Appendix B
Section I

FORMALDEHYDE
HEALTH-BASED MAXIMUM CONTAMINANT LEVEL
SUPPORT DOCUMENT

Office of Science and Research
New Jersey Department Environmental Protection

Prepared by
Gloria B. Post

EXECUTIVE SUMMARY

Formaldehyde is extensively used in industrial processes and in the production of a variety of widely used products. Exposure to humans is primarily by inhalation, and the inhalation route has received the most attention in experimental toxicity studies. Formaldehyde is an irritant at sites of contact and induces nasal cancers in rodents. Oral exposure has been reported to cause oral carcinoma in situ. Estimates of the odor threshold for formaldehyde in water range from 0.8 to 102 mg/L. A health based maximum contaminant level (MCL) of 0.7 ug/L is proposed. This level is predicted to result in an upper bound risk of one in 10 individuals exposed in drinking water. throughout their lifetime.

TABLE OF CONTENTS

BACKGROUND INFORMATION AND PROPERTIES

Chemical Properties

Name:	formaldehyde
Synonyms:	formalin, formol
CAS number:	50-00-0
Chemical formula:	CH_2O
Chemical. structure:	
Molecular weight	30.03
Physical state:	Flammable colorless gas at room temperature. Formaldehyde solution (formalin). Formaldehyde by weight is aqueous solution; normally contains alcohol stabilizers (10-15%).
Melting point:	-92 ^{0}C
Boiling point:	-19.5 $^\circ$C (Formaldehyde gas) 96 $^\circ$C (Formalin)
Vapor pressure:	10mm Hg at -88 $^\circ$C (formaldehyde gas)
Specific gravity/density:	1.08 at 25 $^\circ$C (formalin)
Water solubility:	soluble to 550 g/L
Odor threshold (air):	sensory perception and irritation have been detected at concentration as low as 0.1 ppm (OSHA, 1985).
Odor threshold (water):	average - 50 mg/1 range - 0.8-102 mg/l (Verschueren, 1983)
Conversion factor: ppm = 0.82 mg/m	1

(

U. S.EPA emissions

Production and Use

Formaldehyde is a major industrial chemical, ranking 25th by production volume the U. S. The estimated production in 1985, expressed as equivalent equivalent amount of 37% solution, is 5.5 billion pounds (OSHA, 1985). Because formaldehyde tends to polymerize in aqueous solution, solutions are frequently prepared with alcohol stabilizers. Formaldehyde gas, as such, is not commercially available; paraformaldehyde is a solid, low molecular weight polymer which releases the gas degrades.

Formaldehyde is produced by oxidation of low molecular weight aliphatic hydrocarbons and by catalytic oxidation of methanol. Its major use (approximately 60%) is in the production of resins and plastics including urea-formaldehyde, phenol-formaldehydes, and melamine- formaldehydes. These are used in the manufacture of many products, including plywood, fiberboard, particleboard, permanent fabrics, and housewares. A second major category of usage (approximately 30%) is an intermediate in the production of chemicals such as butanediol, hexamethylenetriamine, and pentaerythritol. Smaller volume, but important, applications include manufacture of fertilizer, use as a disinfectant, as a preservative, and in embalming fluid (IARC, 1982; OSHA, 1985).

Guidelines, Regulations, and Standards

In 1979 the Emergency Response Group of the Committee on Toxicology, of the National Academy of Sciences, recommended a drinking water standard for formaldehyde 110 ug/L to the U.S.EPA, based on health effects in humans exposed orally (National Research Council, 1979).

The current OSHA standard of 3 ppm time-weighted average, 5 ppm ceiling and peak (30 minutes) is under review. A reduction to 1 or 1.5 ppm with elimination of ceiling and peak has been proposed (OSHA, 1985). The ACGIH, in 1982 recommended a time-weighted average concentration of 1 ppm and a short-term exposure limit of 2 ppm.

In 1982, the Consumer Product Safety Commission banned urea-formaldehyde insulation based on formaldehyde's carcinogenic and irritant properties. This ban was overruled by the Fifth Circuit Court in 1983.

