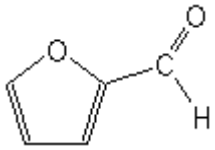
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	98-01-1
Chemical Name	Furfural
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

After oral exposure of rats to ^{14}C-furfural, at least 90% was absorbed in the gastro-intestinal tract. After inhalation exposure of humans, pulmonary retention was 78%. After dermal exposure of humans to liquid furfural, about 3 µg/cm^2/min were absorbed. Dermal absorption of humans exposed to furfural vapours is about 30% of the amount absorbed through inhalation.

Distribution of ^{14}C-furfural was studied in rats at 72 hrs after administration of single doses. The highest concentrations were found in liver and kidney and the lowest concentrations were found in the brain.

In rats and mice, the biotransformation of furfural occurs primarily via two routes. The major part is oxidised to furoic acid that is excreted free or conjugated with glycine as furoylglycine. The minor part condenses with acetic acid to form furanacrylic acid that is excreted after conjugation with glycine as furanacryluric acid. Metabolic profiles of these two species were very similar. After oral exposure the urinary metabolite profile was furoyl-glycine (approx. 80%), furoic acid (2%- 10%), furanacryluric acid 10-35%), furanacrylic acid (2%) and an unidentified very polar metabolite (1-2%). In humans, the main urinary metabolite after inhalation exposure is furoylglycine (120-130% of the amount of furfural retained by inhalation; the excess as compared to inhalation retention was explained by dermal absorption of the vapour). Furanacryluric acid (0.5 – 5%) and negligible amounts of furoic acid are also found. Observed differences in metabolite levels between humans and rodents are most likely due to differences in dose levels (in animals high dose levels may lead to glycine depletion) exposure routes and duration rather than being caused by intrinsic interspecies differences in metabolism.

In animals at 72 hrs post dosing, about 76-100% of the radioactivity was excreted in urine, 2-7% in faeces, 5-7% was exhaled and less than 1% was found in the carcass. Biological half-life of furfural after inhalation in humans is about 2-2.5 hours.

The oral LD_{50} values for rat ranged between 50 and 149 mg/kg bw whereas the oral LD_{50} values for mice and dogs ranged between 400-500 mg/kg and 650-950 mg/kg, respectively. The LD_{50} value for guinea pigs was 541 mg/kg bw. The inhalation LC_{50} for rats after 1-h, 4-h or 6-h exposure was 4075 mg/m^3, 600-924 mg/m^3, and 688 mg/m^3 respectively, whereas the inhalation LC_{50} for mice was 490 mg/m^3 after 6-h exposure. The dermal LD_{50} of >310 mg/kg and <1000 mg/kg were reported for rabbits and guinea pigs, respectively. A dermal dose of 620 mg/kg is reported to be lethal to rabbits. Sublethal effects were seen in the livers of rats after a single exposure by gavage of 50 mg/kg bw. The changes consisted of scattered eosinophilic globules and a significant increase in the number of mitotic hepatocytes. No zonal or massive necrosis was observed.

No standard skin and eye irritation studies were available. Intensive but reversible skin irritation was reported in guinea pigs after three daily 4-hour dermal applications of neat liquid furfural. With 5% furfural a very mild reaction was noted, whereas applications of 1% furfural did not produce any signs of irritation. When applied to intact shaved skin for 4 hours on 20 successive days, undiluted furfural resulted in hyperplasia, hyperkeratosis and exfoliation of the epidermis. Still in guinea pigs, similar but less severe effects were observed with 5 and 1% furfural. In a limited study report, undiluted furfural (45-1000 mg/kg bw) was applied to the shaved non-abraded skin of rabbits (occlusive conditions) for 48 hours. After another 48 hours, mild local irritation was observed in the 45-500 mg/kg bw exposure groups. No data were available on the extent (e.g., scores) and reversibility of this irritation. However, in the 1000 mg/kg bw group, all rabbits died within 12 hours, but no evidence of irritation was observed at the site of administration.

In humans, eye and respiratory tract irritation was attributed to furfural vapours which were detected at concentrations ranging from 20 to 63 mg/m^3. Eye irritation was manifested by itching, burning, tearing and/or redness and respiratory irritation was manifested by frequent nasal irritation (stuffiness, dryness or soreness) and sometimes dryness of the mouth or throat.

