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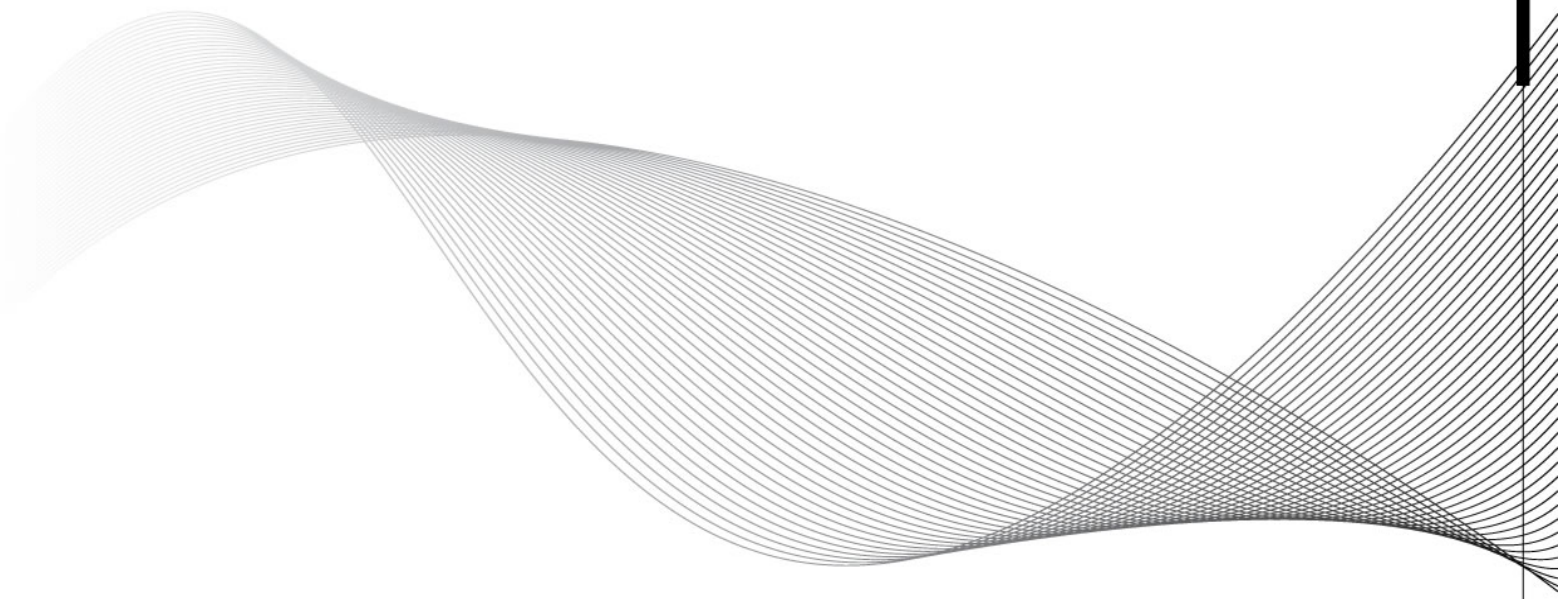

Recommendation from the Scientific Committee on Occupational Exposure Limits for furfuryl alcohol

SCOEL/SUM/129

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8 hour TWA	: not assigned (*see "Recommendation"*)
STEL (15 mins)	: not assigned
Notation	: "skin"

Substance identification

Furfuryl alcohol

Synonyms	2-Furanmethanol, 2-Furancarbinol, 2-hydrosxymethylfuran, Furfural alcohol
EINECS No.	202-626-1
CAS No.	98-00-0
Molecular formula	$C_5H_6O_2$
Structural formula	
MWt	98.1 $gmol^{-1}$
EU-Classification	Xn. R20/21/22 Harmful by inhalation, in contact with skin and if swallowed

(*see co-existing CLP/GHS classification in Annex page 13*).

