

# Furfuryl alcohol

[98-00-0]

## Supplement 2008

<b>MAK value</b>	–
<b>Peak limitation</b>	–
<b>Absorption through the skin (1988)</b>	<b>H</b>
<b>Sensitization</b>	–
<b>Carcinogenicity (2007)</b>	<b>Category 3B</b>
<b>Prenatal toxicity</b>	–
<b>Germ cell mutagenicity</b>	–
<b>BAT value</b>	–

## 1 Toxic Effects and Mode of Action

Furfuryl alcohol induced a slightly higher incidence of nasal tumours and a questionable increase in the incidence of renal tumours in F344 rats exposed to the substance for 2 years via inhalation. Renal tumours were found also in male B6C3F<sub>1</sub> mice. In the 2-year study, signs of local irritation were observed in the noses of rats and mice at the lowest tested concentration of 2 ml/m<sup>3</sup> and above. In animal studies, furfuryl alcohol caused irritation of the skin and eyes. In vitro, the substance was questionably clastogenic in mammalian cells, but not mutagenic in Salmonella mutagenicity tests. In vivo genotoxicity studies yielded negative results.

In humans, lung function parameters were slightly impaired and irritation of the respiratory tract and eyes was observed after exposure to average furfuryl alcohol concentrations of 7 mg/m<sup>3</sup> (1.75 ml/m<sup>3</sup>) and peak exposures of up to more than 40 mg/m<sup>3</sup> (10 ml/m<sup>3</sup>) at the workplace. Furfuryl alcohol was acutely toxic following ingestion and inhalation in rats and after dermal application in rabbits. The acute toxicity varied considerably between the different species.

There are no studies available of the allergenic effects of furfuryl alcohol or any studies specifically of its reproductive toxicity.

## 2 Mechanism of Action

Furfuryl alcohol is metabolized via its oxidation product furfural (see documentation “Furfural” 1998). Oral administration of high furfural doses to rats, led to cholangiocarcinomas or their precursors. It had an initiating effect on mouse skin and led to genotoxic effects in vitro. Therefore, furfural was classified in Carcinogen Category 3B.

The nasal tumours observed in rats can be attributed to the irritation caused by furfuryl alcohol. Also furfural-mediated local genotoxicity might be involved in tumour development. In vivo, the substance was not genotoxic. As, however, only one questionably positive result was obtained in the in vitro genotoxicity tests with furfuryl alcohol with metabolic activation in two chromosomal aberration tests, and the Salmonella mutagenicity tests yielded negative results, the genotoxic potential is, if anything, only weak, and probably of subordinate relevance with regard to the development of nasal tumours.

It is unclear whether the renal tumours are caused by a reactive genotoxic metabolite (furfural) or may be the result of cytotoxicity.

## 3 Toxicokinetics and Metabolism

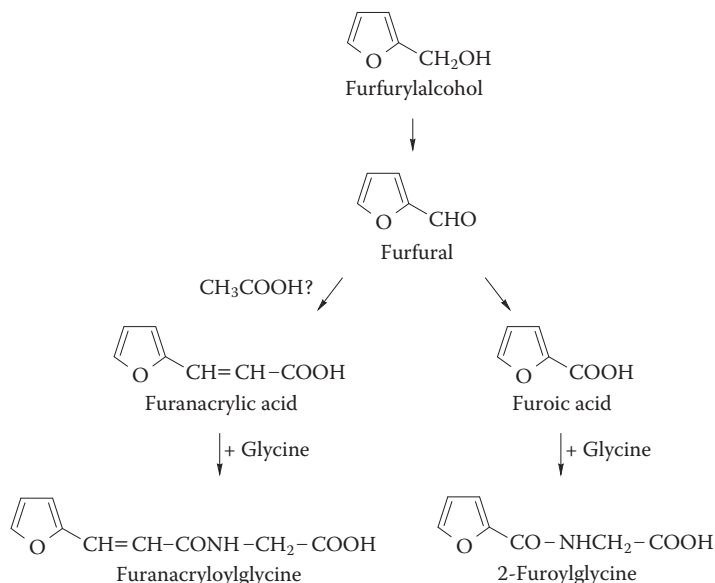
### 3.1 Absorption, distribution and elimination

Up to 72 hours after male F344 rats were given oral doses of radioactively labelled furfuryl alcohol of 0.275–27.5 mg/kg body weight, around 88% of the administered dose was found as metabolites in the urine and 4% of the dose was eliminated with the faeces.  $^{14}\text{CO}_2$  was not detected in the exhaled air. The highest concentrations of radioactivity were found in the liver and kidneys, while the lowest concentrations were detected in the brain (Nomeir et al. 1992).

