/S0926-860X(98)00081-7

Bonvehí JS (2005). Investigation of aromatic compounds in roasted cocoa powder. *Eur Food Res Technol*, 221(1–2):19–29. doi:10.1007/s00217-005-1147-y

Boopathy R, Bokang H, Daniels L (1993). Biotransformation of furfural and 5-hydroxymethyl furfural by enteric bacteria. *J Ind Microbiol*, 11(3):147–50. doi:10.1007/BF01583715

Brands CMJ, van Boekel MAJS (2001). Reactions of monosaccharides during heating of sugar-casein systems: building of a reaction network model. *J Agric Food Chem*, 49(10):4667–75. doi:10.1021/jf001430b PMID:11600005

Buttery RG, Ling LC (1998). Additional studies on flavor components of corn tortilla chips. *J Agric Food Chem*, 46(7):2764–9. doi:10.1021/jf980125b

Buttery RG, Orts WJ, Takeoka GR, Nam Y (1999). Volatile flavor components of rice cakes. *J Agric Food Chem*, 47(10):4353–6. doi:10.1021/jf990140w PMID:10552815

Carrillo JD, Garrido-López A, Tena MT (2006). Determination of volatile oak compounds in wine by headspace solid-phase microextraction and gas chromatography-mass spectrometry. *J Chromatogr A*, 1102(1–2):25–36. doi:10.1016/j.chroma.2005.10.038 PMID:16280128

Castro-Vázquez L, Díaz-Maroto MC, Pérez-Coello MS (2007). Aroma composition and new chemical markers of Spanish citrus honeys. *Food Chem*, 103(2):601–6. doi:10.1016/j.foodchem.2006.08.031

Chemical Sources International (2017). Chem Sources-Online database. Available from: Db2.chemsources.com, accessed 13 April 2017.

Chen J, Ho CT (1999). Comparison of volatile generation in serine/threonine/glutamine-ribose/glucose/fructose model systems. *J Agric Food Chem*, 47(2):643–7. doi:10.1021/jf980771a PMID:10563946

Chen X, Li H, Luo H, Qiao M (2002). Liquid phase hydrogenation of furfural to furfuryl alcohol over Mo-doped Co-B amorphous alloy catalysts. *Applied Catalysis A*, 233(1–2):13–20. doi:10.1016/S0926-860X(02)00127-8

Cocito C, Gaetano G, Delfini C (1995). Rapid extraction of aroma compounds in must and wine by means of ultrasound. *Food Chem*, 52(3):311–20. doi:10.1016/0308-8146(95)92830-D

Cui J, Tan J, Cui X, Zhu Y, Deng T, Ding G, et al. (2016). Conversion of xylose to furfuryl alcohol and 2-methylfuran in a continuous fixed-bed reactor. *ChemSusChem*, 9(11):1259–62. doi:10.1002/cssc.201600116 PMID:27120138

ECHA (2018a). Furfuryl alcohol. Substance information. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.002.388.

ECHA (2018b). Tetrahydrofurfuryl alcohol. Substance information. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.002.387.

EFSA (2004). Report of the CONTAM Panel on provisional findings on furan in food. European Food Safety Authority. *EFSA J*, 137:1–20.

EFSA (2016). Safety and efficacy of furfuryl and furan derivatives belonging to chemical group 14 when used as flavourings for all animal species and categories. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). European Food Safety Authority. *EFSA J*, 14(2):4389.

Ellis WH (1972). Chapter 2.7, Solvents. In: Sward G, editor. Paint testing manual. physical and chemical examination of paints, varnishes, lacquers, and colors. 13th edition. ASTM special technical publication 500. Philadelphia (PA), USA: American Society for Testing and Materials.

Escriche I, Kadar M, Juan-Borrás M, Domenech E (2011). Using flavonoids, phenolic compounds and headspace volatile profile for botanical authentication of lemon and orange honeys. *Food Res Int*, 44(5):1504–13. doi:10.1016/j.foodres.2011.03.049

European Commission (2011). Recommendation from the Scientific Committee on Occupational Exposure Limits for furfuryl alcohol. SCOEL/SUM/129, June 2011. Brussels, Belgium: European Commission.

