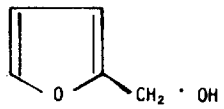
## II. BIOLOGIC EFFECTS OF EXPOSURE

### Extent of Exposure

Furfuryl alcohol is a colorless, faintly odorous liquid that darkens during storage due to auto-oxidation and intermolecular dehydrations [1]. Furfuryl alcohol also is known as 2-furylcarbinol, 2-furylmethanol, 2-furanmethanol, furfural alcohol, and 2-(hydroxymethyl) furan. The structural formula for furfuryl alcohol appears below.




Furfuryl alcohol is a very reactive heterocyclic compound consisting of two moieties, the furan nucleus and a hydroxymethyl group. Because of the latter moiety, furfuryl alcohol undergoes reactions typical of a primary aliphatic alcohol, such as replacements, esterifications, or oxidations [2,3]. The furan ring undergoes substitution of ring hydrogens [2], or can be cleaved to yield aliphatic compounds [3].

Furfuryl alcohol has a boiling point of 170 C (338 F) and is not a highly volatile liquid at room temperature. Its vapor pressure is 1.0 mmHg at 31.8 C (89.2 F), rising to 271 mmHg at 140 C (284 F) [1,2]. The vapor pressures of furfuryl alcohol at various temperatures are presented in Figure IX-1. According to the definitions set forth in 42 CFR 1910.106, furfuryl alcohol has a IIIA combustibility rating. Its fires can be extinguished with water, foam, carbon dioxide, or dry chemicals [2]. Although sensitive to the effects of acids, it remains fairly stable in alkaline media [2,3]. Physical and chemical properties of furfuryl alcohol are presented in Table IX-1.

Furfuryl alcohol is found in processed natural foods including the oils of chicory and roasted coffee, in yellow leaf tobacco, and in heated skim milk [4-11], usually as a result of processing. In a 1932 report from Germany [5], commercially available coffee reportedly contained 0.025-0.125% furfuryl alcohol. By calculation, then, a cup containing 0.25 liter of freshly brewed coffee might contain approximately 1.9 mg of furfuryl alcohol [5]. In yellow leaf tobacco and in heated skim milk, the approximate concentrations of furfuryl alcohol are 80 µg/g and 208 mg/liter, respectively [6,11].

The high-yield industrial production of furfuryl alcohol features the hydrogenation of the aldehyde furfural, as liquid or vapor, in the presence of a suitable metallic catalyst [12], eg, a mixture of metallic nickel and magnesium oxide (60:900 parts W/W) at 90-170 C (194-338 F) and about 200

pounds per square inch (1.38 MPa) [13]. The yield of furfuryl alcohol, from either liquid or vaporized furfural, can be markedly changed by varying the catalysts, pressure, and reaction temperature and time.

Furfuryl alcohol consumption has increased for 30 of the last 40 years of its commercial availability [14]. In 1974, a single producer accounted for the estimated 51-million-pound output of furfuryl alcohol in the United States [15]. According to this producer, nearly 100 million pounds of furfuryl alcohol was used in 1976; usage is expected to increase steadily during the next 5-10 years [14]. All furfuryl alcohol is currently produced at three plants in the United States and at one facility in Belgium.

Furfuryl alcohol is used industrially as a solvent and as a chemical precursor of a host of chemical products, eg, furfuryl halides, furfuryl cyanide, furfuryl ethers, furfuryl esters, and methyl furan. The most important product, however, is furfuryl alcohol resin (commonly called furan resin) [2], the manufacture of which consumes 90-95% of the available furfuryl alcohol [16].

Furfuryl alcohol and furfuryl alcohol-formaldehyde resins are widely used in chemical-resistant construction materials, such as resinous cements, and in asbestos-reinforced equipment and thermosetting compounds. Furan resins, similar to those used to confer chemical resistance, have been used since the late 1950's in both the "hot-box" and "no-bake" methods of binding foundry core sand. The hot-box process, which uses furfuryl alcohol-formaldehyde-urea resin containing 25-45% furfuryl alcohol, cures from within a few seconds to 3 minutes at 177-232 C (351-450 F) to provide good corrosion resistance. The no-bake process with resin containing 50-90% furfuryl alcohol cures without heat within 3 hours and is particularly suited to the production of large foundry cores and molds [17].

Because of its combination of a high boiling point (170 C or 338 F) and excellent water solubility, as well as polarity, furfuryl alcohol is used in industry as a solvent, either alone or in combination with other solvents. For example, automotive acrylic lacquer can be removed completely from drums before their reuse with a hot solution of 40% furfuryl alcohol, 50% water, and 10% trisodium phosphate [2]. In the production of cold-molded grinding wheels, furfuryl alcohol is both a solvent and a temporary plasticizer for phenolic resin. In this process, as a solvent for the powdered phenolic resin, furfuryl alcohol promotes adhesion of the resin to the abrasive grains and becomes a part of the binder solids during curing of the wheels.