In 1984, EPA designated formaldehyde for priority review under the Toxic Substances Control Act (TSCA), because of evidence of its carcinogenicity. The EPA has proposed to classify formaldehyde as a Group BI-Probable Human Carcinogen (E.S.EPA, 1985). In 1985, HUD limited the permitted level of formaldehyde emissons from plywood and particle board to 0.2 ppm and 0.3 ppm, respectively.

ENVIRONMENTAL EXPOSURE

Fate and Transport

Formaldehyde enters the atmosphere from several sources, including combustion products of automobile exhaust, manufacturing, power generation, direct and release of formaldehyde from industrial facilities, photochemical oxidation of atmospheric hydrocarbons, forest fires and burning of vegetation (National Research Council, 1981; IARC, 1982).

Formaldehyde can be removed from the atmosphere by photolysis and reaction with free radicals, and can return to earth in rain (Kitchens et al.., 1986; National Research Council, 1981). The atmospheric half-life is less than one day (Formaldehyde, 1985).

Formaldehyde can enter water from chemical, oil, and coal processing and from production and use of resins containing formaldehyde (IARC, 1982). It was rapidly biodegraded in tap water but not in distilled water (Nazarenko, 1960), Because of its low vapor pressure, there is little potential for volatilization from water.

Formaldehyde can leach into soil from aqueous solutions and from degradation of partially polymerized low molecular weight condensation products (IARC, 1982),and is biodegraded by soil bacteria.

Ambient Levels

Formaldehyde levels are generally higher in indoor than outdoor air. Atmospheric concentrations are normally below 10 to 15 ppb except in areas with photochemical smog or high levels of automobile exhaust, where concentrations of 90 to 150 ppb have been reported (Consensus Workshop, 1984). Due to improvements in control of automotive emissions, atmospheric levels have generally declined during the last 20 years. In a study of four New Jersey cities, daily medians ranged from 4 to 7 ppb, with one-hour maximums of 14-20 ppb (Cleveland, 1977).

Formaldehyde in indoor air arises from pressed wood products, urea- formaldehyde foam insulation, other consumer products, and combustion of cigarettes and other materials. In homes more than five years old, levels are normally below 50 ppb, while levels above 100 ppb often occur in newer homes, energy-efficient homes, and mobile homes (Consensus Workshop, 1984). Levels of up to 3000 ppb have been reported in mobile homes (National Research Council, 1981).

Little information is available regarding formaldehyde contamination of drinking water. Formaldehyde has been detected in rain, mist, and fog (Formaldehyde, 1985). It was not listed in a summary of aldehydes detected in drinking' water and surface water (National Research Council, 1981), but was detected and not quantified in two of ten water supplies (Philadelphia, PA and Miami, FL)in the National Organics Reconnaissance Survey of Suspected Carcinogens in Drinking Water (U.S. EPA, 1975). Isolated incidents of drinking water contamination have been reported. In 1979 an Emergency Response was prepared for the EPA when 160 ug/L formaldehyde was found in well-water in a rural New York community (National Research Council, 1979).

Incidents of formaldehyde contamination have also occurred in the Russian River in California (David Spath, California Department of Health Services, personal communication). One occurrence involved a spill from a railroad car and another a discharge from a plywood manufacturing plant.

METABOLISM AND PHARMACOKINETICS

The metabolism and pharmacokinetics of formaldehyde have been extensively reviewed by several authors (Federal Panel, 1982; Heck and Casanova-Schmitz,' oxidized to CO, 1984; Ulsamer et al., 1984). The following discussion represents a summary of these reviews, unless specific references are given.

Absorption

Formaldehyde can be absorbed after oral, dermal, or inhalation exposure, although dermal absorption is much slower than are the other two routes. In response to the irritation caused by formaldehyde, the respiratory rate and volume decrease, thus limiting the amount of formaldehyde inhaled. This occurs to a greater extent in mice than in rats; this may contribute to eater sensitivity of rats than mice to formaldehyde.

In addition to being absorbed from exogenous sources, formaldehyde is also endogenously, both as a product of normal metabolic pathways, and during the cytochrome P-450 catalyzed oxidative demethylation of xenobiotics.