European Commission (2012). Commission implementing regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. *Off J Eur Union L*, 267(1):1161.

FDA (2005). Determination of furan in foods. Update information. Silver Spring (MD), USA: United States Food and Drug Administration. Available from: https://www.fda.gov/Food/FoodborneillnessContaminants/ChemicalContaminants/ucm078400.htm.

FDA (2017). 21 CFR (Code of Federal Regulations) Chapter 1 (4-1-17 Edition). Part 175 – Indirect food additives: adhesives and components of coatings. Subpart B – Substances for use only as components of adhesives. 175.105 Adhesives. Silver Spring (MD), USA: United States Food and Drug Administration.

FIOH (2018). Register of exposure measurements. Finnish Institute of Occupational Health. [personal communication]

Flament I, Bessiere-Thomas Y (2002). Coffee flavor chemistry. Chapter 5: The individual constituents: structure, nomenclature, origin, chemical and organoleptic properties. Part 5.9: Furans and pyrans. Chichester, UK: Wiley; pp. 212–328.

Flek J, Sedivec V (1978). The absorption, metabolism and excretion of furfural in man. *Int Arch Occup Environ Health*, 41(3):159–68. doi:10.1007/BF00572888 PMID:649206

Florin I, Rutberg L, Curvall M, Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology*, 15(3):219–32. doi:10.1016/0300-483X(80)90055-4 PMID:7008261

Franko J, Jackson LG, Hubbs A, Kashon M, Meade BJ, Anderson SE (2012). Evaluation of furfuryl alcohol sensitization potential following dermal and pulmonary exposure: enhancement of airway responsiveness. *Toxicol Sci*, 125(1):105–15. doi:10.1093/toxsci/kfr271 PMID:22003193

Giannetti V, Boccacci Mariani M, Mannino P, Testani E (2014). Furosine and flavour compounds in durum wheat pasta produced under different manufacturing conditions: Multivariate chemometric characterization. *Lebensm Wiss Technol*, 56(1):15–20. doi:10.1016/j.lwt.2013.10.045

Giri A, Osako K, Ohshima T (2010). Identification and characterisation of headspace volatiles of fish miso, a Japanese fish meat based fermented paste, with special emphasis on effect of fish species and meat washing. *Food Chem*, 120(2):621–31. doi:10.1016/j.foodchem.2009.10.036

Glatt H, Meinl W (2004). Pharmacogenetics of soluble sulfotransferases (SULTs). *Naunyn Schmiedebergs Arch Pharmacol*, 369(1):55–68. doi:10.1007/s00210-003-0826-0 PMID:14600802

Glatt H, Schneider H, Murkovic M, Monien BH, Meinl W (2012). Hydroxymethyl-substituted furans: mutagenicity in *Salmonella typhimurium* strains engineered for expression of various human and

rodent sulphotransferases. *Mutagenesis*, 27(1):41–8. doi:10.1093/mutage/ger054 PMID:21825114

Golubkova T (2011). Bildung von potentiell toxischen Furanderivaten in Lebensmitteln. Austria: Diplomarbeit. Institut für Biochemie TU Graz; pp. 38–40. [German]

Gomez-Arroyo S, Souza V (1985). In vitro and occupational induction of sister-chromatid exchanges in human lymphocytes with furfuryl alcohol and furfural. *Mutat Res*, 156(3):233–8. doi:10.1016/0165-1218(85)90068-0 PMID:4000179

Gómez Plaza E, Gil Munoz R, Carreno Espín J, Fernández López JA, Martínez Cutillas A (1999). Investigation on the aroma of wines from seven clones of Monastrell grapes. *Eur Food Res Technol*, 209(3–4):257–60. doi:10.1007/s002170050489

Grand View Research (2015). Furfural market analysis by application (furfuryl alcohol, solvent) and segment forecasts to 2020. Market research report. San Francisco (CA), USA: Grand View Research. Available from: https://grandviewresearch.com/industry-analysis/furfural-market.