Undiluted liquid furfural was instilled in the eyes of 15 male adult white rabbits. Slight oedema of the conjunctiva was observed after the application of 0.001-0.002 ml. After exposure to 0.04 ml, marked irritation, with eyelid spasm, for about 5 days was reported. The eyes appeared normal on day 7. Application of 0.09-1 ml furfural resulted in eyelid spasm for 7 days with gross corneal opacity. The eyes appeared normal at day 9. Furfural vapour is reported to be irritating to the eyes of rabbits, but no details (e.g., scores) are available.

In a study with two different strains, mice exposed to furfural showed a rapid decrease in respiratory rate with RD_{50} values of 920 mg/m^3 and 1128 mg/m^3. In several repeated exposure studies respiratory tract irritation has been observed. Furfural-induced histopathological changes were observed in the nose in hamsters exposed to furfural vapours at concentrations up to 2165 mg/m^3 for 6 hours/day, 5 days/week for a period of 13 weeks. The changes consisted of focal atrophy of the olfactory epithelium often accompanied by accumulation of sensory cells in the lamina propria as well as the occurrence of cyst-like structures lined by flat or cuboidal epithelium. The incidence and degree of these changes were clearly dose-related and for these local effects a NOAEL and a LOAEL of 77 and 448 mg/m^3, respectively, were determined.

Rabbits were exposed up to 1000 g/m^3 by inhalation, for 4 hours/day, 5 days/week, until death (<80 days) At 1000 g/m^3/h, rabbits showed signs of irritation of the conjunctiva and the mucosa of the upper respiratory tract. At autopsy, the lungs appeared congested and oedematous. Rats (5 animals/sex/group) were exposed to furfural vapour for 28 days at concentrations up to 1280 mg/m^3 for 6 hours/day. Histopathological changes were limited to the nasal passages, consisting of both respiratory epithelial lesions such as squamous metaplasia and atypical hyperplasia, and olfactory epithelial changes characterized by epithelial disarrangement. At the lowest concentrations of 20 and 40 mg/m^3, effects were generally limited to the anterior part of the nose (metaplasia and hyperplasia of transitional respiratory epithelium). At higher exposure concentrations (≥80 mg/m^3), treatment-related changes of the lining epithelium were also seen in more posterior areas of the nose. Incidence and severity were higher at higher concentrations.

Based on the information above, it is concluded that furfural is irritating to skin, eye and respiratory tract. Furfural is not a skin sensitiser based on Buehler and Maximisation tests, among which a test was conducted according to OECD TG 406.

In repeated dose toxicity studies in rats and mice using the oral route of exposure, NOAELs varied from < 11 – 200 mg/kg bw/day. In the study reporting a NOAEL of <11 mg/kg bw/day, male rats at all dose levels exhibited cytoplasmic vacuolization of hepatocytes in the centrilobular region that is considered treatment related based on the occurrence of mild centrilobular necrosis in male rats in an oral carcinogenicity study with gavage administration. In 16-day repeated dose gavage studies with rats and mice exposed up to 240 mg/kg bw

(rats) and 400 mg/kg bw (mice), increased mortality was observed in both species at the highest dose levels. Surviving animals did not show growth retardation or histopathological changes (tissues not specified), but at 120 mg/kg bw/d in rats a slight reduction in activity was observed. Based on this information for rats a NOAEL of 60 mg/kg bw was derived and for mice a NOAEL of 200 mg/kg bw was set. In a 13-week study with rats, furfural was applied via the diet in a microencapsulated form to prevent volatilisation. The doses used were 0, 26-28, 53-57, 82-86 and 160-170 mg/kg bw/day. Minor hepatocellular alterations were seen in males dosed with 82 and 160 mg/kg bw/day. A NOAEL of 53 mg/kg bw/d was set. The lowest NOAEC derived in inhalation studies was < 20 mg/m^3 for local effects that included metaplasia and hyperplasia of transitional respiratory epithelium in the anterior part of the nose of the rat. The lowest NOAEC for systemic effects was 320 mg/m^3. No usable dermal repeated dose studies are available.