Distribution

Inhaled formaldehyde is absorbed primarily through the upper respiratory tract. Following inhalation of (^{14}C) formaldehyde, the anterior nasal mucosa contained much higher concentrations of radioactivity than other organs, including trachea, lung, liver, kidney, intestine, spleen, heart, brain, and testes (Hecket al., 1983).

Formaldehyde itself does not accumulate within the body following exposure (see metabolism, below) and inhalation of 14.4 ppm by rats for 2 hours or 1.9 ppm by humans for 40 minutes did not increase blood formaldehyde levels (Heck et al.,1985). A substantial fraction of the radioactivity from formaldehyde may be retained in the body for several weeks or longer; this is likely due to entry of carbon-14 from formaldehyde into the one-carbon pool from which it is utilized in normal biosynthetic pathways.

Metabolism

Formaldehyde is unique in that it is both an important intermediate in biosynthetic pathways and a highly reactive compound capable of covalently binding to macromolecules and causing toxicity.

Endogenous formaldehyde arises primarily from glycine and serine, as well as other amino acids, choline, and xenobiotics. The naturally occurring formaldehyde concentration in livers from F-344 rats is 0.1 - 0.2 umoles/g wet weight (Heck et al., 1982).

A large fraction of the endogenous formaldehyde reacts with glutathione to form S-hydroxymethylglutathione. This adduct is oxidized by formaldehyde dehydrogenase to the formate derivative, S-formylglutathione, which releases formate; this is an important pathway of elimination of endogenous formaldehyde.

Formaldehyde can also react with tetrahydrofolate to form N_5, N_{10} - methylene tetrahydrofolate. Through this intermediate, the carbon atom derived from formaldehyde enters the one-carbon pool and can be incorporated into all major classes of macromolecules, including proteins, nucleic acids, and lipids.

Because it is rapidly converted to formate, administration of formaldehyde does not result in measurable increases in blood formaldehyde levels. Formate is oxidized to CO_2, incorporated into the one-carbon pool, or excreted in the urine unchanged as N-formyl cysteine, or other metabolites.

Since removal is rapid, systemic covalent binding does not take place to a significant extent (see below). However, binding at the site of entry is of major importance in the causation of toxicity by formaldehyde. Although most of the work in this area to date has involved exposure by inhalation, similar reactions would be expected with oral administration.

Formaldehyde reversibly forms adducts with nucleophilic molecules such as primary and secondary amines, thiols, hydroxyls, and amides. The amine adducts are stabilized by the formation of cross-links. Such reactions in the nucleohistone complex result in DNA-protein and protein-protein cross-links, can be estimated by measuring the increase in insoluble (non-extractable) as opposed to soluble nucleic acids. Inhalation of formaldehyde by F-344 rats resulted in a concentration-dependent increase in cross-linking of the respiratory, but not the olfactory, nasal. mucosa (Casanova-Schmitz and Heck, 1983).

As discussed above, formaldehyde is incorporated into macromolecules both through normal metabolic, pathways and by reacting to form adducts. By simultaneously exposing rats to [^{14}C]-3 an $_{14}$[^{3}H]- labelled formaldehyde and determining the ratios of covalently bound [^{3} H/^{14}C] in the tissues, the relative importance of Human metabolic incorporation and adduct formation can be estimated (Casanova-Schmitz -et al., 1984). This is possible because metabolic incorporation is normally preceded by oxidation which results in loss of [^{3} H], while adduct formation does not involve loss of [^{3}H].

Binding of [^{3}H] and [^{14}C] to DNA, RNA, and protein were measured in respiratory and olfactory nasal mucosa as well as in femoral bone marrow, a tissue with a high rate of turnover which is distant from the site of exposure. After exposure of rats to 0.3, 2, 6, 10, or 15 ppm formaldehyde for 6 hours, pain, a single pre-exposure to unlabelled formaldehyde, metabolic incorporation occurred to protein and DNA in all three tissues while adduct formation was found only in the respiratory mucosa, with adducts to both DNA and protein detected.