Harada R, Yuzuki M, Ito K, Shiga K, Bamba T, Fukusaki E (2017). Influence of yeast and lactic acid bacterium on the constituent profile of soy sauce during fermentation. *J Biosci Bioeng*, 123(2):203–8. doi:10.1016/j.jbiosc.2016.08.010 PMID:27939139

Høie AH, Monien BH, Sakhi AK, Glatt H, Hjertholm H, Husøy T (2015). Formation of DNA adducts in wild-type and transgenic mice expressing human sulfotransferases 1A1 and 1A2 after oral exposure to furfuryl alcohol. *Mutagenesis*, 30(5):643–9. doi:10.1093/mutage/gev023 PMID:25904584

Hoydonckx HE (2007). Furfural and derivatives. In: Ullmann's encyclopedia of industrial chemistry. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

HSE (2017). Exposure to substances hazardous to health in foundries. RR1115 Research Report. Buxton, UK: Health and Safety Executive. Available from: www.hse.gov.uk/research/rrpdf/rr1115.pdf.

Huffman MP, Høie AH, Svendsen C, Brunborg G, Murkovic M, Glatt H, et al. (2016). An in vitro study on the genotoxic effect of substituted furans in cells transfected with human metabolizing enzymes: 2,5-dimethylfuran and furfuryl alcohol. *Mutagenesis*, 31(5):597–602. doi:10.1093/mutage/gew025 PMID:27226491

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49:1–648. Available from: http://monographs.iarc.fr/ENG/Monographs/vol49/index.php PMID:2232124

IFA (2017). GESTIS international limit values. Germany: Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, Available from: http://limitvalue.ifa.dguv.de.

IFC (2016). Furfuryl alcohol. Rotterdam, The Netherlands: International Furan Chemicals BV. Available from: http://www.furan.com/furfuryl_alcohol.html.

IHS Markit (2016). Furfuryl alcohol and furan resins. Chemical economics handbook. IHS Markit. Available from: https://ihsmarkit.com/products/furfuryl-alcohol-and-furan-chemical-economics-handbook.html.

INRS (2018). Solvex. Exposition professionnelle aux substances chimiques [online database]. Paris, France: l'Institut national de recherche et de sécurité pour la prévention des accidents du travail et des maladies professionnelles. Available from: http://www.inrs.fr/publications/bdd/solvex.html. [French]

Irwin RD, Chou BJ, Mellick PW, Miller RA, Mahler J, Roycroft J (1997). Toxicity of furfuryl alcohol to F344 rats and B6C3F1 mice exposed by inhalation. *J Appl Toxicol*, 17(3):159–69. doi:10.1002/(SICI)1099-1263(199705)17:3<159::AID-JAT420>3.0.CO;2-E PMID:9250537

ISO (2000). Workplace air quality - sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography - Part 2: Diffusive sampling method. International Standard 16200-2. Geneva, Switzerland: International Organization for Standardization.

ISO (2001). Workplace air quality - Sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography - Part 1: Pumped sampling method. International Standard 16200-1. Geneva, Switzerland: International Organization for Standardization.

ITC (2012). Furfuryl alcohol from China. Investigation No. 731-TA-703 (third review). United States International Trade Commission Publication 4302. January 2012. Washington (DC), USA: United States International Trade Commission.

Jansson T, Curvall M, Hedin A, Enzell CR (1986). In vitro studies of biological effects of cigarette smoke condensate. II. Induction of sister-chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. *Mutat Res*, 169(3):129–39. doi:10.1016/0165-1218(86)90092-3 PMID:3951466

Jensen S, Ostdal H, Skibsted LH, Thybo AK (2011). Antioxidants and shelf life of whole wheat bread. *J Cereal Sci*, 53(3):291–7. doi:10.1016/j.jcs.2011.01.010

Jerković I, Mastelić J, Tartaglia S (2007). A study of volatile flavour substances in Dalmatian traditional smoked ham: Impact of dry-curing and frying. *Food Chem*, 104(3):1030–9. doi:10.1016/j.foodchem.2007.01.013