Conversion factor: At 20°C and 1013 hPa 1 ppm = 4.08 mg/m3; 1 mg/m3 = 0.245 ppm
This document is based on the recent review of Furfural published by the EU Scientific Committee for Food (SCF), the US NIOSH (National Institute for Occupational Safety Health) review (1979), the JECFA Monograph (2000) and a limited number of other studies of Furfuryl alcohol identified using the on-line database Pubmed.

Physico-chemical properties

At 20 °C and 1013 hPa, Furfuryl alcohol is a colourless liquid with a characteristic "burning" odour and bitter taste, which turns red or brown on exposure to light and air. Its melting point is -15°C and a boiling point of 170 °C. It is miscible with water. The vapour pressure is 53 kPa at 20 °C; the vapour of pure furfuryl alcohol is denser than air. The octanol/water partition coefficient as log P_{ow} is 0.28. The odour threshold is about 28 mg/m3 in humans.

1. Occurrence/Use

Furfuryl alcohol is produced commercially by hydrogenating furfural which is prepared by the acid hydrolysis of pentosan polysaccharides from sources of hemicellulose such as the non-food residues of food crops (eg cereal) or wood wastes. Furfuryl alcohol is also naturally present in some fruits and in tea, coffee and cocoa. Furfuryl alcohol is used in the manufacture of flavourings and as a solvent for dyes and resins, including heat-resistant resins used as binding agents in foundry sand, in the manufacture of fibre-glass reinforced plastic equipment and as corrosion inhibitors in mortar, grout and cement. Furfuryl alcohol is also used as a laboratory reagent.

It is difficult to determine how much furfuryl alcohol is produced and used in the EU. Information from one industry website suggests that about 40,000 tonnes of furfural were used in the EU in 2000. The consumption of furfuryl alcohol is likely to have been somewhat lower than that of furfural. A substantial proportion of the furfuryl alcohol used in Europe may be imported.

1.1. Methods of exposure monitoring and analysis

The UK Health and Safety Executive (2000) have published a method for the sampling of volatile organic compounds in workplace air and their analysis by gas chromatography that is suitable for furfuryl alcohol (Methods for Determination of Hazardous Substances 96).

The US National Institute for Occupational Health and Safety (NIOSH) Analytical Method 2505 (issue 2, 1994) involves collection on solid sorbent tubes and analysis by GC/FID. The limit of detection is stated as 10 µg and the method is suitable for concentrations of 20-600 mg/m3 in air.

There are no fully validated methods of biological monitoring. However, and especially due to the lack of feasibility of recommending an airborne OEL, biological monitoring based on the analysis of 2-furoic acid and its conjugates in urine may be useful to monitor worker populations potentially exposed to furfural. There is an ACGIH BEI for furfural of 200 mg/l 2-furoic acid after hydrolysis of conjugates – the value is that expected after 8-hour inhalation exposure to 2 ppm furfural. Analytical methods are available for 2-furoic acid (after hydrolysis of conjugates) in urine based on HPLC (Tan et al 2003) and by GC with FID (Flek *et al* 1978).

2. Health Effects

2.1. Toxicokinetics

A study with radiolabeled furfuryl alcohol in rats (Nomeir *et al*, 1992) established that more than 90% of the ingested dose was absorbed in the gastrointestinal tract. The furfuryl alcohol was extensively metabolised and the major route of elimination was in urine (about 83-89% compared with 4% in the faeces). The major route of metabolism was oxidation to furfural that subsequently was oxidised to 2-furoic acid and the corresponding alcohol. These metabolites were then conjugated with glycine. Furoylglycine was the major urinary metabolite (73-80% of dose) and furoic acid and furanacrylic acid were minor urinary metabolites. Tissue concentrations of radioactivity were highest for the liver and kidneys.

The acute toxicity data listed in RTECS (see section on acute toxicity) indicates that furfuryl alcohol is also well absorbed following inhalation and that it may also be absorbed through the skin.