### 3.2 Metabolism

The amount of furancarboxylic acid eliminated with the urine by exposed workers (average exposure not specified) correlated linearly with the product of the furfuryl alcohol concentration and the exposure time (Pfäffli et al. 1985).

The following metabolic pathway was determined after male F344 rats were given oral furfuryl alcohol doses of 0.275–100 mg/kg body weight. Initially, furfuryl alcohol is oxidized to furfural. Furfural is either oxidized further to form furoic acid (1%–6%) and then conjugated with glycine to form the main metabolite 2-furoylglycine (73%–80%), or, presumably with acetic acid, converted to furanacrylic acid (3%–8%) and its glycine conjugate (Figure 1; Irwin et al. 1985; Nomeir et al. 1992).



**Figure 1** Metabolism of furfuryl alcohol (according to NTP 1999)

In a 2-year inhalation study with rats, 2-furoylglycine was likewise detected as the main urinary metabolite, and in addition furanacryloylglycine (about 5% of the total amount of 2-furoylglycine) (NTP 1999).

## 4 Effects in Humans

The lung function of 28 foundry workers was examined by means of dynamic spirometry, and the lung function of another 11 exposed persons was additionally investigated using static spirometry. The workers had been exposed for an average of 15 years. The time-weighted average exposure to furfuryl alcohol was between  $7 \text{ mg/m}^3$  ( $1.75 \text{ ml/m}^3$ ) and a maximum of  $15 \text{ mg/m}^3$  ( $3.75 \text{ ml/m}^3$ ), with short-term exposure peaks exceeding  $40 \text{ mg/m}^3$  ( $10 \text{ ml/m}^3$ ). There was additional exposure to respirable dust in concentrations of  $< 2 \text{ mg/m}^3$  and formaldehyde concentrations of  $0.4 \text{ mg/m}^3$  (about  $0.3 \text{ ml/m}^3$ ). In the 28 workers, the incidence of airway symptoms (coughing 6/28, nose 8/28 and throat 11/28; control persons: 1/27, 3/27 and 0/27) and eye symptoms (3/28; control persons: 1/27) was increased and the forced vital capacity post-shift was decreased ( $-0.18 \text{ l}$ ;  $p < 0.05$ ). In the remaining 11 exposed persons, total lung capacity was decreased post-shift. The authors concluded that exposure caused a short-term restriction in lung function, but the underlying mechanism is unclear. Long-term impairment of lung function was not observed,

as the lung function values before the shift were similar to those of the control persons (Åhman et al. 1991).

## 5 Animal Experiments and in vitro Studies

### 5.1 Acute toxicity

There are no recent data available for the acute toxicity of furfuryl alcohol.

### 5.2 Subacute, subchronic and chronic toxicity

#### 5.2.1 Inhalation

In an unpublished study from 1952, 15 rats and 8 mice (no other details) were exposed to 19 ml/m<sup>3</sup> for 6 hours a day, on 5 days a week, over a period of 3 weeks. Body weight gains were not impaired compared with the controls. Diffuse congestion was observed throughout the respiratory tract, but there were no further gross-pathological findings in other organs (NTP 1999).

In a 16-day study, groups of 5 male and 5 female F344 rats were exposed to furfuryl alcohol concentrations of 0, 16, 31, 63, 125 or 250 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. Body weight gains were reduced by a maximum of 15% in the males after concentrations of 31 ml/m<sup>3</sup> and above and in the females after concentrations of 125 ml/m<sup>3</sup> and above. Dyspnoea, hypoactivity, and nasal and ocular discharge were observed after concentrations of 63 ml/m<sup>3</sup> and above. All animals died after 250 ml/m<sup>3</sup>, and one male died after 125 ml/m<sup>3</sup>. All exposed animals developed acute or suppurative inflammation of the nasal cavity, necrosis, regeneration and metaplasia in the respiratory epithelium, and necrosis and degeneration in the olfactory epithelium. A NOAEC (no observed adverse effect concentration) could not be derived (NTP 1999).