Jiménez-Gómez CP, Cecilia JA, Durán-Martín D, Moreno-Tost R, Santamaría-González J, Mérida-Robles J, et al. (2016). Gas-phase hydrogenation of furfural to furfuryl alcohol over Cu/ZnO catalysts. *J Catal*, 336:107–15. doi:10.1016/j.jcat.2016.01.012

Karagül-Yüceer Y, Cadwallader KR, Drake M (2002). Volatile flavor components of stored nonfat dry milk. *J Agric Food Chem*, 50(2):305–12. doi:10.1021/jf010648a PMID:11782199

Kawata K, Ibaraki T, Tanabe A, Yagoh H, Shinoda A, Suzuki H, et al. (2001). Gas chromatographic-mass spectrometric determination of hydrophilic compounds in environmental water by solid-phase extraction with activated carbon fiber felt. *J Chromatogr A*, 911(1):75–83, 9, 75–83. doi:10.1016/S0021-9673(00)01252-8 PMID:11269598

Kim MG, Wasson L, Burris M, Wu Y, Watt C, Strickland RC (1998). Furfuryl alcohol emulsion resins as co-binders for particleboard. *Wood and Fiber Science*, 30(3):238–249. Available from: https://wfs.swst.org/index.php/wfs/article/viewFile/1639/1639.

Kotbagi TV, Gurav HR, Nagpure AS, Chilukuri SV, Bakker (2016). Highly efficient nitrogen-doped hierarchically porous carbon supported Ni nanoparticles for the selective hydrogenation of furfural to furfuryl alcohol. *RSC Advances*, 6(72):67662–8. doi:10.1039/C6RA14078E

Landberg HE, Berg P, Andersson L, Bergendorf U, Karlsson JE, Westberg H, et al. (2015). Comparison and evaluation of multiple users' usage of the exposure and risk tool: Stoffenmanager 5.1. *Ann Occup Hyg*, 59(7):821–35. doi:10.1093/annhyg/mev027 PMID:25858432

Li H, Luo H, Zhuang L, Dai W, Qiao M (2003). Liquid phase hydrogenation of furfural to furfuryl alcohol over the Fe-promoted Ni-B amorphous alloy catalysts. *J Mol Catal Chem*, 203(1–2):267–75. doi:10.1016/S1381-1169(03)00368-6

Liang J, Xie J, Hou L, Zhao M, Zhao J, Cheng J, et al. (2016). Aroma constituents in Shanxi aged vinegar before and after aging. *J Agric Food Chem*, 64(40):7597–605. doi:10.1021/acs.jafc.6b03019 PMID:27641774

Lide DR, editor (2005). CRC handbook of chemistry and physics, 86th ed. 2005–2006. Boca Raton (FL), USA: CRC Press, Taylor & Francis.

Lidums I, Karklina D, Sabovics M, Kirse A (2015). Evaluation of aroma volatiles in naturally fermented kvass and kvass extract. *Research for Rural Development*, 1:143–9.

Low I, Mitchell C (1985). Respiratory disease in foundry workers. *Br J Ind Med*, 42(2):101–5. PMID:3970867

MAK (2016). Furfuryl alcohol. The MAK collection for occupational health and safety 2016. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA.

MAK Commission (2008). Furfuryl alcohol [MAK Value Documentation, 2008]. The MAK-Collection for Occupational Health and Safety. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA. doi:10.1002/3527600418.mb9800e4416

Mandalika A, Qin L, Satob TK, Runge T (2014). Integrated biorefinery model based on production of furans using open-ended high yield processes. *Green Chem*, 16(5):2480–9. doi:10.1039/C3GC42424C

Monien BH, Herrmann K, Florian S, Glatt H (2011). Metabolic activation of furfuryl alcohol: formation of 2-methylfuranyl DNA adducts in *Salmonella typhimurium* strains expressing human sulfotransferase 1A1 and in FVB/N mice. *Carcinogenesis*, 32(10):1533–9. doi:10.1093/carcin/bgr126 PMID:21729924

Monien BH, Schumacher F, Herrmann K, Glatt H, Turesky RJ, Chesné C (2015). Simultaneous detection of multiple DNA adducts in human lung samples by isotope-dilution UPLC-MS/MS. *Anal Chem*, 87(1):641–8. doi:10.1021/ac503803m PMID:25423194