One of the principal industrial hazards in the use of furfuryl alcohol is its polymerization reaction following contact with acids. Highly exothermic, these reactions have resulted in violent explosions [18,19].

Because of its physical and chemical properties, furfuryl alcohol can be safely stored at low temperatures in unlined, airtight containers. Furfuryl alcohol is not affected for up to 6 months during storage in steel tanks, but will slowly change color and become less water soluble when stored for longer periods in the presence of air or trace amounts of acid or when heated [3]. Although not used commercially for this purpose, small amounts of an inorganic or organic base (n-butylamine or piperidine) may be added to stabilize furfuryl alcohol in storage [3].

NIOSH estimates that approximately 9,000 workers in the United States are potentially exposed to furfuryl alcohol [20]. Occupations involving potential exposure to furfuryl alcohol are listed in Table IX-2.

## Historical Reports

As early as 1864, furfuryl alcohol was prepared from furfural by reduction with sodium or sodium amalgam [1,4]. Erdmann [4], in an introduction to his 1902 report on the toxicity of furfuryl alcohol in laboratory animals, described the composition and properties of coffee oil and reviewed previous chemical data on furfuryl alcohol, one of its primary ingredients.

Erdmann [4] administered furfuryl alcohol (derived from coffee oil) to 14 rabbits weighing 1.37-3.10 kg (sex, strain, and use of controls were not described) and to 1 female dog of unstated breed weighing 10.61 kg. The rabbits received furfuryl alcohol in 25 or 50% aqueous solutions, 11 by subcutaneous (sc) injection and 3 by gastric intubation, at single doses ranging from 230 to 1,330 mg/kg of body weight. The sc lethal dose was 526-600 mg/kg. Lethal amounts produced significant decreases in rectal temperature followed by what was described as respiratory paralysis within 4-24 hours. In addition to effects on body temperature and respiration, the rabbits showed a pattern of increased mucus secretion, salivation, and lacrimation. There were also increased frequency of urination and defecation, and, at higher doses, lethargy or sleepiness approaching narcosis, labored breathing, coma, and, terminally, cessation of breathing. A necropsy performed on one rabbit 12 hours after it died revealed no unusual organ changes.

The dog was given furfuryl alcohol as a 50% aqueous solution at a total dose of 520 mg/kg in two sc injections 30 minutes apart [4]. Within minutes after the second injection, sneezing and vomiting began and continued for about 20 minutes and for 2 hours, respectively. Diarrhea, bloody feces, appetite loss, lassitude, and reduction in rectal temperature persisted through the next day. Two days later, however, the dog appeared fully recovered.

Erdmann [4], in his study of three men (including himself), noted that furfuryl alcohol in small, single oral doses of 0.6-1.0 g in 5% aqueous solution consistently increased the rate of respiration.

In 1927, Okubo [21] described the results of in vivo and in vitro studies of the effects of pure furfuryl alcohol on mice, rabbits, and guinea pigs. The mice were injected sc with furfuryl alcohol in physiologic saline (0.5-1.0% solution). At 10 mg/kg, furfuryl alcohol had little or no effect, whereas at 50 mg/kg the mice showed marked respiratory depression, weakened reflexes, and disturbed gait but recovered within 4-5 hours. At 100 mg/kg, furfuryl alcohol was lethal within 3-5 hours, death being attributed to respiratory paralysis. Furfuryl alcohol injected intravenously (iv) at unspecified doses reportedly inhibited respiration and also reduced blood pressure in urethane-anesthetized rabbits.

From the in vitro study, Okubo [21] concluded that furfuryl alcohol, as a 5% solution, rapidly paralyzed both motor and sensory nerves of the frog. A 1% solution, however, paralyzed only the sensory nerves, and these effects were slowly reversible after furfuryl alcohol was replaced by Ringer's solution.

In 1932, Joachimoglu and Klissianis [5] described their studies of furfuryl alcohol in humans and in a dog. Humans were given by mouth a chamomile tea containing up to 150 mg furfuryl alcohol or up to 60 mg furfural [5]. No effects from ingestion of furfuryl alcohol at these levels were reported.

A dog was given furfuryl alcohol, 1 g/day, by stomach tube for 42 days. After a 1-month recovery period, the animal then received furfural, at 1 g/day, by stomach tube for 56 days [5]. The only effect seen was occasional salivation after administration. No changes were evident during the subsequent 1-year observation period.

Effects on Humans

Jacobson et al [22], in 1958, reported the results of experiments conducted on 13 volunteers to determine the odor threshold of furfuryl alcohol. Each volunteer sniffed geometrically increasing concentrations of furfuryl alcohol. The median detectable concentration for furfuryl alcohol was 7-8 ppm (28-32 mg/cu m). All volunteers were able to detect the furfuryl alcohol at 10 ppm (40 mg/cu m), and they described the odor as "sweet," "alcoholic," or "etherlike."