2.2. Acute toxicity

2.2.1. Human data

The short-term effects of high concentrations of inhaled furfuryl alcohol are irritation of the eyes and nose (NIOSH, 1979). No toxic effects have been reported in humans following short-term exposure.

2.2.2. Animal data

There is no recent information about the acute effects of exposure to furfuryl alcohol. RTECS lists LD_{50} values (dose lethal to 50% of a batch of experimental animals), but source studies are not available (Table 1).

Table 1: Acute toxicity data according to RTECS

Route of exposure	Species	LD_{50}
Inhalation	rat	233 ppm/ 4 hour
Oral	rat	177 mg/kg
	mouse	460 mg/kg
Dermal	rat	3825 mg/kg
	rabbit	400 mg/kg
intraperitoneal	rat	650 mg/kg
intravenous	rabbit	650 mg/kg
Subcutaneous	rat	85 mg/kg

2.3. Irritation

There are very few human data. NIOSH (1979) reviewed a study in which no effects were observed at concentrations of 44 mg/m3 and severe eye irritation was reported at 64.5 mg/m3 in foundry workers exposed to furfuryl alcohol during core preparation. The workers were also exposed to formaldehyde (0.4 mg/m^3) and it is unclear what the relative importance of furfuryl alcohol was in the causation of irritation (the irritation threshold for formaldehyde is about 0.1mg/m3). However, although slight eye irritation may occur in some individuals at formaldehyde levels between 0.1 and 0.6 mg/m3, severe irritation and lacrimation are more strongly associated with formaldehyde levels of 4 mg/m3 or above and OSHA concluded that the irritation experienced by the foundry workers was due to the furfuryl alcohol rather than exposure to formaldehyde. Subsequent information provided by the foundry suggested that the threshold for eye irritation arising from exposure to furfuryl alcohol is between 100 and 122 mg/m3 (Undated document on NIOSH website for toxicological reviews titled " *OSHA comments from the January 19, 1989 Final Rule on Air Contaminants Project extracted from 54FR2332 et. seq.*". From http://www.cdc.gov/niosh/pel88/98-00.html).
In another study in foundry workers, 28 workers reported airway symptoms (cough, nose, throat) and eye irritation. Time-weighted exposure levels were 7 mg/m3 with peak values of more than 40 mg/m3 (Ahman et al. 1991).

Cockcroft *et al*. (1980) reported that a 50-year-old mould-maker developed asthma after working with a mixture containing furfuryl alcohol, paraformaldehyde, xylene, and a catalyst containing sulphuric acid, phosphoric acid, and butyl alcohol. In laboratory investigations, the patient's bronchial response to inhaled histamines was increased following exposure to furfuryl alcohol mixed with butyl alcohol or sulphuric acid, but not following exposure to pure furfuryl alcohol or the catalyst.

Dermatitis was reported in two of 15 workers who had skin contact with acid-resistant cement containing furfuryl alcohol (Mastromatteo 1965), but the effects may have been due to other components of the cement and there have been no other reports linking furfuryl alcohol to dermatitis.

There are limited animal experiments that related to irritant responses. In a study described by NIOSH (1979), rats were reported to develop severe eye irritation on exposure to 2832 mg/m3 for 4 hours whereas no effects were observed following repeated six-hour exposures to 77.5 mg/m3. Following application to the skin, a 50% solution of furfuryl alcohol caused skin irritation in guinea pigs.

Overall it seems likely that furfuryl alcohol is irritating to the respiratory tract, eyes and skin but there are no good data from which exposure-response relationships or a threshold level of exposure can be derived.

2.4. Sensitisation

Although furfuryl alcohol is used in a number of industries, there is no evidence linking it to respiratory or dermal sensitisation.
There are no relevant animal data.