In a 16-day study, groups of 5 male and 5 female B6C3F<sub>1</sub> mice were exposed to furfuryl alcohol concentrations of 0, 16, 31, 63, 125 or 250 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. The body weight gains of the males and females were reduced by a maximum of 12% after concentrations of 63 ml/m<sup>3</sup> and above. All animals died after 250 ml/m<sup>3</sup>, and one female died after 125 ml/m<sup>3</sup>. Concentration-dependent histopathological changes in the nasal or olfactory epithelium were found in all exposed animals except for one male of the 16 ml/m<sup>3</sup> concentration group (see parallel study in rats). At 16 ml/m<sup>3</sup>, these changes were described as minimal; a NOAEC could not be derived (NTP 1999).

In a 14-week study, groups of 10 male and 10 female F344 rats were exposed to furfuryl alcohol concentrations of 0, 2, 4, 8, 16 or 32 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. The occurrence of squamous

metaplasia of the transitional epithelium was concentration-dependent and statistically significant in males and females after concentrations of 2 ml/m<sup>3</sup> and above. The incidence of degeneration of the olfactory epithelium was increased after 4 ml/m<sup>3</sup> and above, and squamous metaplasia and goblet cell hyperplasia were observed in the respiratory epithelium after concentrations of 8 ml/m<sup>3</sup> and above. Hypertrophy of the respiratory epithelium lining the nasopharyngeal duct, hyperplasia of the olfactory epithelium, surface exudate and cellular infiltrates in the lamina propria were found after concentrations of 16 ml/m<sup>3</sup> and above. The incidence of metaplasia in the olfactory epithelium of the females was increased at 32 ml/m<sup>3</sup>, as were the spermatid count and the number of spermatid heads. Motility and the concentration of spermatozoa were not affected. There were no significant differences in vaginal cytology. A NOAEC could not be derived (NTP 1999).

In a 14-week study, groups of 10 male and 10 female B6C3F<sub>1</sub> mice were exposed to furfuryl alcohol concentrations of 0, 2, 4, 8, 16 or 32 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. The incidence of degeneration and metaplasia in the olfactory epithelium of the males and hyaline droplets in the respiratory epithelium of the females was concentration-dependent and statistically significant after concentrations of 2 ml/m<sup>3</sup> and above. Chronic inflammation of the olfactory epithelium in males and degeneration in the olfactory epithelium in females were observed at 4 ml/m<sup>3</sup> and above. The incidences of squamous metaplasia of the submucosal glands of the cuboidal epithelium in males and of metaplasia and chronic inflammation in females were increased after concentrations of 8 ml/m<sup>3</sup> and above. Hyaline droplets were found in the respiratory epithelium of the males and squamous metaplasia was detected in the submucosal glands of the cuboidal epithelium of females after concentrations of 16 ml/m<sup>3</sup> and above. There were no significant differences in sperm motility or vaginal cytology. A NOAEC could not be derived (NTP 1999).

A 2-year study was carried out with F344 rats. Groups of 50 males and 50 females were exposed to furfuryl alcohol concentrations of 0, 2, 8 or 32 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. Survival and body weights were reduced in males at 32 ml/m<sup>3</sup>. There were no abnormal clinical findings. Irritation of the nasal mucosa was observed after concentrations of 2 ml/m<sup>3</sup> and above, and the incidence increased with the concentration. Hyperplasia of the lateral nasal mucosa (respiratory or transitional epithelium) proved to be the most sensitive end point (the concentration–effect relationship is so steep that no useful benchmark concentration can be calculated). The severity of nephropathy increased with the concentration. In males, the incidence of mineralization in the kidneys was significantly increased at 32 ml/m<sup>3</sup>. The authors concluded that the increased incidences of parathyroid hyperplasia and fibrous osteodystrophy were signs of renal failure following the increased nephropathy caused by furfuryl alcohol. A NOAEC was not obtained. The tumour incidences are listed in Section 5.7.2 (Table 1; NTP 1999). The changes are indicative of renal damage caused by furfuryl alcohol with effects on hormone-dependent bone metabolism.