Apol [23], in 1973, reported the results of a health hazard evaluation conducted by NIOSH at a foundry. One or two workers on each shift produced cores for iron castings prepared by a two-stage, air-set cure process. The first stage involved the construction of a large core and required 10-15

minutes; the second, the cure stage, required 45 minutes. The substances used in the process included a mixture of furfuryl alcohol and paraformaldehyde, a phosphoric and sulfuric acid mixture, and sand. After these substances were mechanically mixed, they were poured into the mold. This process was usually performed at room temperature; however, in cold weather the sand was heated before mixing. The high temperature of the sand apparently caused the release of furfuryl alcohol and formaldehyde vapors.

During the coremaking and the core-curing stages, air samples were collected with charcoal tubes; all such samplings were repeated when hot sand was used [23]. The furfuryl alcohol concentration was then determined by gas chromatography. During the 15-minute core preparation, under normal temperature conditions, the concentration of furfuryl alcohol was 8.6 ppm (34.4 mg/cu m). When warm sand was used during the same cure period, the concentration of furfuryl alcohol was 10.8 ppm (43.2 mg/cu m). None of the three exposed employees reported any discomfort during those operations. However, when the hot sand was used during the 15-minute core preparation, the concentration of furfuryl alcohol was 15.8 ppm (63.4 mg/cu m) with a formaldehyde concentration of 0.33 ppm (0.41 mg/cu m). Under these conditions, the two persons present (an employee and a NIOSH representative) experienced lacrimation and wanted to leave the vicinity of the operation. These observations do not clarify whether the irritation was due to furfuryl alcohol, to formaldehyde, to other compounds conceivably present, or to the combined effects of two or more substances. Although the skin of the exposed employee also came into contact with the furfuryl alcohol, no signs of skin irritation were evident during the process, and, according to the authors, none had occurred previously.

Burton and Rivera [24], in 1972, reported results of another NIOSH health hazard evaluation study performed at a different foundry. The foundry produced large ferrous castings, an operation that involved production of no-bake resin cores and molds. In the course of the operation, three men handled a mixture of 1,000 pounds of sand, 15 pounds of base resin (containing furan resin, furfuryl alcohol, and some urea-formaldehyde resin), and 4.5 pounds of catalyst (containing toluene sulfonic acid, isopropyl alcohol, and water). These ingredients were mixed in an automatic mixer and then poured into wood molding forms.

Air samples of unspecified volume were collected for an unstated duration from the work and personnel areas by charcoal tubes and MSA personal monitor pumps [24]. The results revealed that, of the 10 exposed workers, 4 coremakers were exposed to furfuryl alcohol at 66, 32, 30, and 25 mg/cu m. One coremaker was exposed at an undetectable concentration. No furfuryl alcohol was detectable in the breathing zones of three assistant coremakers and one of two apprentices, the remaining apprentice being exposed to furfuryl alcohol at 11 mg/cu m.

The investigators [24] also reported that the 8-hour TWA exposure concentrations of furfuryl alcohol were 25 mg/cu m in the breathing zone of a coremaker and less than 20 mg/cu m in the breathing zones of an assistant coremaker and an apprentice. They pointed out that none of the workers had any of the signs and symptoms that they considered attributable to furfuryl alcohol, ie, ocular irritation, headache, nausea, or dizziness; the investigators did not cite their basis for inferring these to be the effects of furfuryl alcohol. Burton and Rivera concluded that there was no hazard from furfuryl alcohol up to 66 mg/cu m.

Mastromatteo [25], in 1965, described adverse health effects in workers exposed to furfuryl alcohol during the production of acid-resistant cements and binders for foundry sand. Two of 15 bricklayers who had skin contact with the acid-resistant cement developed dermatitis. In one incident, while 15 workers were applying an acid-resistant lining containing furfuryl alcohol to a large pickling tank during hot weather, 7 experienced respiratory irritation, including mild sore throat, severe bronchitis accompanied by intermittent coughing, and chest pain; 2 were hospitalized. Because there was also exposure to acid-resistant cement, the possible contribution of furfuryl alcohol to the skin and respiratory irritations cannot be evaluated.

An investigation reported by Sanders [26] involved four male workers exposed to furfuryl alcohol. They performed laboratory work with furfuryl alcohol and furfural from 2 months to 5 years and had skin contact in small amounts and light vapor exposure daily; however, more extensive skin contact and heavy vapor exposure also occurred, but less frequently. Medical histories and examinations of the workers revealed no significant findings.

## Animal Toxicity

### (a) Inhalation

The results of a study with commercial furfuryl alcohol, performed by Woods and Seevers [27], were reported in 1954. For this study, mice, rats, rabbits, dogs, and monkeys were exposed to furfuryl alcohol vapor for 6 hours. The animals were exposed in a 195-liter gas-tight chamber. The vapor was produced in an evolution chamber by passing air through furfuryl alcohol (50-200 g) at a constant temperature. The mixture of air and furfuryl alcohol vapor was regulated and metered before being passed through the exposure chamber. Controls were exposed to air alone. Deaths were recorded only if they occurred within 48 hours after exposure.

