Tetrahydrofurfuryl Alcohol

Document History
Published: 1993
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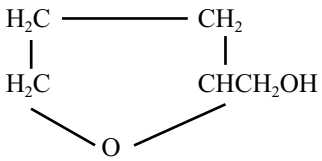
I. IDENTIFICATION

Chemical Name: Tetrahydrofurfuryl Alcohol
Synonyms: THFA; Tetrahydro-2-furanmethanol;
CAS Number: 97-99-4
Molecular Formula: $C_5H_{10}O_2$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–6]

Physical State and Appearance: Colorless liquid
Odor Description: Mild, somewhat ethereal odor
Odor Threshold: No data available
Molecular Weight: 102.1
Conversion Factors: 1.0 ppm = 4.17 mg/m^3
1.0 mg/m^3 = 0.24 ppm
Melting Point: -80ºC (-112ºF)
Boiling Point: 178ºC (352ºF) at 760 mm Hg
Vapor Pressure: 0.9 mm Hg at 25ºC (77ºF)
Saturated Vapor Concentration: 1200 ppm at 25ºC (77ºF)
Flammability Limits: LEL: 1.5%; UEL 9.7% in air
Flash Point: (closed cup) 74ºC (165ºF)
Autoignition Temperature: 282ºC (540ºF)
Specific Gravity: 1.05 at 20ºC (68ºF)
Solubility in Water: 100 %
Stability: Stable
Reactivity and Incompatibilities: Reacts with strong oxidizers, acids or bases

III. USES[1–3,7]

Primary use is as a solvent in many different types of applications such as in polymers, paint strippers and pesticide formulations. It is also used as a chemical intermediate. Commercial grades are typically 98-99% THFA, with other components being primarily 1,2-Pentanediol and water.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy:

1. *Oral Toxicity*[2,6,8]

Rat:	LD_{50}	1600-3700 mg/kg
Mouse:	LD_{50}	2300 mg/kg
Guinea Pig:	LD_{50}	800-3000 mg/kg

2. *Eye Irritation*[2,6,9]

Rabbit: Mildly to moderately irritating

3. *Skin Absorption*[8]

Guinea Pig LD_{50} >5000 mg/kg

4. *Skin Irritation*[2,6,8,10]

Guinea Pig: Slightly irritating

Rabbit: Slightly irritating

Mouse: 24-hour, occluded contact of 100% THFA with bare skin did not cause any significant change in histology.

5. *Skin Sensitization*[8]

Guinea Pig: Not a sensitizer (test method not available)

6. *Inhalation Toxicity*[2]

Rat: 4-hour exposure at 4700 ppm (4 animals) resulted in no deaths over 14-day post-exposure observation period. Only reported effect was narcosis, but no details of post exposure examination are reported

B. Subacute Toxicity:

Groups of three rabbits were orally dosed at 0, 30, 100, 300, or 1000 mg/kg for 5 consecutive days. All 3 animals at the highest dose expired before the third day. All others survived, but all animals in exposed groups suffered loss of appetite and significant weight loss compared to controls.

Behavioral observations noted included decreased motor activity, unsteady walk, and prostration in the two highest dose groups. A no-observed-adverse-effect level (NOAEL) was not established. Post exposure examination of those animals which survived did not demonstrate any gross abnormalities of those organs examined at necropsy.[11]

C. Subchronic Toxicity

Oral toxicity in rats was evaluated in a 90-day dietary study. Groups of 15 male and 15 female Charles River albino rats were fed diets containing 0, 1000, 3000, or 10,000 ppm, by weight of THFA (equivalent to doses of approximately 0, 65–80, 200–240, and 650–800 mg/kg-day). Clinical pathology was performed at Days 45 and 84 to compare hematology, blood chemistry, and urinalysis between high dose and control animals, and no significant differences were noted. Body weight gain and food consumption were significantly reduced for both the mid-dose and high-dose groups, however, the authors attributed this primarily to unpalatability of the diet. Organ weights and organ-to-body weight ratios were assessed for brain, heart, kidney, liver, spleen and gonads. Although some significant differences were noted, the authors attribute all these variations to the weight gain depression, except for changes in the testis weight of high-dose males. In addition to the significantly reduced absolute and relative weight of the testis in high-dose males, 14 of 15 animals were observed upon histopathological examination to have moderate degeneration and complete absence of spermatogenesis. Low-dose and mid-dose animals were not subjected to histopathological examination. This study established a lowest-observed-adverse-effect level of 200–240 mg/kg-day, but the absence of histopathological examinations in the low-dose and mid-dose animals makes it questionable whether a no-adverse-effect level was determined.[12]