2.5. Repeated dose toxicity

2.5.1. Human data

There have been very few studies of the effects of workplace exposure to furfuryl alcohol and the available information is largely limited to that reviewed by NIOSH (1979). In a foundry where furfuryl alcohol was released during core preparation, no irritation, headache, or dizziness was reported among workers exposed to 8-hour TWA concentrations of about 20-25 mg/m3, with excursions up to 64 mg/m3. A study of four laboratory workers exposed to furfuryl alcohol vapour and who had skin contact with furfuryl alcohol on a daily basis reported no adverse effects, but no quantitative exposure information was available (NIOSH, 1979). Ahman *et al* (1991) reported small effects on lung function in 39 moulders and core-makers exposed to furan resin sand. The time-weighted average exposure to furfuryl alcohol was about 7 mg/m3, with peak values exceeding 40 mg/m3. Concurrent exposure to respirable dust and formaldehyde was less than 2 mg/m3 and 0.4 mg/m3 respectively. Exposed subjects showed an average decrease of 0.2 l in forced vital capacity but no fall in any other lung-function variable. According to the authors, the mechanism of this lung function impairment was unclear. The remaining 11 exposed subjects demonstrated a post-shift decrease in total lung capacity. No long term effects on lung function were observed.

2.5.2. Animal data

Furfuryl alcohol

The National Toxicology Program (NTP) have reported inhalation studies in rats and mice undertaken over 16 days, 14 weeks and 2 years with furfuryl alcohol (NTP, 1999). In all three experiments, animals were exposed for 6 hours/day, 5 days/week.

In the 16 day study, rats exposed to 1020 mg/m3 all died within the first two days of exposure. One rat exposed to 510 mg/m3, died on day 5 and the other rats exposed to 510 mg/m3 showed reduced weight gain. Male, but not female rats, also showed reduced weight gain at 127 mg/m3 and 257 mg/m3. Both male and female rats showed dyspnoea, hypoactivity and nasal and ocular discharge at exposures above 257 mg/m3 and all the exposed animals developed lesions in the nasal respiratory epithelium and olfactory epithelium. Similar effects were seen in mice and all but one of the exposed animals developed lesions in the nasal respiratory and/or olfactory epithelium. The lowest observed adverse effects level (LOAEL) in both species was 127 mg/m3, but the no observed adverse effects level (NOAEL) was not established.

In the 14 week study, a reduction in body weight gain was seen in female rats exposed to 131 mg m^{-3} and in mice, the heart weights of the 131 mg/m3 males was significantly reduced. A dose-related increase in the severity of lesions of the respiratory and olfactory epithelium was observed in both species. The LOAEL in both species was 8 mg/m3, but the NOAEL was not established.

In the 2 year study, animals were exposed to 0, 8, 16 or 131 mg/m3. Male rats exposed to 131 mg/m3 showed reduced body weights and all died by week 99 of the study. An increased incidence of non-neoplastic histological changes of the nose was observed in rats at all exposure concentrations. Neoplastic changes in the nose and in the kidneys were also observed and these are described in Section 5.7 of this document. Renal toxicity was also observed and rats exposed to 131 mg/m3 showed parathyroid gland hyperplasia and fibrous osteodystrophy arising from renal toxicity (table 2; appendix). In mice, the mean body weights of all the exposed females were reduced during the second year of the study. Female mice exposed to 131 mg/m3 developed focal corneal opacities. Male mice showed kidney damage that increased in severity with increasing concentration (table 3; appendix). The most sensitive endpoint was hyperplasia of the lateral wall of the nose in male and female rats. The dose-response-curve is very steep and therefore it is not possible to estimate a benchmark dose. **The LOAEL in both species was 8 mg/m3 (2 ppm), but the NOAEL was not established.**

A much earlier study undertaken by Savolainen and Pfaffli (1983) exposed rats for 6 hours/day, 5 days/week to fufuryl alcohol vapour concentrations of 100, 200 and 400 mg/m3. All the exposed animals showed reduced weight gains and changes in enzyme activity in the brain. The authors concluded that furfuryl alcohol may have significant mitochondrial effects in the brain that lead to glial cell degeneration and initiation of demyelination.