Mice in groups of 12-24, exposed to furfuryl alcohol at 47-243 ppm (188-972 mg/cu m), had no mortality [27]. Mice exposed at 597 ppm (2,388 mg/cu m) had a 92% mortality. An $LC_{50}$ for mice of 397 ppm (1,588 mg/cu m)

can be approximated from the data provided. Groups of 24 rats exposed to furfuryl alcohol at 47-180 ppm (188-720 mg/cu m) showed a dose-related mortality. An $LC_{50}$ for rats of 85 ppm (340 mg/cu m) can be approximated from the data provided. Higher exposure levels of furfuryl alcohol, ranging from 243 to 597 ppm (972 to 2,388 mg/cu m), killed all animals.

Exposure of groups of two rabbits to furfuryl alcohol at 47-416 ppm (188-1,664 mg/cu m) produced no deaths [27]. Exposure of groups of two dogs to furfuryl alcohol at 40-349 ppm (160-1,396 mg/cu m) produced no deaths. Exposure of one monkey at 260 ppm (1,040 mg/cu m) had no harmful effects that were evident.

The effects of repeated exposures to furfuryl alcohol vapor were also studied [27]. Exposures of one male and one female dog for 6 hours/day, 5 days/week for 4 weeks, at an average concentration of 239 ppm (956 mg/cu m) had no apparent effect except a slight bronchial inflammation. Similar exposure of one monkey for 3 days had no apparent effect.

In 1952, Comstock and Oberst [28] reported on the acute and subacute inhalation toxicity of furfuryl alcohol in male Wistar rats (150-200 g) and mice (20-30 g). In the acute toxicity study, air at 2 liters/minute was passed through furfuryl alcohol and then through a 10-liter vacuum desiccator acting as the inhalation chamber. This was assumed to ensure an approximate saturated test atmosphere in the chamber that also contained a small quantity of liquid furfuryl alcohol. The concentration of the vapor, however, was calculated from the mass of compound trapped in a collection bubbler containing glacial acetic acid and from the sample volume as measured by a wet-test meter. The furfuryl alcohol of the absorbing medium was determined using a titrimetric method.

Thirty rats were divided into five groups of six rats each. Three groups were exposed for 4 hours, and the remaining two groups were exposed for 8 hours to the saturated furfuryl alcohol vapor.

Acute exposure of rats to saturated furfuryl alcohol vapor, approximately 700 ppm (2,800 mg/cu m), resulted in 22% and 25% deaths after 4- and 8-hour exposures, respectively [28]. Deaths occurring within 14 days were recorded. Signs arising from these exposures included initial excitement, drowsiness, apparent sleepiness, and irritation of the eyes, which became red within 8 minutes.

In a subacute toxicity experiment, these investigators [28] exposed rats and mice in a 410-liter dynamic gassing chamber at an average concentration of 19 ppm (76 mg/cu m). The 15 rats were exposed for 6 weeks and 8 mice for 3 weeks, for 6 hours/day, 5 days/week. Additional animals (five rats and two mice) were also exposed for earlier necropsy.

Subacute exposure of the rats and mice to furfuryl alcohol vapor at a daily average concentration of 19 ppm (76 mg/cu m) resulted in no deaths except for one rat after the third exposure and one mouse after nine exposures. Signs of toxicity noted included restlessness during the initial 5-10 minutes of exposure and drowsiness that continued throughout the exposure. Both test and control animals gained weight at the same rate.

Necropsies of the animals revealed diffuse congestion of the entire respiratory tract without significant cellular changes in the case of both acute and subacute exposures [28]. All other organs of the animals remained unchanged. The authors also suggested that, because of its low vapor pressure (0.98 mmHg at 38 C or 100.4 F), furfuryl alcohol would not be expected to pose a serious occupational vapor hazard unless a prolonged exposure or a massive spill occurred in hot weather.

Jacobson et al [22], in an investigation of the toxicity of a liquid propellant mixture containing furfuryl alcohol, aniline, and hydrazine, studied the acute toxicity of furfuryl alcohol vapor in rats. Male Wistar rats, weighing 200-275 g, were exposed in groups of 10 for 4 hours to furfuryl alcohol. An $LC_{50}$ of 233 ppm (932 mg/cu m) was estimated from the concentration-mortality curve. Jacobson et al [29] found that all exposed rats exhibited signs of lethargy, exophthalmos, rales, and a porphyrin nasal discharge.