Excretion

The elimination of (^{14}C) formaldehyde administered by several different routes has been determined. Rats inhaling 0.6 or 13 ppm eliminated 40% as CO_2 17% in urine, and 57 in feces, while 35% to 38% remained in the body after 70 hours (Heck et al., 1983). After oral administration, 40% was also CO_2 (Buss et al., 1964), while after subcutaneous or intravenous injection a much greater portion (approximately 80%) was converted to CU_2 (DuVigneud et al.,1950; Neely, 1964; Mashford and Jones,1982). The reasons for these differences are not known. The principal urinary, metabolite is formate; several minor urinary metabolites also occur.

Human Exposure and Body Burden

Human exposure to formaldehyde arises from a variety of sources. It was estimated in 1981 that 1.34 million U.S. workers are occupationally exposed to formaldehyde, with about 10% of these exposures at levels of 1 ppm or greater (OSHA, 1985). Exposure also occurs in both indoor and outdoor air, with higher levels in newer homes, mobile homes, and energy efficient homes. Consumer product such as cosmetics, disinfectants, fabrics, rugs, and furniture represent an additional source of exposure. Formaldehyde is formed during combustion, including the burning of cigarettes, and it has been detected in fruits and vegetables.

Typical daily intakes through air have been estimated to be 50-500 ug, with a higher exposure (4500 ug) to persons living in energy efficient homes. Exposure through drinking water has not been adequately investigated. Carbonated beverages have been reported to contain approximately 8000 ug/L formaldehyde (Ames, 1185).

HEALTH EFFECTS

OVERVIEW

Effects associated with formaldehyde occur primarily at sites of contact. These include irritation of eyes and upper respiratory tract, as well as sensitization and tissue damage of upper respiratory tract. Numerous epidemiological studies have not determined conclusively whether formaldehyde is carcinogenic in man. Inhalation of formaldehyde causes nasal cancers in rodents; oral exposure been reported to cause oral carcinoma *in situ* in rabbits.

Human

While the effects of inhalation and dermal exposure to formaldehyde have been well documented, little information is available in regard to the effects of formaldehyde ingestion in humans. Two subjects ingested formaldehyde daily for 13 weeks, in increasing doses from 22 to 200 mg/kg. No adverse effects,, were noted except for mild pharyngeal and gastric discomfort, which was alleviated' by diluting the formaldehyde prior to ingestion (Yonkman et al., 1941). In a study reported in 1919, ingestion of 100-200 mg per day by volunteers caused gastric pain, headache, throat irritation, and skin rash (National Academy of Sciences, 1979).

Many studies involving both experimentally controlled and occupational exposures have demonstrated that formaldehyde causes irritation of the eyes, nose, and throat, headaches, direct skin irritation, and skin sensitization resulting in dermatitis and uriticaria (Consensus Workshop, 1984; OSHA, 1985). lese effects occur at decreasing concentrations as the period of the exposure increases, In general, 1 ppm formaldehyde causes irritation within a few minutes; no threshold for irritation has been established. Higher concentrations (10-20 ppm) increase the severity of symptoms, while 50 to 110 ppm can cause severe damage to the respiratory tract. Formaldehyde has also occasionally caused allergic sensitization of the respiratory tract (Federal Panel, 1982).

Numerous epidemiological studies have examined the relationship between formaldehyde exposure and cancer, and these have been extensively reviewed (IARC, 1982; Consensus Workshop, 1984; Ulsammer et al. , 1984; OSHA, 1985) . In general, occupational exposures can be divided into two categories: professionals using formaldehyde as a tissue preservative (anatomists, pathologists, and embalmers) and industrial workers involved in the production and use of formaldehyde. The two groups differ in the temporal pattern and level of exposure. The findings of these studies were summarized and evaluated by the Consensus Workshop (1984). A problem with drawing firm conclusions from these studies occurs because the sample sizes may not have been large enough to detect moderate increases in the cancer rate (IARC, 1982; OSHA, 1985).