Furfural has the potential to cause chromosomal aberrations and gene mutations *in vitro*. Furfural does not induce chromosome aberrations and SCEs in bone marrow cells of mice after i.p. treatment. There was limited evidence for chromosomal breaks from a less reliable *in vivo* Comet assay in mice. Furfural was negative in *in vivo* UDS tests with rat and mouse hepatocytes. Orally administered furfural was unable to induce gene mutations in the liver of λlacZ transgenic mice. Overall, it is concluded based on a weight of evidence approach that furfural is not genotoxic.

It appears that furfural is carcinogenic in animals after oral administration. In 103-week oral gavage studies in rats and mice, furfural was carcinogenic in mice whereas less convincing evidence was found in rats. An increased incidence of hepatocellular adenomas was found in male and female mice at 175 mg/kg bw/d and at the same dose, male mice showed an increased incidence of hepatocellular carcinomas. A low incidence of uncommon cholangiocarcinomas and bile duct dysplasia with fibrosis were observed in male rats dosed with 60 mg/kg bw/d whereas no effects were seen in female rats. It should be noted that in both species, some target organ (liver) toxicity was observed at dose levels below those that induced tumours. No adequate inhalation and dermal exposure carcinogenic studies were available. Co-carcinogenic effects of furfural on the respiratory tract of hamsters were suggested based on a study where hamsters were treated with furfural alone or in combination with benzo(a)pyrene. Similarly, co-carcinogenic effects of furfural were also studied in oral and dermal studies when applied together with 2-acetylaminofluorene or tetradecanoylphorbol-acetate. Although the mode of action underlying the carcinogenic activity of furfural after oral exposure is still unclear, it is apparently not genotoxic. Rather, the tumours appear to be induced via a mechanism involving liver toxicity. The oral NOAEL was set at 53 mg/kg bw/d, which was one of the doses used in a repeated dose dietary study.

No fertility studies were available with furfural. However, no effects were found on the reproductive organs of both male and female F344/N rats and B6C3F1 mice in two-year gavage studies at dose levels up to 60 mg/kg in the rats and up to 175 mg/kg bw in mice. The animals were dosed 5d/wk. The following relevant tissues were examined: epididimys, penis, preputial gland, prostate, seminal vesicles, testes, coagulating gland, clitoral gland, ovaries, uterus, vagina, and tissues from all endocrine glands. In (sub)chronic inhalation exposure studies, hamsters were exposed to furfural at levels up to 2165 mg/m^3, 6h/d, 5d/wk. The following relevant tissues were examined: testes, prostate and uterus. In these studies no treatment related effects were observed at any dose level on the tissues mentioned. In a developmental toxicity study in rats administered furfural by oral gavage at doses up to 150 mg/kg bw/d for days 6-15 of gestation (OECD TG 414), the NOAEL for developmental effects was ≥ 100 mg/kg bw/d. At the highest dose level, developmental toxicity was not observed, but due to high death rates among the dams, the sensitivity of the study was insufficient. The NOAEL for maternal toxicity was < 50 mg/kg bw/day based on exophthalmia during gestation day 6-18 at all dose levels. No treatment-related effects were found at scheduled necropsy in the females. Furfural is not considered to be a reproductive toxicant.

Environment

Furfural is a liquid with a melting point of -36.5 to -39˚C and a boiling point of 162˚C at 1013 hPa. The vapour pressure of furfural is 1.33-1.73 hPa at 18.5˚C, its water solubility is 83 g/l at 20˚C and its log K_{ow} is 0.41.

Furfural reacts rapidly with hydroxyl radicals in the atmosphere; this reaction has an estimated half-life of 0.44 days. Night time destruction of furfural by nitrate radicals may be important in urban areas. Direct photochemical degradation is expected to occur but no data exist for this process. Furfural is not expected to hydrolyse under

environmental conditions. In contrast, furfural is readily biodegradable under both aerobic (93.5% degradation after 28 days in a modified MITI test according to OECD TG 301C) and anaerobic conditions. Volatilisation of furfural from surface waters is not expected to be rapid because Henry law's constant for furfural has been calculated to range from 0.2 $Pa.m^3/mol$ to 0.375 $Pa.m^3/mol$. Calculated K_{oc} values range from 1- 40 l/kg (a K_{oc} of 17.1was calculated using a QSAR for non-hydrophobics). These values suggest that furfural is highly mobile in soil. Furfural may volatilize from soil to the atmosphere but this process is not expected to be rapid. Furfural in the atmosphere can be removed by wet deposition. Based on Level III distribution modelling using EPISUITE (assuming equal and continuous releases to air, water and soil), it is estimated that the majority of furfural released to the environment will partition mainly into soil (53.2%) and water (45.6%) with small amounts to air (1.1%) and sediment (<0.1%). With the SimpleTreat model the distribution of furfural in a Sewage Treatment Plant was simulated, showing that the substance will be degraded for 87% and the remaining part will go to the water compartment (13%). Because of high water solubility and low log K_{ow}, furfural is not expected to bioaccumulate. Calculated BCF for fish and worm are 1.41 l/kg and 0.95 l/kg, respectively.