**Table 1** Effects of furfuryl alcohol after 2-year inhalation exposure of rats and mice (NTP 1999)

	Concentration [ml/m <sup>3</sup> ]			
	0	2	8	32
<b>F344 rats</b>				
<b>nose</b>				
– suppurative inflammation				
♂	3 <sup>a</sup> /50 <sup>b</sup> (1.0)	6/50 (1.5)	17/50** (1.7)	44/50** (2.1)
♀	4/49 (2.3)	1/50 (2.0)	5/48 (1.4)	23/49** (1.7)
Bowman's glands				
– hyperplasia				
♂	0/50	0/50	22/50** (1.0)	49/50** (2.3)
♀	0/49	0/50	24/48** (1.0)	46/49** (2.2)
lateral mucosa				
– hyperplasia				
♂	1/50 (1.0)	49/50** (1.5)	50/50** (2.4)	50/50** (3.5)
♀	0/49	39/50** (1.3)	48/48** (2.1)	49/49** (3.5)
– epithelial metaplasia				
♂	1/50 (1.0)	1/50 (1.0)	8/50* (1.1)	33/50** (1.3)
♀	0/49	1/50 (1.0)	0/48	24/49** (1.0)
olfactory epithelium				
– atrophy				
♂	1/50 (1.0)	12/50** (1.1)	47/50** (1.8)	50/50** (2.4)
♀	0/49	6/50* (1.3)	44/48** (1.7)	49/49** (2.3)
– fibrosis				
♂	0/50	1/50 (1.0)	26/50** (1.0)	40/50** (2.0)
♀	0/49	0/50	16/48** (1.3)	31/49** (1.7)
– hyperplasia				
♂	0/50	1/50 (1.0)	42/50** (1.0)	40/50** (1.8)
♀	0/49	0/50	31/48** (1.2)	41/49** (1.5)
– metaplasia				
♂	1/50 (1.0)	8/50* (1.3)	37/50** (1.5)	49/50** (2.2)
♀	0/49	5/50* (1.2)	37/48** (1.5)	48/49** (2.2)
respiratory epithelium				
– hyperplasia				
♂	0/50	26/50** (1.8)	50/50** (2.5)	50/50** (3.5)
♀	0/49	18/50** (1.4)	40/48** (2.1)	49/49** (3.2)
– epithelial metaplasia				
♂	0/50	0/50	3/50 (1.0)	26/50** (1.4)
♀	0/49	0/50	2/48 (1.0)	10/49** (1.2)
<b>kidneys</b>				
– mineralization				
♂	2/50 (3.0)	2/50 (3.0)	2/50 (4.0)	28/50** (3.3)
♀	0/50	1/49 (2.0)	0/49	0/50

**Table 1** (Continued)

	Concentration [ml/m <sup>3</sup> ]			
	0	2	8	32
– nephropathy				
♂	50/50 (2.9)	49/50 (2.9)	50/50 (3.1)	50/50 (3.7)**
♀	47/50 (1.9)	45/49 (1.9)	47/49 (1.9)	47/50 (2.4)**
<b>parathyroid</b>				
– hyperplasia				
♂	9/49 (2.1)	5/45 (3.0)	12/50 (2.4)	39/49** (3.6)
<b>bone</b>				
– fibrous osteodystrophy				
♂	2/50 (2.0)	5/50 (2.2)	6/50 (2.5)	34/50** (3.2)
<b>B6C3F<sub>1</sub> mice</b>				
<b>nose</b>				
– suppurative inflammation				
♂	7/50 (1.4)	11/49 (1.2)	27/49** (1.3)	28/50** (1.7)
♀	5/50 (1.2)	12/48** (1.1)	25/49** (1.5)	42/50** (2.0)
Bowman's glands				
– hyperplasia				
♂	0/50	10/49** (1.2)	48/49** (1.3)	46/50** (1.7)
♀	0/50	33/48** (1.1)	46/49** (2.8)	47/50** (3.1)
– epithelial metaplasia				
♂	0/50	6/49* (1.0)	35/49** (1.1)	47/50** (1.5)
♀	1/50	1/48 (1.0)	34/49** (1.1)	46/50** (1.5)
lateral mucosa				
– epithelial metaplasia				
♂	0/50 (1.0)	9/49** (1.0)	10/49* (1.7)	20/50** (1.5)
♀	3/50 (1.0)	14/48** (1.4)	16/49** (1.4)	36/50** (1.9)
olfactory epithelium				
– atrophy				
♂	1/50 (1.0)	12/49** (1.1)	47/49** (1.8)	50/50** (2.4)
♀	0/50	6/48* (1.3)	44/49** (1.7)	49/50** (2.3)
– hyaline degeneration				
♂	2/50 (1.5)	3/49 (1.7)	21/49** (1.3)	39/50** (2.0)
♀	7/50 (1.3)	14/48 (1.4)	28/49** (1.8)	45/50** (2.2)
– metaplasia				
♂	0/50	12/49** (1.0)	49/49** (1.0)	50/50** (1.8)
♀	0/50	31/48** (1.2)	49/49** (3.0)	49/50** (3.6)
respiratory epithelium				
– hyaline degeneration				
♂	5/50 (1.0)	18/49** (1.1)	42/49** (1.3)	45/50** (1.2)
♀	19/50 (1.4)	44/48** (1.5)	49/49** (1.3)	48/50** (1.4)

