（別紙４）

U.S. Environmental Protection Agency

Integrated Risk Information System

Formaldehyde (CASRN 50-00-0)

view QuickView

List of IRIS Substances

Select a Substance go

Full IRIS Summary QuickView

MAIN CONTENTS

Reference Dose for Chronic Oral Exposure (RfD) go

0419

Formaldehyde; CASRN 50-00-0

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Formaldehyde

File First On-Line 10/01/1989

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/01/1990
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	05/01/1991

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name – Formaldehyde
CASRN – 50-00-0
Last Revised – 09/01/1990

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of

this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced weight gain, histopathology in rats Rat 2-Year Bioassay Til et al., 1989	NOAEL: 15 mg/kg/day LOAEL: 82 mg/kg/day	100	1	2E-1 mg/kg/day

* Conversion Factors: none

I.A.2. Principal and Supporting Studies (Oral RfD)

Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27: 77-87.

Formaldehyde was administered daily in drinking water to Wistar rats (70/sex/dose) for up to 24 months at mean doses of 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Up to 10 rats/sex/dose were sacrificed and examined after 12 months and 18 months of treatment; the remainder was sacrificed and examined at 24 months. Mean body weights of the high-dose group were decreased in males from week 1 and in females from week 24 through termination. Food intake was significantly decreased in all high-dose males with females showing a similar but less consistent decrease in food intake. A 40% decrease in drinking water intake was reported in all high-dose animals while those rats receiving the middle dose showed a slight but generally insignificant decrease in liquid intake. Changes in urinalyses, and hematological and clinical chemistry parameters, were not dose-related, so were not considered to be related to formaldehyde intake. Among the high-dose males, significant decreases were seen in the absolute heart and liver weights at 18 months and at termination; in testes weights at 18 months; and in kidney weights at termination. High-dose females showed significant increases in the relative kidney weights at 12 and 24 months. Relative brain weights were significantly increased in high-dose males at all three examination periods and in females at termination only. Relative testes weights were significantly increased in high-dose males at termination. These relative organ weight increases were generally ascribed to the decreased body weights observed. A significant increase in mortality among males receiving the 15 mg/kg/day dose was not considered toxicologically significant.

Gross examination at 12, 18, and 24 months revealed a raised, thickening of the limiting ridge of the forestomach in most high-dose rats and in some rats of both sexes from other groups. Irregular mucosal thickening of the forestomach and glandular stomach were seen in several rats of the high-dose group and in occasional rats of other groups. The incidence of discoloration and irregularity of the kidney surface and atrophy of the testes was lower in the high-dose group as compared with controls.

Significant histopathological changes of the gastrointestinal tract were found in high-dose males and females and included chronic atrophic gastritis of the glandular stomach from week 53 on, as well as focal ulceration and glandular hyperplasia at the terminal examination. The incidence of focal papillary epithelial hyperplasia and focal hyperkeratosis of the forestomach was significantly increased in both sexes at the terminal examination. These effects of formaldehyde on the gastric mucosa were considered cytotoxic in nature. A significant increase in the incidence of papillary necrosis of the kidneys was reported in both sexes of high-dose rats at the terminal examination. No

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

- Summary of Risk Estimates
- Dose-Response Data
- Additional Comments
- Discussion of Confidence

EPA Documentation, Review and, Contacts

- Bibliography
- Revision History
- Synonyms

treatment-related gastric tumors were observed in this study. The incidence and type of tumors observed in other organ systems were common to this strain and similar to those found in aging rats, 30 were not considered toxicologically significant. A NOAEL of 15 mg/kg/day in male rats was indicated in this study.

Formaldehyde was administered daily in the drinking water of Sprague-Dawley rats (15/sex/dose) at doses equivalent to 0, 50, 100, or 150 mg/kg/day for 90 days (Johannsen et al., 1986). Male and female high-dose rats (150 mg/kg/day) and male rats receiving the 100 mg/kg/day dose showed a significant decrease in body weight gain. A dose-related decrease in the intake of drinking water was reported in both sexes of treated rats. Food intake and feed efficiency was comparable among all groups. No statistically significant differences were seen in urinalyses, or hematological and blood chemistry parameters. No treatment-related histopathological findings were observed. A NOAEL of 50 mg/kg/day was indicated for rats.

