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_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Formaldehyde
CASRN -- 50-00-0
Last Revised -- 05/01/1991

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification -- B1; probable human carcinogen, based on limited evidence in humans, and sufficient evidence in animals. Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. An increased incidence of nasal squamous cell carcinomas was observed in long-term inhalation studies in rats and in mice. The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde.

__II.A.2. Human Carcinogenicity Data

Limited. At least 28 relevant epidemiologic studies have been conducted. Among these, two cohort studies (Blair et al., 1986, 1987; Stayner et al., 1988) and one case-control study (Vaughan et al., 1986a,b) were well-conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks. Blair et al. studied workers at 10 plants who were in some way exposed to formaldehyde (largely through resin formation) and observed significant excesses in lung and nasopharyngeal cancer deaths. Despite a lack of significant trends with increasing concentration or cumulative formaldehyde exposure, lung cancer mortality was significantly elevated in analyses with or without a 20-year latency allowance. No explicit control was made for smoking status. Stayner et al. reported statistically significant excesses in mortality from buccal cavity tumors among formaldehyde-exposed garment workers. The highest SMR was for workers with long employment duration (exposure) and follow-up period (latency). The Vaughan et al. nasal and pharyngeal cancer case-control study examined occupational and residential exposures, controlling for smoking and alcohol consumption. It showed a significant association between nasopharyngeal cancer and having lived 10 or more years in a mobile home, especially for mobile homes built in the 1950s to 1970s, a period of increasing formaldehyde- resin usage. No exposure measurements were available.

The 25 other reviewed studies had limited ability to detect small to moderate increases in formaldehyde risks owing to small sample sizes, small numbers of observed site-specific deaths, and insufficient follow-up. Even with these potential limitations, 6 of the 25 studies (Acheson et al., 1984; Hardell et al., 1982; Hayes et al., 1986; Liebling et al., 1984; Olsen et al., 1984; Stayner et al., 1985) reported significant associations between excess site-specific respiratory (lung, buccal cavity, and pharyngeal) cancers and exposure to formaldehyde. Some of these studies looked at potential confounders (such as wood-dust exposure) in greater detail; they did not discern sinonasal cancer incidence excesses of the size predicted. Others (Liebling et al., 1984; Stayner et al., 1985) overlapped the Acheson et al. (1984), Hardell et al. (1982) and Hayes et al. (1986) studies; the improved design and nonoverlapping portions of the later studies (Blair et al., 1986; Stayner et al., 1988) reinforce the conclusions of the earlier studies. Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated. Although the common exposure in all of these studies was formaldehyde, the epidemiologic evidence is categorized as "limited" primarily because of the possible exposures to other agents. Such exposures could have contributed to the findings of excess cancers.

__II.A.3. Animal Carcinogenicity Data

Sufficient. Consequences of inhalation exposure to formaldehyde have been studied in rats, mice, hamsters and monkeys. The principal evidence comes from positive studies in both sexes of two strains of rats (Kerns et al., 1983; Albert et al., 1982; Tobe et al., 1985) and males of one strain of mice (Kerns et al., 1983), all showing squamous cell carcinomas.

For the CIIT, Kerns et al. (1983) exposed about 120 animals/sex/species (Fischer 344 rats and B6C3F1 mice) to 0, 2, 5.6 or 14.3 ppm, 6 hours/day, 5 days/week for 24 months. Five animals per group were sacrificed at 6 and 12 months and 20 per group were killed at 18 months. At 24 and 27 months the number sacrificed is unclear. The studies were terminated at 30 months. From the 12th month on, male and female rats in the highest dose group (14.3 ppm) showed significantly increased mortality compared with controls. In the 5.6- ppm group, male rats showed a significant increase in mortality from 17 months on. Female mice showed generally comparable survival across dose groups, as did male mice, but the male mice as a whole showed increased mortality because of housing problems. Squamous cell carcinomas were seen in the nasal cavities of 51/117 male rats and 52/115 female rats at 14.3 ppm (HDT) by experiment's end (as many as 35 carcinomas had been identified in males by month 18 based on EPA analysis notes and Kerns (Chart 8). At 5.6 ppm, 1/119 male rats and 1/116 female rats showed squamous cell carcinomas of the nasal cavity. No such tumors were seen at 0 or 2 ppm. Polypoid adenomas of the nasal mucosa were seen in rats at all doses (0 ppm: 1/118 M, 0/114 F; 2 ppm: 4/118 M, 4/118 F; 5.6 ppm: 6/119 M, 0/116 F; 14.3 ppm: 4/117 M, 1/115 F) in a significant dose-related trend, albeit one that falls off after a peak. Among the mice, squamous cell carcinomas were seen in two males at 14.3 ppm. No other lesions were noteworthy.

Sellakumar et al. (1985) exposed male Sprague-Dawley rats, 100/group, 6 hours/day, 5 days/week for lifetime to 10 ppm HCl and to 14 ppm formaldehyde. This was a combined exposure HCl and formaldehyde were administered simultaneously, and each was administered separately. An equal number of rats received an air control. HCl was administered to determine if tumor response was enhanced by an additional irritant effect or by the combining of formaldehyde and HCl to form bis-(chloromethyl)ether (BCME). Groups receiving formaldehyde alone or with HCl showed an increase in nasal squamous cell carcinomas; those without formaldehyde were free of carcinomas and other tumors (0/99 in each group), although rhinitis and hyperplasia were of comparable incidence.