**Table 1** (Continued)

	Concentration [ml/m <sup>3</sup> ]			
	0	2	8	32
– epithelial metaplasia				
♂	0/50	2/49 (1.0)	10/49** (1.1)	20/50** (1.4)
♀	1/50 (1.0)	9/48** (1.8)	21/49** (1.7)	39/50** (1.9)
– necrosis				
♂	1/50 (2.0)	0/49	0/49	1/50 (1.0)
♀	0/50	0/48	2/49 (2.5)	3/50 (1.3)
– regeneration				
♂	0/50	1/49 (1.0)	13/49** (1.0)	21/50** (1.0)
♀	0/50	0/48	9/49** (1.0)	13/50** (1.2)
<b>kidneys</b>				
– nephropathy				
♂	49/50 (1.2)	48/49 (1.4)	43/49 (1.5)	47/50 (1.8)
♀	41/50 (1.0)	35/48 (1.1)	40/49 (1.2)	39/49 (1.0)
renal tubules				
– degeneration				
♂	0/50	0/49	1/49 (1.0)	48/50** (1.0)

<sup>a)</sup> affected animals; average severity (1–4; minimal to marked) in brackets

<sup>b)</sup> tested animals

\*  $p < 0.05$  and \*\*  $p < 0.01$  compared with the incidence in controls (poly-3 test for incidences; Mann-Whitney U test for severity)

In a 2-year study, groups of 50 male and 50 female B6C3F<sub>1</sub> mice were exposed to furfuryl alcohol concentrations of 0, 2, 8 or 32 ml/m<sup>3</sup> in whole-animal exposure chambers for 6 hours a day, on 5 days a week. The survival and body weights of the males and the survival of the females were normal. The body weights of the exposed female mice were lower than those of the control animals. Focal corneal opacity was found in the female mice after 32 ml/m<sup>3</sup>. Irritation of the nasal mucosa was observed after concentrations of 2 ml/m<sup>3</sup> and above, and its incidence increased with the concentration. After 32 ml/m<sup>3</sup>, the incidence of renal tubule degeneration was significantly increased. The severity of nephropathy increased with the concentration. A NOAEC was not obtained. The tumour incidences are listed in Section 5.7.2 (Table 1; NTP 1999).

### 5.2.2 Ingestion

In an unpublished study from 1952, moderate degeneration of hepatocytes and tubular epithelial cells in the renal cortex was observed in rats given doses of 75, 150 or 300 mg/kg body weight. In mice given doses of 300 or 600 mg/kg body weight, these findings were more pronounced and included necrosis and vacuolation in the cytoplasm (no other details; NTP 1999).



Male and female F344 rats and B6C3F<sub>1</sub> mice were given gavage doses of furfuryl alcohol of 0, 38, 75, 150 or 300 mg/kg body weight for 13 weeks; mice were additionally given 600 mg/kg body weight. All rats died after exposure to 150 mg/kg body weight and above, and some mice died after exposure to 300 mg/kg body weight and above. The absolute liver and kidney weights of the rats were increased at 75 mg/kg body weight. The body weights of the mice were reduced by 15% at 600 mg/kg body weight. No other differences in body weights were observed either in rats or in the remaining groups of mice (unpublished data; no other details; NTP 1999).

### 5.3 Local effects on skin and mucous membranes

Furfuryl alcohol is irritating to the skin (ECB 2000) and eyes in rabbits (documentation "Furfuryl alcohol" 1996; ECB 2000). The substance is irritating to the nasal mucosa in rats and mice (see Section 5.2.1; NTP 1999).

### 5.4 Allergenic effects

There are still no data available for the allergenic effects of furfuryl alcohol.

### 5.5 Developmental and reproductive toxicity

There are still no data available for this end point. After 14-week inhalation exposure, the spermatid count and the number of spermatid heads were increased in rats after furfuryl alcohol concentrations of 32 ml/m<sup>3</sup>. Motility or the concentration of spermatozoa were not affected. There were no significant differences in vaginal cytology (see Section 5.2.1; NTP 1999).