In a second 90-day study, groups of 40 rats (20 of each sex) were continuously provided *ad libitum* diets containing 0, 500, 1000, 5000, or 10,000 ppm THFA by weight (equivalent to doses of approximately 0, 30–40, 65–80, 330–400, and 650–800 mg/kg-day). Those fed 10,000 ppm had significantly depressed body weight gains, and the males in the 1,000 and 5,000 ppm groups also experienced depressed body weight gains. Males in both the 5000 and 10,000 ppm groups had decreased absolute organ weights for the following, except as noted: brain, kidneys (at 10,000 only), liver, seminal vesicles, epididymides, prostate, testes, and adrenal gland. Females in the 10,000 ppm group also had significantly reduced brain weight. Significantly altered organ to body weight ratios (relative organ weights) were also observed as follows:

Liver	Decreased	Males	All exposed groups
Liver	Increased	Females	5000 & 10,000
Brain	Increased	Males	5000 & 10,000
Kidneys	Increased	Males	5000 & 10,000
Kidneys	Increased	Females	5000
Epididymides	Decreased	Males	5000 & 10,000
Testes	Decreased	Males	10,000
Ovaries	Increased	Females	10,000

Changes were also noted in multiple serum chemistry measurements (glucose, total protein, globulin, and calcium) in males in the three highest exposure groups, while multiple changes in hematology factors (hemoglobin, MCH, MCHC, and platelets) were noted in the two highest exposure groups of both sexes. Histopathology was to be included in a subsequent report, but that report was not located. This study indicated a lowest-observed-adverse-effect level of approximately 30–40 mg/kg-day, but the absence of the histopathology studies leaves uncertainty.[13]

In another 90-day feeding study, groups of beagle dogs (8 animals per group, 4 of each sex) were fed, *ad libitum*, diets containing 0, 1000, 3000, or 6000 ppm, by weight of THFA (equivalent to doses of approximately 0, 40, 120, and 240 mg/kg-day). Although no effect on food consumption was noted, significantly depressed body weight gain was noted in half of the highest exposure group. No abnormalities were noted in blood chemistry, hematology, or urinalysis (performed after 42 and 85 days on study). All organ weights were within normal limits at the end of the exposure with the exception of testes weights which were significantly lower in all exposed males. Upon gross and histopathological examination, all the high dose males were noted to have severe testicular atrophy. Males from the 3000 ppm group also demonstrated decreased spermatogenic activity. Except for occasional prostatic atrophy in the high dose males, no other significant pathologic examination observations were noted.[14]

In an apparent follow up study, groups of male beagle dogs (4 per group) were offered diets containing 0, 200, 400, or 800 ppm THFA (equivalent to doses of approximately 0, 10, 20, and 30 mg/kg-day). Food was provided 3 hours per day

over 90 consecutive days and the animals were evaluated for testicular maturation. No treatment related effects were noted, indicating a no-observed-adverse effect level in beagle dogs at approximately 30 mg/kg-day.[15]

In a 90-day dermal exposure study, groups of rats were dosed at 0, 100, 300, or 1000 mg/kg-day. Each group initially consisted of 17 males and 12 females. After the 37th day, 5 males from each group were sacrificed and examined for testicular effects. By the end of the study, males exposed to 300 mg/kg-day or greater were found to have decreased numbers of sperm and decreased rates of sperm production, although the reproductive organs appeared normal otherwise. Those in the low dose group were not significantly different from the controls. Depressed body weight gain was seen in both sexes in the 1,000 mg/kg-day group, but not in the other groups. No other effects were noted, indicating a no-observed-adverse effect level of 100 mg/kg-day.[16]