Similarly, formaldehyde was administered in the diet of pure-bred beagle dogs (4/sex/dose) at doses of 0, 50, 75, or 100 mg/kg/day for 90 days. A significant decrease in body weight gain was reported in the high-dose dogs of both sexes with no effect on weight gain at the two lower dose levels. A reduced food consumption and feed efficiency was observed in dogs at all treatment levels. No treatment-related effects were seen on hematological, blood chemistry, or urinalysis parameters, nor were any treatment-related lesions observed. The gastrointestinal mucosa was not affected by formaldehyde intake. A NOAEL of 75 mg/kg/day was indicated.

Marks et al. (1980) administered formaldehyde as an aqueous solution to pregnant CD-1 mice at oral doses of 74, 148, and 185 mg/kg on days 6 to 15 of gestation. The high dose was lethal to most of the treated mice by day 18. Mortality was 1/35 and 22/34 among dams treated at 148 and 185 mg/kg/day, respectively. In the high-dose group, the number of resorption sites was increased and mean litter size was slightly decreased. No effects on fetus size, and no gross or microscopic skeletal or soft tissue abnormalities were observed.

Hurni and Ohder (1973) exposed pregnant beagle dogs (9 to 11/group) to formaldehyde in the diet at levels of 125 or 375 ppm from 4 days after mating through day 56. Assuming that 1 ppm in the diet of a 10-kg dog consuming 250 g of dry chow/day equals 0.025 mg/kg/day (Lehman, 1959), this would correspond to doses of 3 or 9 mg/kg/day. The dogs were weighed weekly, and the pups were weighed at birth and twice weekly thereafter. Feeding of formaldehyde had no effect on pregnancy rate, maternal body weight, or duration of gestation. Mean litter sizes were within normal ranges. No effects were reported on growth or mortality. All pups were inspected for defects at birth and at 8 weeks postpartum. Stillborns, as well as pups dying before weaning, were autopsied and examined for internal and skeletal anomalies. Normal behavior, appearance, mobility and muscular coordination were reported for all dogs observed for up to 9 months.

Seidenberg et al. (1987) evaluated formaldehyde in the Chernoff/Kavlock developmental toxicity screen. Formaldehyde was administered by gavage at 540 mg/kg/day to pregnant ICR/SIM mice on gestation days 8 through 12. The mice were allowed to deliver, then several neonatal growth and viability parameters were measured in the offspring. Comparative statistical analysis of these parameters between treated animals and concurrent (vehicle-treated) controls revealed no significant effect on any perinatal parameter examined.

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF -- None

__I.A.4. Additional Studies/Comments (Oral RfD)

Based on this 2-year study in rats in which a NOAEL is identified, the uncertainty factor of 100 is considered appropriate for extrapolating results to humans. This study consisted of adequate numbers of animals of both sexes as well as a thorough examination of toxicological and histological parameters.

Takahashi et al. (1986) conducted a two-stage carcinogenesis bioassay in male Wistar rats. The animals were administered N-methyl-N'-nitro-N- nitrosoguanidine (MNNG) at 100 mg/L in the drinking water for the first 8 weeks of the study, followed by administration of 0.5% formalin (dose not specified) in the drinking water during weeks 8 through 40. Other groups of animals received just MNNG or formalin (dose not specified). The animals were sacrificed at the termination of dosing and the stomachs were examined grossly and microscopically. The actual doses of formaldehyde received by the test animals is not known, because dose concentrations were not reported, and drinking water consumption was not measured. Formalin did not produce malignant tumors when given alone. In animals receiving just formalin, forestomach papillomas occurred in 8/10 animals. In rats given MNNG alone, adenocarcinoma of the pylorus occurred in 1/30 rats, preneoplastic hyperplasia of the pylorus occurred in 7/30 rats, and adenocarcinoma of the duodenum occurred in 3/30 rats. In the group administered both MNG and formalin, forestomach papillomas occurred in 15/17 animals, adenocarcinoma of the pylorus in 4/17, preneoplastic hyperplasia of the pylorus in 7/17, and adenocarcinoma of the duodenum in 1/17.

__I.A.5. Confidence in the Oral RfD

Study -- High
Database -- Medium
RfD -- Medium

Confidence in the critical study is high since it consisted of adequate numbers of animals of both sexes, as well as a thorough examination of toxicological and histological parameters. Confidence in the database is medium as several additional chronic bioassays and reproductive and developmental stuides support the critical effect and study. Medium confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- U.S. EPA, 1989

Other EPA Documentation -- None

Agency Work Group Review -- 11/17/1989, 05/17/1990, 06/20/1990

Verification Date -- 06/20/1990

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

Back to top

_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Formaldehyde
CASRN -- 50-00-0

Not available at this time.