Moon JK, Shibamoto T (2010). Formation of volatile chemicals from thermal degradation of less volatile coffee components: quinic acid, caffeic acid, and chlorogenic acid. *J Agric Food Chem*, 58(9):5465–70. doi:10.1021/jf1005148 PMID:20405916

Morales ML, Benitez B, Troncoso AM (2004). Accelerated aging of wine vinegars with oak chips: evaluation of wood flavour compounds. *Food Chem*, 88(2):305–15. doi:10.1016/j.foodchem.2004.04.004

Munro IC, Danielewska-Nikiel B (2006). Comparison of estimated daily intakes of flavouring substances with no-observed-effect levels. *Food Chem Toxicol*, 44(6):758–809. doi:10.1016/j.fct.2005.10.008 PMID:16325977

Murkovic M, Swasti YR (2013). Chapter 3: 5-Hydroxymethyl-furfural and furfuryl alcohol: occurrence, exposure and detection. In: Pedreschi Plasencia F, Ciesarová Z, editors. Chemical food safety and health. Haupagge (NY), USA: Nova Science Publishers Inc.

National Library of Medicine (2018). TOXNET databases. Bethesda (MD), USA: National Library of Medicine. Available from: https://toxnet.nln.nih.gov, accessed 21 April 2018.

Nilsson A, Lagesson V, Bornehag C-G, Sundell J, Tagesson C (2005). Quantitative determination of volatile organic compounds in indoor dust using gas chromatography-UV spectrometry. *Environ Int*, 31(8):1141–8. doi:10.1016/j.envint.2005.04.003 PMID:15936080

NIOSH (1972). Health hazard evaluation report 72-10-15. Cincinnati (OH), USA: National Institute for Occupational Safety and Health, United States Department of Health, Education and Welfare.

NIOSH (1973). Health hazard evaluation report 73-116-0085. Cincinnati (OH), USA: National Institute for Occupational Safety and Health, United States Department of Health, Education and Welfare.

NIOSH (1979). Criteria for a recommended standard: occupational exposure to furfuryl alcohol. DHEW (NIOSH) Publication No. 79-133. Atlanta (GA), USA: Center for Disease Control, National Institute for Occupational Safety and Health.

NIOSH (1994). Furfuryl alcohol: Method 2505. In: NIOSH manual of analytical methods, fourth edition. Issue 2; 2–4.

NIOSH (2015). Furfuryl alcohol. Atlanta (GA), USA: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH (2016). Furfuryl alcohol. NIOSH pocket guide to chemical hazards. Atlanta (GA), USA: National Institute for Occupational Safety and Health. Available from: https://www.cdc.gov/niosh/npg/npgd0298.html, accessed 10 May 2018.

Nomeir AA, Silveira DM, McComish MF, Chadwick M (1992). Comparative metabolism and disposition of furfural and furfuryl alcohol in rats. *Drug Metab Dispos*, 20(2):198–204. PMID:1352210

NTP (1999). Toxicology and carcinogenesis studies of furfuryl alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*, 482:1–248. PMID:12571681

O'Driscoll A, Leahy JJ, Curtin T (2017). The influence of metal selection on catalyst activity for the liquid phase hydrogenation of furfural to furfuryl alcohol. *Catal Today*, 279:194–201. doi:10.1016/j.cattod.2016.06.013

OECD (2018). 2-Furanmethanol. OECD Existing Chemicals Database. Available from: https://hpvchemicals.oecd.org/ui/AllChemicals.aspx.

Okaru AO, Lachenmeier DW (2017). The food and beverage occurrence of furfuryl alcohol and b-myrcene - two emerging potential human carcinogens? *Toxics*, 5(1):9. doi:10.3390/toxics5010009 PMID:29051441

Oliva-Teles MT, Delerue-Matos C, Alvim-Ferraz MC (2005). Determination of free furfuryl alcohol in foundry resins by chromatographic techniques. *Anal Chim Acta*, 537(1–2):47–51. doi:10.1016/j.aca.2005.01.001

OSHA (2018). Chemical exposure health data [online database]. Washington (DC), USA: Occupational Safety and Health Administration. Available from: https://www.osha.gov/opengov/healthsamples.html.