In an unpublished study cited by NIOSH (1979), rats and mice exposed for 6 hours/day for 6 weeks to 77.5 mg/m3 furfuryl alcohol showed moderate pulmonary congestion, but no significant signs of toxicity and no evidence of eye irritation (Comstock and Oberst, 1952).

Furfural

Given that furfuryl alcohol is oxidised to furfural during metabolism, studies with furfural may be relevant to the toxicology of furfuryl alcohol. However, the local irritating activity of furfural is expected to be higher than that of furfuryl alcohol.

Rats were exposed for furfural for 28 days by gavage to 6-192 mg/kg/day, or by inhalation to concentrations of 20-1280 mg/m3 (6 h/day, 5 days/week) or 160-1280 mg/m3 (3 h/day, 5 days/week). Oral exposure resulted in mortality, and in increases in absolute and relative kidney and liver weight in surviving females of the highest dose group. It was concluded that the NOEL for oral toxicity was 96 mg/kg/day compared with a NOEL for systemic inhalation toxicity of 92 mg/kg/day (corresponding to 320 mg/m3 for 6 hours/day or 640 mg/m3 for 3 hours/day) assuming 100% absorption. Exposure of rats by inhalation for 6 hours/day induced mortality at concentrations of 640 mg/m3 and above withi n 1-8 days. No serious clinical effects were observed at 640 mg/m3 (3 hours/day) and at 320 mg/m3 (3 and 6 hours/day) and below, but histopathological changes were seen in the nose even at the lowest concentration of 20 mg/m3. The nasal effects increased in incidence and severity with increasing concentration. No NOAEL for exposure by inhalation can be deduced for furfural (Arts et al. 2004).
A more recent 90 day oral study with furfural found adverse effects on the liver in rats at 90 mg/kg/day and in mice at 150 mg/kg/day (Jonker, 2000 - unpublished industry study cited by the EU Scientific Committee on Food, 2003). A NOEL of 54 mg/kg/day was identified by Jonker.

No long-term feeding studies have been undertaken with furfuryl alcohol but the results of the NTP (1990) study of furfural may be informative. Furfural (99% pure) was administered by gavage to rats and mice for 16 days, 13 weeks, or 2 years. In the 16 day studies, 8 out of 10 rats that received 240 mg/kg died within 3 days. In the 13 week studies, rats received doses ranging from 11 to 180 mg/kg, and mice received doses from 75 to 1,200 mg/kg. Most rats that received 180 mg/kg died. Mean relative and absolute liver and kidney weights were increased in male rats that received 90 mg/kg, and cytoplasmic vacuolization of hepatocytes was observed at all doses. Almost all mice that received doses of 600 or 1,200 mg/kg died within the first 3 weeks. Mean absolute liver weights and liver weight to body weight ratios were increased in females that received 300 mg/kg. Centrilobular coagulative necrosis and/or multifocal subchronic inflammation of the liver were observed at all doses. In the 2-year studies rats received 0, 30, and 60 mg/kg and mice received 0, 50, 100, and 175 mg/kg. The survival of low dose female rats, and mice was unaffected by chemical exposure whereas that of the male animals was reduced. No effects on body weight were observed. The incidence of centrilobular necrosis of the liver was increased in exposed male rats and multifocal pigmentation and chronic inflammation of the subserosa of the liver was observed in the exposed mice. A number of neoplastic changes of the liver were observed in both rats and mice (see section 5.7 below).

2.6. Mutagenicity

Furfuryl alcohol has given mixed results in mutagenic test systems and a summary is provided in JECFA (2000). Most reverse mutation tests in strains of *Salmonella typhimurium* have given negative results. The results of *in vitro* sister chromatid exchange assays and chromosome aberration assays have been mixed and positive results have been reported in one assay for gene conversion. Negative results were reported for sex-linked recessive 1 lethal mutation. The NTP (1999) reported that no induction of sister chromatid exchanges, chromosomal aberrations or micronuclei was observed in the bone marrow cells of male mice exposed to furfuryl alcohol.