No nasal cancers were observed in any of the eleven studies evaluated by the Consensus Workshop (1984). Nasal cancer is of interest because experimental exposure of animals to formaldehyde causes nasal cancer (see Carcinogenicity, below). Two recent case-control studies (Olsen et al., 1984, Hayes, 1986) suggested that exposure to formaldehyde increases the incidence of nasal cancer, Additionally, two cases involving nasal cancer in persons exposed to formaldehyde have been reported (Infante and Kang, 1984; Halperin et al., 1983).

The Consensus Workshop (1984) found no significant association between formaldehyde exposure and cancer of a number of sites including the buccal cavity, pharynx, lung, prostate, skin, bladder, kidney, and gastrointestinal tract. In a race-age-sex adjusted proportionate mortality ratio study, the incidence of buccal and pharyngeal cancer in chemical workers exposed to formaldehyde was significantly increased.However, exposure to formaldehyde could not be completely separated from exposure to the many other chemicals used at the plant (Liebling et al., 1984). In regard to lung cancer, a significant increase in lung cancer incidence occurred in a British factory where exposure was high. A relationship was seen between degree of exposure and lung cancer, but this trend disappeared when length of exposure was considered (Consensus Workshop, 1984).

A significant increase in the incidence of brain cancer, especially gliomas and astrocytomas, and leukemia has been observed in several different studies of professional workers .(embalmers, anatomists, and pathologists), but not in industrial workers, who are exposed to formaldehyde (Consensus Workshop, 1984).

A recently reported large-scale historical cohort study conducted by the NCI involved 26,561 workers at 10 plants for approximately 600,000 person years(Blair et al., 1986). No increased mortality or cancer rate was associated with exposure to formaldehyde. No increase in the rate of brain cancer or leukemia was observed. Increased rates of Hodgkin's disease, lung, and prostate cancer' the area occurred, but these were not related to the extent of formaldehyde exposure. While the incidence of cancer of the buccal cavity and pharynx was lower than expected, the rates at specific site, the nasopharynx and oropharynx, were significantly increased. Additionally, two recent studies of garment workers' exposed to formaldehyde (Stayner et al., 1985, Stayner et al., 1986) have detected a significant increase in cancer of the buccal cavity.

Animal

Acute. The oral LD_{50} for formaldehyde is 800 mg/kg in rats and 260 mg/kg in guinea pigs (IARC, 1982).

Acute exposure by inhalation causes irritation to the eyes, skin, and upper respiratory tract in animals, similar to the effects in humans, as described above. Exposure of animals to high levels (greater than 100 ppm) cause severe epithelia effects, such as salivation, dvspnea, vomiting, and death (IARC, 1982).

The respiratory rate is decreased by exposure to formaldehyde. This protective mechanism occurs at a much lower formaldehyde concentration in mice than in rats; it may contribute to the greater sensitivity of rats than mice (see discussed below; Heck and Casanova-Schmitz, 1984).

Subchronic/Chronic .Formaldehyde toxicity occurs primarily at the point of contact. Although hepatotoxicity has been reported (reviewed by Beall and Ulsamer, 1984), these reports generally cannot be correlated with duration or level of exposure (Gibson, 1984). Furthermore, exposure to formaldehyde does not increase the blood concentration (Heck et al., 1985) or cause covalent binding in arrow (Casanova-Schmitz et al., 1984, see Metabolism above).

The effects of formaldehyde ingestion have received relatively little attention. A Russian review article (Nazarenko, 1960) summarized several ingestion studies. Deaths occurred in dogs given as little as 2 mg/kg formaldehyde for 50 days, while rabbits were less sensitive. Rats given 1, 5, and 20 mg/L in drinking water for 11 weeks showed no histological changes, while 100 mg/L for an unspecified period was reported to affect liver and spleen.

A recent report (Johannsen et al., 1986) described the effects of oral administration of formaldehyde in rats and dogs. This was the most completely conducted and reported oral study found after an extensive literature search. Pilot studies (14 days) were conducted to determine the maximum tolerated doses in the two species. Sprague-Dawley rats (15 per sex group) were administered 0,50,100, or 150 mg/kg per day in drinking water and beagle dogs (4 per sex per group)were administered 0, 50, 75 or 100 mg/kg per day in their food for 90 days. Parameters evaluated included food and water consumption, weight gain, hematology, blood and urine chemistry, organ weight, and gross and microscopic pathology. The only effect observed was decreased weight gain which was statistically significant in male and female dogs at 100 mg/kg, in male rats at 100 and 150 mg/kg, and in female rats at 150 mg/kg. This decreased weight gain was associated with decreased food intake in dogs but not in rats. No effects were seen on the other parameters including histology of any organ including the gastrointestinal mucosa.