Park D, Maga JA (2006). Identification of key volatiles responsible for odour quality differences in popped popcorn of selected hybrids. *Food Chem*, 99(3):538–45. doi:10.1016/j.foodchem.2005.08.019

Parkash MK, Caldwell J (1994). Metabolism and excretion of [^{14}C]furfural in the rat and mouse. *Food Chem Toxicol*, 32(10):887–95. doi:10.1016/0278-6915(94)90086-8 PMID:7959443

Pasqualone A, Michele Paradiso V, Summo C, Caponio F, Gomes T (2014). Influence of drying conditions on volatile compounds of pasta. *Food Bioproc Techol*, 7(3):719–31. doi:10.1007/s11947-013-1080-1

Perez RF, Fraga MA (2014). Hemicellulose-derived chemicals: one-step production of furfuryl alcohol from xylose. *Green Chem*, 16(8):3942–50. doi:10.1039/C4GC00398E

Pérez-Palacios T, Petisca C, Casal S, Ferreira IMPLVO (2014). Changes in chemical composition of frozen coated fish products during deep-frying. *Int J Food Sci Nutr*, 65(2):212–8. doi:10.3109/09637486.2013.854739 PMID:24215289

Pérez-Palacios T, Petisca C, Henriques R, Ferreira IMPLVO (2013). Impact of cooking and handling conditions on furanic compounds in breaded fish products. *Food Chem Toxicol*, 55:222–8. doi:10.1016/j.fct.2012.12.058 PMID:23340093

Pérez-Palacios T, Petisca C, Melo A, Ferreira IMPLVO (2012). Quantification of furanic compounds in coated deep-fried products simulating normal preparation and consumption: optimisation of HS-SPME analytical conditions by response surface methodology. *Food Chem*, 135(3):1337–43. doi:10.1016/j.foodchem.2012.05.100 PMID:22953863

Pérez-Prieto LJ, López-Roca JM, Martínez-Cutillas A, Pardo-Mínguez F, Gómez-Plaza E (2003). Extraction and formation dynamic of oak-related volatile compounds from different volume barrels to wine and their behavior during bottle storage. *J Agric Food Chem*, 51(18):5444–9. doi:10.1021/jf0345292 PMID:12926895

Petisca C, Henriques AR, Pérez-Palacios T, Pinho O, Ferreira IMPLVO (2013b). Study of hydroxymethylfurfural and furfural formation in cakes during baking in different ovens, using a validated multiple-stage extraction-based analytical method. *Food Chem*, 141(4):3349–56. doi:10.1016/j.foodchem.2013.05.128 PMID:23993492

Petisca C, Pérez-Palacios T, Farah A, Pinho O, Ferreira IMPLVO (2013a). Furans and other volatile compounds in ground roasted and expresso coffee using headspace solid-phase microextraction: effect of roasting speed. *Food Bioprod Process*, 91(3):233–41. doi:10.1016/j.fbp.2012.10.003

Petisca C, Pérez-Palacios T, Pinho O, Ferreira IMPLVO (2014). Optimization and application of a HS-SPME-GC-MS methodology for quantification of furanic compounds in espresso coffee. *Food Anal Methods*, 7(1):81–8. doi:10.1007/s12161-013-9601-0

Pfaffli P, Tossavainen A, Savolainen H (1985). Comparison of acid excretion techniques inhaled furfuryl alcohol vapour with urinary furoic in exposed workers by chromatographic techniques. *Analyst (Lond)*, 110:387–9. doi:10.1039/AN9851000377

Pico J, Martínez MM, Bernal J, Gómez M (2017). Evolution of volatile compounds in gluten-free bread: from dough to crumb. *Food Chem*, 227:179–86. doi:10.1016/j.foodchem.2017.01.098 PMID:28274420

Pritchard JB, French JE, Davis BJ, Haseman JK (2003). The role of transgenic mouse models in carcinogen identification. *Environ Health Perspect*, 111(4):444–54. doi:10.1289/ehp.5778 PMID:12676597