Groups, initially including 14 male and 10 female rats each, were exposed for 6 hours per day, 5 days per week for 13 weeks, at airborne concentrations of 0, 50, 150, or 500 ppm (whole body). Four males in each group were sacrificed at the end of the 34th exposure and examined for spermatogenic effects. During exposure, intermittent whole-body spasms were frequently observed, in a dose-related manner, in all exposed animals. One-hour post-exposure observations revealed hyperactivity in a dose-related manner in all test groups. Males exposed to 150 ppm or greater exhibited decreased food consumption and experienced depressed body weight gains, with some high-dose animals actually experiencing body-weight losses during some weeks on study. Weight gains in the females were within normal limits. At both the interim and final examination, males in the high dose group were found to have decreased sperm counts and decreased sperm motility with an increased number of abnormal sperm. Mean and relative prostate weights were reduced in both the mid and high dose groups. Mean absolute seminal vesicle weight, and absolute and relative epididymidal weights were also decreased in high dose males. No treatment-related effects on sperm count or sex organ/gland weights were noted in the low dose animals. A no-observed adverse effect level was not determined in this study, since significant adverse effects were still observed at the lowest exposure concentration of 50 ppm.[17]

D. Chronic Toxicity/Carcinogenicity:

No data found.

E. Reproductive/Developmental Toxicity

Groups of 8 pregnant rats were dosed by gavage on days 6 through 15 of gestation at 0, 10, 50, 100, 500, or 1000 mg/kg-day. The two highest dose groups exhibited maternal toxicity in the form of decreased food consumption and depressed body weight gains, and also experienced 100% resorption of the fetuses. At 100 mg/kg-day, mean body weights of the fetuses were depressed and 5 of the 124 fetuses exhibited external malformations of the tail (filamentous tail). No abnormalities were observed at 10 or 50 mg/kg-day.[18]

F. Genotoxicity/Mutagenicity

TFHA was negative in the Ames assay, with and without S-9 activation, in strains TA-98, TA-100 and TA-102 of *S. typhimurium*.[19]

G. Metabolism/Pharmacokinetics:

No data found.

V. HUMAN USE AND EXPERIENCE

One manufacturer reported occupational exposures in the range of 0.3 to 2.0 ppm, and did not report any complaints at this level.[2]

VI. RATIONALE

THFA has low order acute toxicity and low irritation potential. Limited evidence indicates that it is not a mutagen or sensitizer. There is limited evidence that THFA may be teratogenic in rats at doses of 100 mg/kg-day or higher.

Although reports are available for several subchronic toxicity studies for THFA, these are of varying quality and some of the most important are available only in summary form.

Two of the 90-day feeding studies cited above indicated no-observed-adverse-effect levels (NOAEL). In the older rat study, the NOAEL was at doses equivalent to about 65 to 80 mg/kg-day, while in the dog study the NOAEL was at doses equivalent to about 30 mg/kg-day.

A more recent 90-day feeding study in rats did not demonstrate a NOAEL, reporting some minimal toxic effects at doses equivalent to about 30 to 40 mg/kg-day. These minimal effects were not associated with the reproductive organs.

The 90-day inhalation study in rats indicated non-specific effects, which are presumably central nervous system effects, at 50 ppm. This study did not test levels below 50 ppm and thus did not establish a NOAEL.

Considering the absence of an established NOAEL, and general lack of human data, caution is indicated in extrapolating to a recommended airborne exposure guide.

Dermal toxicity does not indicate an acute hazard by that route. The 90-day dermal exposure study established a NOAEL of 100 mg/kg-day. The studies indicate that, while the hazard via dermal exposure may not be as important as from respiratory exposure, it may significantly add to the overall exposure. Thus a "skin" notation is recommended.

Although there are indications that acute exposures can result in significant effects, the recommended OEL is expected to be sufficiently low to also guard against such acute effects.

VII. RECOMMENDED OEL

8-hour time-weighted average: 0.5 ppm (2 mg/m^3); Skin

VIII. REFERENCES

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