(b) Ocular

In a 1954 report, Woods and Seevers [27] described the ocular effects of undiluted furfuryl alcohol on a group of four rabbits. Instillation of undiluted alcohol (0.05 ml or 56 mg) slowly into one eye of each rabbit resulted in eye inflammation, viscid mucoid secretion, corneal opacity, and eyelid swelling. The eye returned to normal 40-64 days after treatment; one rabbit died of other causes after 43 days. Instillation of 0.02 ml (23 mg) furfuryl alcohol produced the same, but less severe, results as those observed with the larger dose; the eye of each rabbit returned to normal after 2-8 days.

Comstock and Oberst [28] reported that rats developed eye redness within 8 minutes after a single exposure to saturated furfuryl alcohol vapor, ie, 700 ppm (2,800 mg/cu m) for 4 or 8 hours. No evident eye irritation, however, occurred in either rats or mice during repeated exposure at 19 ppm (75 mg/cu m). These rats were exposed for 6 hours/day, 5 days/week for a total of 30 exposures; the mice were exposed for 6 hours/day, 5 days/week for 3 weeks.

(c) Dermal

Woods and Seevers [27] studied the effects of topical application of furfuryl alcohol to rabbits, guinea pigs, and mice. Undiluted furfuryl

alcohol at 400-1,100 mg/kg produced a dose-related mortality in rabbits [27]. An $LD_{50}$ of 657 mg/kg can be estimated from the data provided. Administration of furfuryl alcohol at 2,200 mg/kg killed all rabbits tested. An $LD_{50}$ of 4,920 mg/kg can be estimated from the data provided on dermal application to mice. Dermal administration of 8,500 mg/kg to three guinea pigs caused no deaths. From these results, Woods and Seevers concluded that percutaneous toxicity was much greater in rabbits than in mice or guinea pigs and that furfuryl alcohol was the least toxic to unshaved guinea pigs percutaneously.

In 1974, Chernousov [30] studied the allergenic and irritating properties of furfuryl alcohol on guinea pigs. In the study of the irritating properties, 50%, 10%, and 1% solutions in acetone were applied daily for 12 days to a 2.25-sq cm area of skin on the lateral surface of the torso. To determine the sensitizing properties of furfuryl alcohol, the investigator dissolved 150 µg in 0.2 ml of absolute Freund's adjuvant, or 40, 20, or 10 µg in acetone, and applied it topically to the hind paw pad or to the ear skin. Control animals (156 guinea pigs) received only Freund's adjuvant or acetone. Intracutaneous sensitization was tested on the 14th day. On the 21st day, the titers of humoral antihapten antibodies and the degree of leukocyte-specific agglutination (LSA) were determined. The minimum sensitizing dose of furfuryl alcohol producing humoral antibodies was 40 µg; for positive LSA response it was 20 µg. From these data, the author characterized furfuryl alcohol as a weak allergen. Chernousov believed that the antigenicity of furfuryl alcohol may be due to the unsaturated moiety of the furfuryl alcohol molecule. The irritating effects of furfuryl alcohol, which included skin dryness, hyperemia, desquamation, and necrosis, were observed in guinea pigs administered the 50% solution.

Camp [31] reported the results of topical application of furfuryl alcohol to the skin of one dog and three rats. After daily application of 11.3 g undiluted furfuryl alcohol to the hairless skin of the dog for 10 days, no toxic signs were observed other than local skin surface changes, ie, hardness or roughness. One rat that received a dermal application of 1.36 ml (1.53 g) of furfuryl alcohol died following respiratory failure, almost an hour after application. Necropsy results from that animal included congested lungs, decreased size of the heart, and darkened liver. Because of the absence of proper control data, the inadequate number of tests performed, and the uncertainty regarding the purity of the furfuryl alcohol used, these results are of questionable validity.

In a 1949 report, Prince [32] stated that furfuryl alcohol can be absorbed through the skin and could give rise to hematuria. The dermal $LD_{50}$ was not determined, but 11 of 12 rats died as a result of four applications of 300-1,400 mg/kg of the alcohol. The author recommended that gloves and goggles be worn when furfuryl alcohol is used in open vessels. Other precautions that were recommended included immediate washing in the event of skin contact with the furfuryl alcohol.

Sanders [26] reported that 15 ml (16.9 g) of furfuryl alcohol, when applied to the clipped skin of rabbits, was usually lethal. Dermal application of 5 ml (5.6 g) of furfuryl alcohol daily for 30 days resulted in no toxic effects in rabbits.

(d) Oral

Woods and Seevers [27] administered furfuryl alcohol as a 2 or 4% aqueous solution by gastric intubation to male Sprague-Dawley rats weighing approximately 225-275 g. With the 4% aqueous solution, the $LD_{50}$ of furfuryl alcohol was determined to be 149 mg/kg (95% confidence limits of 142-156 mg/kg). With the 2% aqueous solution, however, the oral toxicity of furfuryl alcohol was decreased as demonstrated by the $LD_{50}$ of 451 mg/kg (95% confidence limits of 444-463 mg/kg). The authors reported an oral $LD_{50}$ of 132 mg/kg for undiluted furfuryl alcohol, although no data were provided to substantiate the value. In all the tested animals, the only toxic sign reported was terminal convulsion. The investigators concluded that furfuryl alcohol was absorbed fairly completely through the gastrointestinal tract of the rats.