Qian M, Reineccius G (2002). Identification of aroma compounds in Parmigiano-Reggiano cheese by gas chromatography/olfactometry. *J Dairy Sci*, 85(6):1362–9. doi:10.3168/jds.S0022-0302(02)74202-1 PMID:12146465

Rodriguez-Arnaiz R, Ramos Morales P, Moctezuma RV, Bernal Salas RM (1989). Evidence for the absence of mutagenic activity of furfuryl alcohol in tests of germ cells in *Drosophila melanogaster*. *Mutat Res*, 223(3):309–11. doi:10.1016/0165-1218(89)90124-9 PMID:2500595

Sachse B, Meinl W, Glatt H, Monien BH (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*, 35(10):2339–45. doi:10.1093/carcin/bgu152 PMID:25053625

Sachse B, Meinl W, Glatt H, Monien BH (2016b). Ethanol and 4-methylpyrazole increase DNA adduct formation of furfuryl alcohol in FVB/N wild-type mice and in mice expressing human sulfotransferases 1A1/1A2. *Carcinogenesis*, 37(3):314–9. doi:10.1093/carcin/bgw006 PMID:26775039

Sachse B, Meinl W, Sommer Y, Glatt H, Seidel A, Monien BH (2016a). Bioactivation of food genotoxicants 5-hydroxymethylfurfural and furfuryl alcohol by sulfotransferases from human, mouse and rat: a comparative study. *Arch Toxicol*, 90(1):137–48. doi:10.1007/s00204-014-1392-6 PMID:25370010

Schirle-Keller JP, Reineccius GA (1992). Chapter 19: Reaction-kinetics for the formation of oxygen-containing heterocyclic compounds in model systems. In: Teranishi R, Takeoka GR, Güntert M, editors. Flavor precursors: thermal and enzymatic conversions (ACS Symposium Series 490); pp. 244–258.

Spalding JW, French JE, Stasiewicz S, Furedi-Machacek M, Conner F, Tice RR, et al. (2000). Responses of transgenic mouse lines p53(+/-) and Tg.AC to agents tested in conventional carcinogenicity bioassays. *Toxicol Sci*, 53(2):213–23. doi:10.1093/toxsci/53.2.213 PMID:10696769

Spillman PJ, Pollnitz AP, Liacopoulos D, Pardon KH, Sefton MA (1998). Formation and degradation of furfuryl alcohol, 5-methylfurfuryl alcohol, vanillyl alcohol, and their ethyl ethers in barrel-aged wines. *J Agric Food Chem*, 46(2):657–63. doi:10.1021/jf970559r PMID:10554294

Sriram D, Yogeeswari P (2010). Medicinal chemistry. Second edition. Hyderabad, India: BITS Pilani.

Stich HF, Rosin MP, Wu CH, Powrie WD (1981). Clastogenicity of furans found in food. *Cancer Lett*, 13(2):89–95. doi:10.1016/0304-3835(81)90133-6 PMID:7198003

Sujatha PS (2008). Monitoring cytotoxic potentials of furfuryl alcohol and 2-furyl methyl ketone in mice. *Food Chem Toxicol*, 46(1):286–92. doi:10.1016/j.fct.2007.08.008 PMID:17904264

Tennant RW, Spalding J, French JE (1996). Evaluation of transgenic mouse bioassays for identifying carcinogens and noncarcinogens. *Mutat Res*, 365(1–3):119–27. doi:10.1016/S0165-1110(96)90016-0 PMID:8898993

Tesfaye W, Morales ML, Benítez B, García-Parrilla MC, Troncoso AM (2004). Evolution of wine vinegar composition during accelerated aging with oak chips. *Anal Chim Acta*, 513(1):239–45. doi:10.1016/j.aca.2003.11.079

Tschickardt M (2012). Furfuryl alcohol [air monitoring methods, 2003]. The MAK collection for occupational health and safety; pp. 95–107. Available from: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.am9800e0008/abstract.