Tobe et al. (1985) conducted a 28-month study of male Fischer 344 rats (about 2 weeks younger than those in Kerns et al., 1983). Groups of 32 rats were exposed

6 hours/day, 5 days/week to 0, 0.3, 2.0, 3,3, or 15 ppm formaldehyde in aqueous solution methanol; another group of 32 was exposed to methanol only (vehicle control). Animals were sacrificed at 12, 18, and 24 months. Exposure to 15 ppm ended at 24 months; at that point, mortality was 88%. At 28 months mortality was 60% in the control group and 32% in the 0.3 dose group. Squamous cell carcinomas were seen at 15 ppm in 14/27 rats surviving past 12 months, compared with 0/27 in the controls. No polypoid adenomas were observed; the increased incidences of rhinitis and hyperplasia were dose-related.

While these three rodent studies are principal in the weight of evidence, inhalation studies have been carried out in other strains and species. Dalbey (1982), as part of a promotion experiment, exposed male Syrian golden hamsters to 10 ppm formaldehyde 5 times/week, 5 hours/day throughout their lifetimes, 132 animals were untreated controls. Although survival time was significantly reduced in the treated group, no tumors were observed in either treated or control groups. Rusch et al. (1983) carried out a 6-month toxicity study in 6 male cynomolgus monkeys, 40 F344 rats (20M, 20F), and 20 Syrian golden hamsters (10M, 10F) with 22 hours/day, 7 days/week exposure to three levels of formaldehyde with corresponding controls. The highest dose tested was 2.95 ppm. The short duration of the assay, the small sample sizes, and, possibly, the low concentrations tested, limited the sensitivity of the assay to detect tumors. In the highest dose group in both rats and monkeys, incidences of squamous metaplasia/hyperplasia of the nasal turbinates were significantly elevated.

__II.A.4. Supporting Data for Carcinogenicity

Mutagenic activity of formaldehyde has been demonstrated in viruses, Escherichia coli, Pseudomonas fluorescens, Salmonella typhimurium and certain strains of yeast, fungi, Drosophila, grasshopper and mammalian cells (Ulsamer et al., 1984). Formaldehyde has been shown to cause gene mutations, single strand breaks in DNA, DNA-protein crosslinks, sister chromatid exchanges and chromosomal aberrations. Formaldehyde produces in vitro transformation in BALB/c 3T3 mouse cells, BHK21 hamster cells and C3H-10TI/2 mouse cells, enhances the transformation of Syrian hamster embryo cells by SA7 adenovirus, and inhibits DNA repair (Consensus Workshop on Formaldehyde, 1984).

When inhaled, acetaldehyde, the closest aldehyde to formaldehyde in structure, causes cancers in the nose and trachea of hamsters, and nasal cancers in rats.

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_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None.

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_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Inhalation Unit Risk – 1.3E-5 per (ug/cu.m)

Extrapolation Method – Linearized multistage procedure, additional risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration

E-4 (1 in 10,000)	8E+0 ug/cu.m
E-5 (1 in 100,000)	8E-1 ug/cu.m
E-6 (1 in 1,000,000)	8E-2 ug/cu.m

__II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type – squamous cell carcinoma
Test Animals – Rat/F344, males
Route – inhalation
Reference – Kerns et al., 1983

---------- Dose ----------		
Administered (ppm)	**Human Equivalent (mg/kg)/day**	**Tumor Incidence**
0	0	0/156
2	2	0/159
5.6	5.6	2/153
14.3	14.3	94/140

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

In the Kerns et al. (1983) study, rats that died at 11 months (prior to appearance of the first squamous cell carcinoma) were not considered at risk. Those sacrificed at 12 and 18 months were treated as though they would have responded in the same proportion as rats remaining alive at the respective sacrifice times and those living beyond 24 months were included with animals sacrificed at 24 months. From the estimates of the probability of death with tumor within 24 months and its variance, the number of animals at risk and the number with tumors were derived for a 24-month study with no 12- or 18-month kills. These rounded numbers are shown above and were used for significance tests and modeling.

The unit risk should not be used if the air concentration exceeds 8E+2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

The experimental range is close to expected human exposures. Estimated lifetime excess risks from six epidemiologic studies are close to upper bound risks based on animal data (usually within 1 order of magnitude for four types of estimated occupational and residential exposure). Animal-based estimates derived using time in the model were similar but would have required the use of more assumptions in the calculations. Three non-zero doses were used in addition to controls in the study on which calculations are based, with a large number of animals per group. Male and female incidences were close throughout the exposure groups.

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_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document – U.S. EPA, 1987

The OTS Assessment of Health Risk has received wide internal and external

review.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 02/03/1988

Verification Date -- 02/03/1988

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

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).

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_VI. Bibliography

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_VI.A. Oral RfD References

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