All available ecotoxicity results were obtained using freshwater species. Short-term LC_{50} values in fish range from 10.5 to 32 mg/l with *Poecilia reticulata* being the most sensitive species. It is noted that the LC_{50} value of 10.5 mg/l (measured) for P. *reticulata* was derived from a 14-d prolonged toxicity test, while the other LC_{50} values for fish (ranging from 16 to 32 mg/l; based on data for four different fish species) were derived from 48-h to 96-h acute toxicity tests. For the invertebrate *Daphnia magna* there are two acute LC_{50} values, from different studies, being a 24-h LC_{50} of 29 mg/l (nominal) and a 72-h LC_{50} of 13 mg/l. Acute toxicity data for aquatic plants are not available. However, NOEC values of 2.7 and 31 mg/l (nominal) were obtained for blue and green algae, respectively, based on 8-day tests. A long-term NOEC of 0.33 mg/l, based on measured test concentrations, was obtained for fish in a 12-day early-life stage toxicity test using embryo and sac-fry stages of the zebrafish. A NOEC of 1.9 mg/l (measured) was obtained for *Daphnia magna* in a 21-day flow-through life-cycle toxicity test. An EC_{50} value of 760 mg/l was obtained for activated sludge bacteria. NOEC values ranging from 0.59 to 16 mg/l were obtained for microorganisms.

Exposure

Furfural is produced industrially from pentosan polysaccharides that are natural substances in non-food residues and food crops. Furfural is produced in two European Union countries and imported by several EU countries from countries outside the EU. EU production and import for the year 2000 was assessed to be about 41,000 to 44,000 tonnes whereas export was estimated to be 1000 tonnes. The world production of furfural is estimated to be greater than 240,000 tonnes/year.

Furfural has numerous applications. The primary uses are as starting material for the production of derivatives (75% of total use) and use as extraction solvent in refineries (13.5% of total use). Other uses include manufacturing of refractories and pesticides, use as a chemical trace in gas-oil, as a solvent or reactive solvent, wetting agent, biocide, decolourizing agent for wood resin, flavour component in a range of food, fragrance in cosmetic products, reagent in analytical chemistry, in road construction and metal refining.

Furfural may be released to the environment during its manufacture, formulation or use in commercial products. In addition, humans are exposed to furfural because of its ubiquitous natural occurrence in various food sources such as fruits, vegetables, wine, bread and in several essential oils of plants. As an unintentional source, furfural is a major contaminant of the sulfite pulping processes used in the pulp and paper industry. It is also formed as a by-product in the treatment of hemicellulose feed stocks and in the refuse of chemical and fuel production. Furfural may also be released to the environment via the smoke from burning wood and tobacco.

Occupational exposure may occur during production of furfural and during its use in several industries. The routes of exposure for the worker are through inhalation and via dermal contact. Occupational Exposure Limits (OEL values) are available, but not harmonized.

The two most important sources of furfural exposure for the consumer are its use as fragrance material in cosmetic products and its use as flavouring substance in several food categories. Furfural concentrations in cosmetic products are reported up to a maximum of 0.1%. In the European Union, the average maximum use

level of furfural in food categories ranges from 4.2 to 63 mg/kg.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (acute toxicity, skin, eye and respiratory tract irritation, limited evidence for carcinogenicity). Member countries are invited to perform an exposure assessment for workers, and if necessary, a risk assessment.
Note: A risk assessment performed in the context of the EU Existing Substances Regulation (793/93/EEC) in the European Union is available.

Environment: The chemical is currently of low priority for further work. The substance has properties indicating a hazard for the environment (acute toxicity to fish and invertebrates between 10 and 100 mg/l). However, the chemical is of low priority for further work because of its ready biodegradation and its limited potential for bioaccumulation.