Tukacs JM, Bohus M, Dibób G, Mika LT (2017). Ruthenium-catalyzed solvent-free conversion of furfural to furfuryl alcohol. *RSC Advances*, 7(6):3331–5. doi:10.1039/C6RA24723G

Vanderhaegen B, Neven H, Verstrepen KJ, Delvaux FR, Verachtert H, Derdelinckx G (2004). Influence of the brewing process on furfuryl ethyl ether formation during beer aging. *J Agric Food Chem*, 52(22):6755–64. doi:10.1021/jf0490854 PMID:15506813

Vargas-Hernández D, Rubio-Caballero JM, Santamaría-Gonzales J, Moreno-Tost R, Mérida-Robles JM, Pérez-Cruz MA, et al. (2014). Furfuryl alcohol from furfural hydrogenation over copper supported on SBA-15 silica catalysts. *J Mol Catal Chem*, 383–384:106–13. doi:10.1016/j.molcata.2013.11.034

Vazquez L, Verdu A, Miquel A, Burlo F, Carbonell-Barrachina AA (2007). Changes in physico-chemical properties, hydroxymethylfurfural and volatile compounds during concentration of honey and sugars in Alicante and Jijona turrón. *Eur Food Res Technol*, 225(5):757–67. doi:10.1007/s00217-006-0479-6

Vázquez-Araújo L, Enguix L, Verdú A, García-García E, Carbonell-Barrachina AA (2008). Investigation of aromatic compounds in toasted almonds used for the manufacture of turron. *Eur Food Res Technol*, 227(1):243–54. doi:10.1007/s00217-007-0717-6

Villaverde MM, Bertero NM, Garetto TF, Marchi AJ (2013). Selective liquid-phase hydrogenation of furfural to furfuryl alcohol over Cu-based catalysts. *Catal Today*, 213:87–92. doi:10.1016/j.cattod.2013.02.031

Virtamo M, Tossavainen A (1976). Gases formed from furan binding agents. *Scand J Work Environ Health*, 2(Suppl 1):50–3. doi:10.5271/sjweh.2832 PMID:968465

Wang Y, Kays SJ (2000). Contribution of volatile compounds to the characteristic aroma of baked "jewel" sweet potatoes. *J. Am Soc. Hort. Sci*, 125(5):638–43.

Westberg HB, Seldén AI, Bellander T (2001). Exposure to chemical agents in Swedish aluminum foundries and aluminum remelting plants–a comprehensive survey. *Appl Occup Environ Hyg*, 16(1):66–77. doi:10.1080/104732201456140 PMID:11202030

WHO (2001). Safety evaluation of certain food additives and contaminants. Prepared by the Fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Available from: http://www.inchem.org/documents/jecfa/jecm.

WHO (2012). Evaluation of certain food additives. Seventy-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, Switzerland: World Health Organization. WHO Technical Report Series, No. 974; pp. 1–183. Available from: http://www.who.int/foodsafety/publications/jecfa-reports/en/.

Wnorowski A, Yaylayan VA (2000). Influence of pyrolytic and aqueous-phase reactions on the mechanism of formation of Maillard products. *J Agric Food Chem*, 48(8):3549–54. doi:10.1021/jf9913099 PMID:10956148

Yang X, Peppard T (1994). Solid-phase microextraction for flavor analysis. *J Agric Food Chem*, 42(9):1925–30. doi:10.1021/jf00045a018

Yaylayan VA, Keyhani A (2000). Origin of carbohydrate degradation products in L-Alanine/D-[(13)C]glucose model systems. *J Agric Food Chem*, 48(6):2415–9. doi:10.1021/jf000004n PMID:10888560

Yu A-N, Sun BG, Tian DT, Qu WY (2008). Analysis of volatile compounds in traditional smoke-cured bacon(CSCB) with different fiber coatings using SPME. *Food Chem*, 110(1):233–8. doi:10.1016/j.foodchem.2008.01.040 PMID:26050188

Yuan JP, Chen F (1999). Simultaneous separation and determination of sugars, ascorbic acid and furanic compounds by HPLC-dual detection. *Food Chem*, 64(3):423–7. doi:10.1016/S0308-8146(98)00091-0