2.7. Carcinogenicity

2.7.1. Humans

No human carcinogenicity data are available for furfuryl alcohol or furfural.

2.7.2. Animals

In the 2 year NTP (1999) study with furfuryl alcohol in rats (table 2; appendix) and mice (table 3; appendix) described above, nose and kidneys were the target organs. In the nose of rats and mice, signs of irritation with hyperplasia, metaplasia and degeneration were observed at all concentrations tested (≥8 mg/m3 or 2 ppm). The combined incidence of respiratory epithelium adenoma, carcinoma, or squamous cell carcinoma was significantly increased only in male rats of the high exposure group (131 mg/m3 or 32 ppm; see Table 2), but not in female rats or in mice. In the kidneys, nephropathy was observed with high incidence in all groups of rats and mice including controls. In the high exposure group, the incidence of mineralization, the severity of nephropathy and the incidence of renal tubule hyperplasia were significantly increased in rats; however, the incidence of renal tubule adenoma or carcinoma was not significantly increased. In male mice of the high exposure group, the incidences of renal tubule degeneration and adenoma or carcinoma were significantly increased.

2.8. Reproductive toxicity

There appear to be no published data relevant to the reproductive toxicity of furfuryl alcohol.

Recommendation

There are very little human data on furfuryl alcohol available. The results of limited studies (Ahman *et al*, 1991 and studies reviewed by NIOS, 1979) suggest that high levels of exposure may lead to respiratory and ocular irritation and slightly impaired lung function with an unclear threshold.

The results of two-year inhalation studies in rats and mice suggest that repeated exposure to 8 mg/m3 (2 ppm) of furfuryl alcohol causes nasal lesions arising from respiratory irritation (NTP, 1999). A NOAEL has not been established. Also with furfural, to which furfuryl alcohol is metabolised, no NOAEL for inhalation exposure can be established. Exposure to a concentration of 131 mg/m3 (32 ppm) furfuryl alcohol was associated with a significant increase in adenoma, carcinoma, or squamous cell carcinoma (combined) in male rats and in a significant increase in renal tubule adenoma or carcinoma in male mice. The genotoxicity data are equivocal. Consequently, the mechanism for induction of the nasal and kidney tumours is unclear. It might involve cytotoxicity or genotoxicity after metabolic conversion to furfural. From the rat inhalation study it is not possible to identify a concentration without effects (e.g. nasal hyperplasia and metaplasia and olfactory atrophy, Tables 2 and 3).

There appear to be no relevant published reproductive toxicity data for furfuryl alcohol.

No OEL can be established.
An OEL can be discussed, when an appropriate inhalation study in rats provides information on the NOEL and on the dose response relationship. Moreover, sufficient information on the carcinogenic mechanism is required.

So far, sensory irritation and slightly impaired lung function in humans and histopathological signs of irritation in animals have been observed at concentrations as low as 2 ppm so that an OEL is expected to be well below this exposure concentration.

Due to the low dermal LD_{50} in rabbits, a skin notation is warranted. Although furfuryl alcohol is used in a number of industries, there is no evidence linking it to respiratory or dermal sensitisation. There are no relevant animal data. **A sensitiser notation is,** therefore, **not warranted**.

To assess total exposure, biomonitoring is recommended by analysis of 2-furoic acid and its conjugates in urine. According to ACGIH, the BEI for furfural is 200 mg/l 2-furoic acid after hydrolysis of conjugates -expected after 8-hour exposure to 2 ppm furfural.