A parallel study in mice did not reveal any significant changes in the spermatid count, sperm motility or vaginal cytology after exposure to furfuryl alcohol concentrations up to 32 ml/m<sup>3</sup> (see Section 5.2.1; NTP 1999).

### 5.6 Genotoxicity

Various genotoxicity tests carried out by the NTP are described below (NTP 1999). Further genotoxicity tests (Salmonella mutagenicity test, SCE in vitro: results negative; chromosomal aberrations in vitro: results positive, Drosophila: results negative) were described in the documentation from 1992 (documentation "Furfuryl alcohol" 1996).

### 5.6.1 In vitro

SCE (sister chromatid exchange) was induced in CHO cells (a cell line derived from Chinese hamster ovary) by furfuryl alcohol concentrations of 16–500 µg/ml in the absence of S9 mix from rat liver, but not in the presence of S9 mix. The induction of chromosomal aberrations was not observed in CHO cells treated with furfuryl alcohol concentrations of up to 500 µg/ml in the absence of S9 mix. In the presence of S9 mix, an increase in aberrations was found in the first test with furfuryl alcohol concentrations of 500 and 1000 µg/ml, but not in the second test (up to 1600 µg/ml); therefore, the overall result was regarded as questionable (NTP 1999). In the in vitro test for chromosomal aberrations with CHO cells already described in the 1992 documentation which yielded positive results (documentation “Furfuryl alcohol” 1996), concentrations of 2.5 mM (furfuryl alcohol concentrations of about 250 µg/ml) and above increased the frequency of chromatid breaks and chromatid exchange with metabolic activation. The effect of furfuryl alcohol was weaker without metabolic activation (Stich et al. 1981). The NTP (NTP 1999) criticized the form of documentation that was used in this publication, which made it difficult to evaluate the results.

### 5.6.2 In vivo

Intraperitoneal injection of furfuryl alcohol into mice up to the MTD (maximum tolerated dose; 150 to 300 mg/kg body weight) did not induce SCE, chromosomal aberrations or micronuclei in the bone marrow. The frequency of SCE was determined 23 or 42 hours after administration, and aberrations were evaluated 17 or 36 hours after administration. Micronuclei were examined at 24-hour intervals beginning 24 hours after the last of 3 administered doses; there was a change in the ratio of polychromatic to normochromatic erythrocytes, but it was not related to the dose (Abbott et al. 1991; NTP 1999).

In a chromosomal aberration test, Swiss albino mice were given 0.5 ml of an aqueous furfuryl alcohol solution containing 0.1%, 0.2% or 0.4% of the substance (about 0.5, 1 or 2 mg/animal; doses of about 25, 50 and 100 mg/kg body weight assuming a body weight of 20 g). The MTD was not determined. Furfuryl alcohol was administered by gavage either just once or once a day for 5 days. Two animals per dose were examined 6, 12, 18, 24, 36, 48 or 72 hours after the last administration. The mitotic index was reduced by furfuryl alcohol in a dose-dependent manner; this was significant at the 5% level only in the high dose group with a decrease of 15%. At 0.4%, the incidence of chromosomal aberrations was described as significantly increased 12 to 36 hours after administration for both types of treatment (Sujatha and Subramanyam 1994). In this study, only 2 animals were used per dose group and interval. This neither complies with OECD Test Guideline 475, nor is it possible to carry out an acceptable statistical evaluation. A further deficiency of the study is that the types of aberration were not defined: no distinction is made between gaps and breaks, centric fusions and centromeric associations, or fragments and terminal deletions. The data presented in the tables were insufficient since only

absolute aberration counts were given without any reference to the number of cells evaluated. This study has so many inadequacies that it cannot be used as evidence of a clastogenic effect of furfuryl alcohol.

## 5.7 Carcinogenicity

### 5.7.1 Short-term tests

Furfuryl alcohol did not lead to cell transformation in the SHE test (Syrian hamster embryo cell transformation assay) up to the cytotoxic concentration range (Kerckaert et al. 1996).