Boyland [33], in 1940, reported an acute oral $LD_{50}$ of 40 mg/mouse. The weight of the mouse was not given by the author, but, assuming a weight of 20 g, the $LD_{50}$ can be estimated at about 2,000 mg/kg.

Paul et al [34], in 1949, identified the major urinary metabolites excreted following administration of furfuryl alcohol and other related furan compounds. The metabolites were identified by UV absorption. Albino rats weighing 300-400 g, fasted overnight, were given by gastric intubation 20 mg of furfuryl alcohol suspended in sucrose solution. Urine was collected every 2 hours for 6 hours, combined, and then analyzed. The major urinary metabolite was identified as furoyl glycine. The proportion of the dose excreted as furoyl glycine was not stated for furfuryl alcohol, but closely related compounds were metabolized to the extent of approximately 60%.

In a 1949 abstract, Gajewski and Alsdorf [35] reported on the acute toxicity of oral administration of furfuryl alcohol to white rats. Furfuryl alcohol was administered to the rats orally as a 2% aqueous solution. The oral $LD_{50}$ for the rats was determined to be 275 mg/kg. When death occurred, it was attributed to respiratory paralysis. Rats administered unspecified amounts of the alcohol in their drinking water for 20 days lost weight and showed lack of appetite.

Prince [32] found an $LD_{50}$ of just over 0.1 ml/kg (over 0.11 g/kg) for furfuryl alcohol when it was administered by stomach tube to rats. No other observed effects were included in this report; however, necropsies revealed severe hemorrhage and edema of the lungs as well as congestion of the liver; hematuria was also present. The oral $LD_{50}$ reported by Prince agrees with the value of 132 mg/kg given by Woods and Seevers [27].

(e) Intravenous

In the previously mentioned 1949 abstract, Gajewski and Alsdorf [35] reported observing flaccid paralysis, which disappeared after about 30 minutes, in rabbits given furfuryl alcohol iv in a 10% aqueous solution; however, the paralysis became permanent with larger but unspecified doses. The $LD_{50}$ for the rabbits was 650 mg/kg.

Fine and Wills [36], in 1950, reported the effects of furfuryl alcohol on rabbits and cats. Pentobarbital-anesthetized cats were given a 20% solution of furfuryl alcohol in saline by vein at the rate of 100 mg furfuryl alcohol/kg every 10 minutes. The first injection of 100 mg/kg produced only a slight and temporary decrease in the blood pressure and respiration. After the total dose of furfuryl alcohol exceeded 500-600 mg/kg, each injection resulted in a severe drop in blood pressure and in a temporary apnea. After a total dose of 800-1,400 mg/kg, the animals died from respiratory paralysis. The cardiac effects of furfuryl alcohol in anesthetized rabbits, as recorded directly from the exposed heart and by the electrocardiograph (ECG), also were studied. With increasing doses of furfuryl alcohol, there was little change in the heart rate (chronotropic effect), but the intensity of contraction of both auricles and ventricles was progressively depressed (inotropic effect) as seen from the severely altered ECG characteristics. With lethal doses, the chronotropic effect was abolished as expected; however, a negative inotropic effect on the heart was evident from the ECG. This latter effect appeared to be reversed readily by perfusing the heart with fluid containing no furfuryl alcohol. Fine and Wills suggested that the cardiac changes produced by furfuryl alcohol may be due to a direct action on the myocardium.

Administration of furfuryl alcohol (100 mg/kg over 10 seconds) caused CNS depression in the rabbit, as indicated by the EEG recordings [36]. Fine and Wills pointed out that such results were similar to those produced by certain anesthetics and could be used to combat such CNS stimulants as metrazol, benzedrine, and ephedrine. They observed that furfuryl alcohol tended to affect the brain more readily than it did other organs because central respiratory depression was the usual cause of death.

(f) Subcutaneous

Woods and Seevers [27] reported the acute effects resulting from sc administration of furfuryl alcohol to rats and rabbits. $LD_{50}$'s were 78 mg/kg and 96 mg/kg for undiluted and for 4% aqueous furfuryl alcohol, respectively. The $LD_{50}$ for rabbits administered undiluted furfuryl alcohol was 796 mg/kg. Necropsy of the rats and rabbits revealed pulmonary edema and, in the rats, mottled lungs. The $LD_{50}$ of neat furfuryl alcohol in the rabbit was approximately one-tenth that for the rats, indicating considerable species variation in the acute toxicity of furfuryl alcohol.