Table. 2. Incidences (and severity) of non-neoplastic and neoplastic lesions in **rats** in the 2-year inhalation study of furfuryl alcohol (NTP 1999)

		Concentration [mg/m3]			
Nose		0	8	16	131
Suppurative inflammation	♂ ♀	3/50[a] (1.0)[b] 4/49 (2.3)	6/50 (1.5) 1/50 (2.0)	17/50** (1.7) 5/48 (1.4)	44/50** (2.1) 23/49** (1.7)
Glands, hyperplasia	♂ ♀	0/50 0/49	0/50 0/50	22/50** (1.0) 24/48 (1.0)	49/50** (2.3) 46/49** (2.2)
Lateral wall, hyperplasia	♂ ♀	1/50 (1.0) 0/49	49/50** (1.5) 39/50** (1.3)	50/50** (2.4) 48/48** (2.1)	50/50** (3.5) 49/49** (3.5)
Lateral wall, squamous metaplasia	♂ ♀	1/50 (1.0) 0/49	1/50 (1.0) 1/50 (1.0)	8/50* (1.1) 0/48	33/50** (1.3) 24/49** (1.0)
Olfactory epithelium, atrophy	♂ ♀	1/50 (1.0) 0/49	12/50** (1.1) 6/50* (1.3)	47/50** (1.8) 44/48** (1.7)	50/50** (2.4) 49/49** (2.3)
Olfactory epithelium, fibrosis	♂ ♀	0/50 0/49	1/50 (1.0) 0/50	26/50** (1.0) 16/48** (1.3)	40/50** (2.0) 31/49** (1.7)
Olfactory epithelium, hyperplasia	♂ ♀	0/50 0/49	1/50 (1.0) 0/50	42/50** (1.0) 31/48** (1.2)	40/50** (1.8) 41/49** (1.5)
Olfactory epithelium, metaplasia	♂ ♀	1/50 (1.0) 0/49	8/50* (1.3) 5/50* (1.2)	37/50** (1.5) 37/48** (1.5)	49/50** (2.2) 48/49** (2.2)
Respiratory epithelium, hyperplasia	♂ ♀	0/50 0/49	26/50** (1.8) 18/50** (1.4)	50/50** (2.5) 40/48** (2.1)	50/50** (3.5) 49/49** (3.2)
Respiratory epithelium, squamous metaplasia	♂ ♀	0/50 0/49	0/50 0/50	3/50 (1.0) 2/48 (1.0)	26/50** (1.4) 10/49** (1.2)
Lateral wall, adenoma	♂ ♀	0/50 0/49	1/50 0/50	0/50 1/48	0/50 0/49
Respiratory epithelium, adenoma	♂ ♀	0/50[c] 0/49[d]	0/50 0/50	1/50 0/48	0/50 1/49
Respiratory epithelium, carcinoma	♂	0/50[e]	0/50	0/50	1/50
Respiratory epithelium, squamous cell carcinoma	♂	0/50[e]	0/50	0/50	3/50
Adenoma, carcinoma, or squamous cell carcinoma (combined)	♂ ♀	0/50 0/49	1/50 0/50	1/50 1/48	4/50* 1/49

[a] number of animals with lesion/number of animals examined;
*p < 0.05; **p < 0.01

[b] severity grade of lesion (range 1-4, minimal to marked),

[c] historical control incidence: 1/897 (0.1%±0.5%), range: 0--2%

[d] historical control incidence: 1/892 (0.1%± 0.5%), range: 0--2%

[e] historical control incidence: 0/897

Table. 3. Incidences of non-neoplastic and neoplastic lesions in **mice** in the 2-year inhalation study of furfuryl alcohol (NTP 1999)