### 5.7.2 Long-term studies

In the 2-year study described in Section 5.2.1 with furfuryl alcohol concentrations of 0, 2, 8 or 32 ml/m<sup>3</sup>, the animals were examined for tumours at the end of the exposure period (Table 2). Because of the questionable increase in tumour incidences, an extended evaluation was carried out with 8 additional sections per kidney in addition to the standard evaluation. Adenomas and carcinomas of the nasal mucosa were observed in F344 rats. The incidence of these tumours was significantly increased in the males of the high concentration group compared with that in the control group. In male rats, a marginal increase in renal tumours was recorded only after additional kidney sections had been evaluated, but the authors did not regard this increase as substance-related. A marginally increased incidence of renal adenomas was detected in females; the increase was concentration-dependent, but not significant. Although renal tumours are rarely observed in female rats, the authors considered it to be uncertain whether their occurrence was related to the test substance, as the number of renal adenomas was only marginally higher after the exposure concentration was increased 16-fold, while the incidence of renal tubule hyperplasia was considerably increased. No nasal tumours were found in mice, but precursors such as metaplasia were observed in the respiratory and olfactory epithelium at the low concentration. In the male mice of the high concentration group, the incidence of renal tumours was increased and above the highest range of the historical controls (inhalation studies up to 1996 carried out in the contract laboratory of the NTP for this study). This applies to both adenomas and carcinomas. The tumours occurred only in the high concentration group, with simultaneous degeneration of the renal tubules, which may be regarded as evidence of renal toxicity. The NTP concluded that there was “some evidence” of carcinogenicity in male rats on the basis of nasal tumours, “equivocal evidence” in female rats on the basis of renal tumours, “some evidence” in male mice on the basis of renal tumours and “no evidence” in female mice. The Commission regarded the nasal tumours in rats and the renal tumours in mice as substance-induced and relevant to humans.

**Table 2** Incidences of tumours and their precursors in the 2-year study in F344 rats and B6C3F<sub>1</sub> mice (NTP 1999)

Author:	NTP 1999			
Substance:	furfuryl alcohol (purity: > 98%)			
Species:	rat, F344/N, 50 ♂/50 ♀			
Administration route:	inhalation			
Concentration:	0, 2, 8, 32 ml/m <sup>3</sup>			
Duration:	2 years, 5 days/week, 6 hours/day			
Toxicity:	2 ml/m <sup>3</sup> and above: local irritation, survival and body weights of the ♂ animals of the high concentration group ↓			
Tumours:				
	Concentration [ml/m <sup>3</sup> ]			
	0	2	8	32
<b>nose</b>				
lateral wall				
– adenomas				
♂	0 <sup>a)</sup> /50 <sup>b)</sup>	1/50 (2%)	0/50	0/50
♀	0/49	0/50	1/48 (2%)	0/49
respiratory epithelium				
– adenomas				
♂ <sup>c)</sup>	0/50	0/50	1/50 (2%)	0/50
♀ <sup>d)</sup>	0/49	0/50	0/48	1/49 (2%)
– carcinomas				
♂ <sup>e)</sup>	0/50	0/50	0/50	1/50 (2%)
– squamous cell carcinomas				
♂ <sup>e)</sup>	0/50	0/50	0/50	3/50 (6%)
sum of nasal tumours				
♂	0/50	1/50 (2%)	1/50 (2%)	4/50* (8%)
♀	0/49	0/50	1/48 (2%)	1/49 (2%)
<b>kidneys</b>				
– renal tubule hyperplasia				
♂ <sup>f)</sup>	10/50 (2.4)	7/50 (2.3)	7/50 (2.3)	25/50** (2.8)
♀ <sup>f)</sup>	2/50 (1.0)	1/49 (2.0)	3/49 (2.0)	11/50* (2.0)
– adenomas				
♂ <sup>g), h)</sup>	1/50 (2%)	1/50 (2%)	2/50 (4%)	0/50
♀ <sup>g), i)</sup>	0/50	0/49	0/49	2/50 (4%)
♂ <sup>f)</sup>	2/50 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
♀ <sup>f)</sup>	0/50	0/49	2/49 (4%)	2/50 (4%)
– carcinomas				
♀ <sup>g), j)</sup>	0/50	1/49 (2%)	0/49	0/50
♀ <sup>f)</sup>	0/50	1/49 (2%)	0/49	0/50