(g) In Vitro Tests of Mutagenicity

Recently, the mutagenic potential of furfuryl alcohol has been studied [37] by the Ames test [38] in which 500 µg of furfuryl alcohol was added to each plate and the number of induced revertants compared with the spontaneous ones. Salmonella typhimurium strains TA 198, TA 100, TA 1535, TA 1537, and TA 1538 were tested with 4-nitroquinoline-N-oxide, benzo(a)pyrene, N-methyl-N-nitroso-nitrosoguanide, 9-aminoacridine, and 2-aminofluorene, respectively, as positive controls, giving in each case strongly positive results. When furfuryl alcohol was tested with and without S-9 microsomal preparations, the number of revertants above background was not considered significant in any strain tested.

Correlation of Exposure and Effect

The results of exposure of mice [27,28], rats [22,27,28], rabbits, dogs, and monkeys [27] to furfuryl alcohol vapor have been reported. In mice, 92% mortality was observed after a 6-hour exposure to furfuryl alcohol at 2,388 mg/cu m. A similar exposure of rats at 972 mg/cu m, however, resulted in 100% mortality after 6 hours. One 6-hour exposure of a monkey at 1,040 mg/cu m resulted in only slight lacrimation. When two dogs were exposed to furfuryl alcohol vapor at 956 mg/cu m for 6 hours/day, 5 days a week, for 4 weeks, the only observed effect was slight bronchial inflammation.

No effects were observed in rats and mice at furfuryl alcohol concentrations up to 76 mg/cu m after thirty 6-hour exposures [28]. Two rabbits exposed to furfuryl alcohol vapor at 188 mg/cu m for 6 hours [27] and one monkey exposed three times at an average furfuryl alcohol concentration of 956 mg/cu m for 6 hours also showed no effects.

Workplace exposure to furfuryl alcohol also may occur via dermal contact. Furfuryl alcohol is readily absorbed through the skin of animals [27,30-32]. Death occurred in rabbits after dermal application of 700 mg of furfuryl alcohol [27] and in rats after four applications of 300-1,400 mg/kg each [32]. For the rats, 92% mortality was reported, as was hematuria in an unspecified number of animals [32]. A rabbit receiving 5.6 g of furfuryl alcohol/day for 30 days showed no visible effects [26]; this was also the case when 11.3 g/day of furfuryl alcohol was applied to the hairless skin of a dog for 10 days [31]. Dermal application to guinea pigs of furfuryl alcohol at 8,500 mg/kg body weight and 3,200 mg/kg and 400 mg/kg in mice and rabbits, respectively, did not have any apparent effects [27]. However, 50%, 10%, and 1% solutions of furfuryl alcohol in acetone applied daily to guinea pig skin for 12 days resulted in skin dryness, hyperemia, and desquamation [30]. Since these local skin effects were not observed in other studies in which animals received furfuryl alcohol cutaneously, it is likely that the observed surface changes were caused by

the acetone carrier rather than by furfuryl alcohol, an inference consistent with the excellent lipid solvent characteristics of acetone. With the 50% solution, necrosis also was observed. Sensitization tests were performed on guinea pigs by topical administration, to the ear skin or hind paw, of furfuryl alcohol in acetone or in Freund's adjuvant [30]. After 14 days, titers of humoral antihaptens and the degree of LSA were determined. The minimum sensitizing amount of furfuryl alcohol that produced humoral antibodies was 40 µg. In humans, dermatitis has been reported in two workers handling acid-resistant cement, which probably contained, among other possible irritants, liquid furfuryl alcohol [25]; but it is not clear which component was responsible.

Studies have shown that furfuryl alcohol has caused eye irritation in animals [27,28]. Furfuryl alcohol vapor at 2,800 mg/cu m caused eye redness in rats after 8 minutes of exposure [28]. When instilled directly into the eye of a rabbit, 56 or 23 mg furfuryl alcohol produced severe eye irritation and corneal opacity, which were reversible after 40-64 days or 2-8 days, respectively [27].

The only report of ocular effects from furfuryl alcohol vapor in humans was lacrimation in one worker and one visitor performing a survey of possible health hazards. The exposure, measured at 63.4 mg/cu m furfuryl alcohol and 0.4 mg/cu m formaldehyde, lasted about 15 minutes. As was previously discussed, it is not clear whether this eye irritation was due to either component, both components, or to unknown airborne materials.

Although the primary routes of workplace exposure to furfuryl alcohol are by inhalation or by skin or eye contact, some ingestion also may occur. The oral toxicity of furfuryl alcohol has been studied in rats and dogs. In rats, the oral $LD_{50}$ is between 132 and 451 mg/kg [27,35]. A dog of unspecified weight was administered furfuryl alcohol at 1 g/day for 42 days with no apparent effects [5]. Similarly, humans, after ingesting 40-150 mg (0.57-2.14 mg/kg) of furfuryl alcohol, showed no effects [5].