		Concentration [mg/m3]			
Nose		0	8	16	131
Suppurative inflammation	♂ ♀	7/50 (1.4) 5/50 (1.2)	11/49 (1.2) 12/48** (1.1)	27/49** (1.3) 25/49** (1.5)	28/50** (1.7) 42/50** (2.0)
Glands, hyperplasia	♂ ♀	0/50 0/50	10/49** (1.2) 33/48** (1.1)	48/49** (1.3) 46/49** (2.8)	46/50** (1.7) 47/50** (3.1)
Glands, squamous metaplasia	♂ ♀	0/50 1/50	6/49* (1.0) 1/48 (1.0)	35/49** (1.1) 34/49** (1.1)	47/50** (1.5) 46/50** (1.5)
Lateral wall, squamous metaplasia	♂ ♀	0/50 (1.0) 3/50 (1.0)	9/49** (1.0) 14/48** (1.4)	10/49* (1.7) 16/49** (1.4)	20/50** (1.5) 36/50** (1.9)
Olfactory epithelium, atrophy	♂ ♀	1/50 (1.0) 0/50	12/49** (1.1) 6/48* (1.3)	47/49** (1.8) 44/49** (1.7)	50/50** (2.4) 49/50** (2.3)
Olfactory epithelium, hyaline degeneration	♂ ♀	2/50 (1.5) 7/50 (1.3)	3/49 (1.7) 14/48 (1.4)	21/49** (1.3) 28/49** (1.8)	39/50** (2.0) 45/50** (2.2)
Olfactory epithelium, metaplasia	♂ ♀	0/50 0/50	12/49** (1.0) 31/48** (1.2)	49/49** (1.0) 49/49** (3.0)	50/50** (1.8) 49/50** (3.6)
Respiratory epithelium, hyaline degeneration	♂ ♀	5/50 (1.0) 19/50 (1.4)	18/49** (1.1) 44/48** (1.5)	42/49** (1.3) 49/49** (1.3)	45/50** (1.2) 48/50** (1.4)
Respiratory epithelium, squamous metaplasia	♂ ♀	0/50 1/50 (1.0)	2/49 (1.0) 9/48** (1.8)	10/49** (1.1) 21/49** (1.7)	20/50** (1.4) 39/50** (1.9)
Respiratory epithelium, necrosis	♂ ♀	1/50 (2.0) 0/50	0/49 0/48	0/49 2/49 (2.5)	1/50 (1.0) 3/50 (1.3)
Respiratory epithelium, regeneration	♂ ♀	0/50 0/50	1/49 (1.0) 0/48	13/49** (1.0) 9/49** (1.0)	21/50** (1.0) 13/50** (1.2)
Kidney					
Nephropathy	♂ ♀	49/50 (1.2) 41/50 (1.0)	48/49 (1.4) 35/48 (1.1)	43/49 (1.5) 40/49 (1.2)	47/50 (1.8) 39/49 (1.0)
Renal tubule, degeneration	♂	0/50	0/49	1/49 (1.0)	48/50** (1.0)
Renal tubule, hyperplasia[c]	♂	4/50 (1.5)	8/49 (1.0)	3/49 (1.0)	5/50 (2.0)
Renal tubule, adenoma[c]	♂	0/50[d]	0/49	0/49	3/50
Renal tubule, carcinoma[c]	♂	0/50[e]	0/49	0/49	2/50
Renal tubule, adenoma or carcinoma[c]	♂	0/50[f]	0/49	0/49	5/50*

*p < 0.05; **p < 0.01

[a]number of animals with lesion/number of animals examined;

[b]severity grade of lesion (range 1-4, minimal to marked),

[c] single section and step sections combined

[d] historical control incidence: 3/1093 (0.3%±0.6%), range: 0--2%

[e] historical control incidence: 1/1093 (0.1%±0.4%), range: 0--2%

[f] historical control incidence: 4/1093 (0.4%±1.0%), range: 0--4%

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ANNEX. Classification and hazard statements following Regulation (EC) No 1272/2008 Annex VI table 3.1 arising from translation of classifications listed in Annex I to directive 67/548/EEC for furfuryl alcohol

Carc. 2	H351	Suspected of causing cancer
Acute Tox. 3*	H331	Toxic if inhaled.
Acute Tox. 4*	H312	Harmful in contact with skin
Acute Tox. 4 *	H302	Harmful if swallowed.
STOT RE 2 *	H373**	May cause damage to organs through prolonged or repeated exposure
Eye Irrit. 2	H319	Causes serious eye irritation.
STOT SE 3	H335	May cause respiratory irritation