**Table 2** (Continued)

sum of renal tumours				
♂ <sup>g)</sup>	1/50 (2%)	1/50 (2%)	2/50 (4%)	0/50
♀ <sup>g), k)</sup>	0/50	1/49 (2%)	0/49	2/50 (4%)
♂ <sup>f)</sup>	2/50 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
♀ <sup>f)</sup>	0/50	1/49 (2%)	2/49 (4%)	2/50 (4%)
Author:	NTP 1999			
Substance:	furfuryl alcohol (purity: > 98%)			
Species:	mouse, B6C3F <sub>1</sub> , 50 ♂/50 ♀			
Administration route:	inhalation			
Concentration:	0, 2, 8, 32 ml/m <sup>3</sup>			
Duration:	2 years, 5 days/week, 6 hours/day			
Toxicity:	2 ml/m <sup>3</sup> and above: local irritation			
Tumours:				
	Concentration [ml/m <sup>3</sup> ]			
	0	2	8	32
<b>kidneys</b>				
– renal tubule hyperplasia <sup>f)</sup>				
♂	4/50 (1.5)	8/49 (1.0)	3/49 (1.0)	5/50 (2.0)
– adenomas				
♂ <sup>g), l)</sup>	0/50	0/49	0/49	2/50 (4%)
♂ <sup>f)</sup>	0/50	0/49	0/49	3/50 (6%)
– carcinomas				
♂ <sup>g), m)</sup>	0/50	0/49	0/49	2/50 (4%)
♂ <sup>f)</sup>	0/50	0/49	0/49	2/50 (4%)
sum of renal tumours				
♂ <sup>g), n)</sup>	0/50	0/49	0/49	4/50 (8%)
♂ <sup>f)</sup>	0/50	0/49	0/49	5/50* (10%)

a) affected animals; average severity (1–4; minimal to marked) of hyperplasia in brackets

b) tested animals

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

f) sum of the incidences from standard evaluation and 8 additional sections per kidney

g) standard evaluation

h) historical control incidence: 9/902 (1.0% ± 1.2%); range: 0–4%

i) historical control incidence: 1/898 (0.1% ± 0.5%); range: 0–2%

j) historical control incidence: 4/898 (0.5% ± 0.9%); range: 0–2%

k) historical control incidence: 5/898 (0.6% ± 0.9%); range: 0–2%

l) historical control incidence: 3/1093 (0.3% ± 0.6%); range: 0–2%

m) historical control incidence: 1/1093 (0.1% ± 0.4%); range: 0–2%

n) historical control incidence: 4/1093 (0.4% ± 1.0%); range: 0–4%

\*  $p < 0.05$  and \*\*  $p < 0.01$  compared with incidence in the controls (poly-3 test for incidences; Mann-Whitney U test for severity)

## 6 Manifesto (MAK value/classification)

The inhalation of furfuryl alcohol caused slight, but significant increases in the incidences of tumours in the nasal epithelium of male rats and increases in the incidences of renal tumours in female rats that, however, were not significant. The renal tumours were observed in female animals at the high concentration; nephropathy was also increased at this concentration. In male mice, the incidence of renal tumours was slightly, but significantly increased, and was accompanied by degeneration of the renal tubules, a sign of cytotoxicity.

The nasal tumours might have been caused by the genotoxic effects of the metabolite furfural or by irritation, which seems to be more likely because the in vitro chromosomal aberration tests with furfuryl alcohol yielded only questionably positive results and the tests in vivo were negative. Since the mechanism of the development of renal tumours is unclear, furfuryl alcohol has been classified in Carcinogen Category 3B.

In the absence of a NOAEC, no MAK value can be derived from the data. In a 2-year study, signs of local irritation were observed in the noses of rats and mice at the lowest concentration tested of 2 ml/m<sup>3</sup> and above.

Workplace experience has shown that irritation of the respiratory tract and eyes occurs after exposure to concentrations of 1.75 ml/m<sup>3</sup> and above with peak concentrations of more than 10 ml/m<sup>3</sup>. The previous MAK value of 10 ml/m<sup>3</sup> is too high and has been withdrawn. The maximum workplace concentration must be below 2 ml/m<sup>3</sup> by a wide margin.

There are no recent data available for sensitization caused by furfuryl alcohol. Therefore, the substance has not been given the designation “Sa” or “Sh” (for substances that cause sensitization of the airways or skin).

There are no recent data available for the absorption of furfuryl alcohol through the skin. On account of its low dermal LD<sub>50</sub> in rabbits, the substance has already been designated with an “H” (supplement “Furfuryl alcohol” 2003). This designation has been retained.

The valid in vivo genotoxicity tests yielded negative results. In view of the positive results obtained in an earlier in vitro study for chromosomal aberrations, a local genotoxic potential cannot be ruled out. However, on the basis of the available data furfuryl alcohol has not been classified as a germ cell mutagen.

There are still no valid developmental toxicity studies available. As no MAK value can be derived, furfuryl alcohol has not been classified in a pregnancy risk group.

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