Fine and Wills [36] stated that furfuryl alcohol had a direct, depressive action on the heart. A total of 600-800 mg/kg, when administered by vein to cats, caused a severe blood pressure drop and temporary apnea, and 800-1,400 mg/kg resulted in death by respiratory paralysis. (A dose of 600 mg/kg in a 70-kg man breathing 10 cu m/workday would be equivalent to 4,200 mg/cu m, so it does seem likely that the effects observed by Fine and Wills would be relevant to the question considered in Chapter V of the appropriateness of a permissible limit of 200 mg/cu m.)

Furfuryl alcohol has been found to be acutely toxic by most routes of administration relevant to an occupational health standard. The data indicate that, in most cases, death occurred as a result of CNS depression and subsequent respiratory paralysis. Furfuryl alcohol is readily absorbed

by all routes, as exemplified by the similar $LD_{50}$'s by oral and sc routes of administration in rats. For example, the oral $LD_{50}$'s of 110 mg/kg [32] and 132 mg/kg [27] were less than twice the sc $LD_{50}$ of 78 mg/kg [27]. Similarly, when 4% furfuryl alcohol was used, the oral $LD_{50}$ of 149 mg/kg for rats was close to the sc $LD_{50}$ of 96 mg/kg [27]. Similar evidence is found by comparing the $LD_{50}$ values in rabbits by iv, sc, and oral routes of administration, reported to be 650 mg/kg [35], greater than 500-526 mg/kg [4], and less than 1,000 mg/kg [4], respectively.

The metabolic pathway and excretion pattern of furfuryl alcohol were studied by Paul et al [34], who found that in rats, 65-70% of orally administered furfuryl alcohol was excreted as furoyl glycine. No information on human biotransformation of furfuryl alcohol has been found.

The effects of furfuryl alcohol on humans and animals are summarized in Tables II-1, II-2, and II-3.

## Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports were found on whether there are carcinogenic or teratogenic effects from furfuryl alcohol. There was one report [37] that indicated that furfuryl alcohol was not mutagenic in tests with Salmonella in vitro.

TABLE II-1

EFFECTS OF FURFURYL ALCOHOL VAPOR ON HUMANS

| Number of Subjects | Exposure | | Observations | Reference |
|---|---|---|---|---|
| | Amount | Duration | | |
| 13 | 32 mg/cu m | A few seconds | Odor threshold | 22 |
| 3 | 63.4 mg/cu m with 0.4 mg/cu m formaldehyde | 15 min | Lacrimation | 23 |
| 10 | Up to 66 mg/cu m with 0.24-0.91 mg/cu m formaldehyde | (Probably a few seconds) | Eye irritation | 24 |

TABLE II-2

EFFECTS OF FURFURYL ALCOHOL VAPOR ON ANIMALS

| Species | Exposure | | Observations | Reference |
|---|---|---|---|---|
| | Amount | Duration | | |
| Mouse | 2,388 mg/cu m | 6 hr | Killed 92% | 27 |
| " | 188 mg/cu m | " | No apparent effect | 27 |
| Rat | 2,800 mg/cu m | 4-8 hr | Excitement, eye redness, drowsiness, cyanosis, lung congestion; killed 22-25% | 28 |
| " | 933 mg/cu m | 4 hr | Lethargy, exophthalmos, rales, porphyrin nasal discharge; killed 50% | 27 |
| " | 188-972 mg/cu m | 6 hr | Killed 8-100% | 27 |
| Rabbit | " | " | No apparent effect | 27 |
| Dog | 160 mg/cu m | " | " | 27 |
| Monkey | 1,040 mg/cu m | " | Slight lacrimation | 27 |
| Mouse | 76 mg/cu m | 30 6-hr exposures | No apparent effect | 28 |
| Rat | " | " | Persistent drowsiness | 28 |
| Dog | 956 mg/cu m | 20 6-hr exposures | Bronchial inflammation | 27 |
| Monkey | " | 3 6-hr exposures | No apparent effect | 27 |

TABLE II-3

DERMAL EFFECTS OF FURFURYL ALCOHOL ON ANIMALS

| Species | Exposure | | Observations | Reference |
|---|---|---|---|---|
| | Amount | Duration | | |
| Mouse | 6.9 g/kg | -- | Killed 89% within 48 hr | 27 |
| " | 3.2 g/kg | -- | No apparent effect | 27 |
| Rat | 0.3-1.4 g/kg | 4 applications | Hematuria; killed 92% | 32 |
| " | 1.53 g | 1 hr | Respiratory failure, lung congestion | 31 |
| Guinea pig | 8.5 g/kg | -- | No apparent effect | 27 |
| Rabbit | 16.9 g | -- | Death | 26 |
| " | 0.7 g/kg | -- | Killed 58% within 48 hr | 27 |
| " | 0.4 g/kg | -- | No apparent effect | 27 |
| Guinea Pig | 50%, 10%, 1% solutions | Daily/12 d | Skin dryness, hyperemia, desquamation accompanied by necrosis with 50% solution | 30 |
| Rabbit | 5.6 g | Daily/30 d | No apparent effect | 26 |
| Dog | 11.3 g | Daily/10 d | " | 31 |