The effects of long-term formaldehyde inhalation are primarily limited to areas at which formaldehyde enters the body. Cymolgus monkeys (6 male per group), Fischer 344 rats (20 per sex per group), and Syrian golden hamsters (10 per sex per group) were exposed to 0, 0.19, 0.98, and 2.95 ppm for 22 hours per day, daily for 26 weeks (Rusch et al., 1983). No treatment related mortality was Body weight, organ weights, and respiratory tract pathology were evaluated at the conclusion of the experiment. Exposure of monkeys to 2.95 ppm caused hoarseness, congestion, and nasal squamous cell metaplasia. Rats exposed to this concentration exhibited nasal squamous metaplasia and decreased body and liver weight, while hamsters were not affected.

A carcinogenicity bioassay involved exposure of rats and mice to 0, 2,6, or 15 ppm, 6 hours per day, 5 days per week, for two years.This study is described in more detail under Carcinogenicity (CIIT, 1981). Pathological examination of approximately 50 tissues per animal revealed treatment related lesions only in nasal cavity and proximal trachea; these included purulent rhinitis, epithelial dysplasia, and squamous metaplasia involving alterations in the epithelial cell types present in these areas.

Investigators at CIIT have conducted a number of studies on the mechanism of formaldehyde toxicity to the nasal tissues. Some of the biochemical work was discussed above under Metabolism. Formaldehyde exposure causes paralysis of the mucocliliary apparatus; this apparatus is important in protecting the nasal respiratory areas from damage (Morgan et al. , 1986).

Reproductive, Embryotoxic, and Teratogenic

Formaldehyde appears to have little, if any, potential for reproductive toxicity or teratogenicity. In most of the studies evaluating these effects, formaldehyde was administered orally. Marks et al. (1980) administered 0, 14, 148, or 185 mg/kg to mice on days 6 through 15 of gestation. There were 76 animals in the control group and 29-34 in each treated group. Over 60% of the animals in the highest dose group died, but no evidence of reproductive toxicity was observed in any dose group. Exposure of beagles to 600 or 1250 pp hexamethylenetetramine, which is metabolized to formaldehyde in vivo, in the diet on day 4 through 56 of gestation resulted in stillbirths, increased postnatal mortality, and decreased fetal growth rate in the higher dose group; no malformations were observed (Hurni and Ohder, 1973). Exposure of male and female rats (12 per control group, and 24 per treatment group) to 1% hexamethylenetetramine in drinking water, from two weeks prior to mating through pregnancy, did no cause malformations (Della Porta, et al., 1970). Finally, daily exposure of rat (16 per sex per group) to 100 mg/kg hexamethylenetetranine for two generations did not impair fertility (Natvig et al., 1971).

Behavioral and Central Nervous System

Non-specific effects such as increased thirst, dizziness, headache, tiredness, and insomnia have been reported by persons exposed to levels of 1 ppm or more (National Research Council, 1981). Reports on association of formaldehyde exposure with psychological and behavioral problems are difficult to interpret because of inadequate controls, and because awareness of formaldehyde odor may cause a person to become anxious and fearful (Consensus Workshop, 1984).

Genetic

Formaldehyde causes mutations in a number of test systems including , Drosophila, fungi, bacteria and mammalian cells (Auerbach et al. , 1977; Federal Panel, 1985) including cultured human lymphoblasts (Goldmacher and Thilly, 1983). It has also been found capable of transforming Balb/c3T3 mouse cells (Brusick, 1983) and BHK hamster cells (Ashby and Lefevre, 1983).

Additionally, formaldehyde has been shown to induce single-strand DNA breaks, DNA-protein crosslinks, sister chromatid exchange, and chromosome aberrations in vitro (reviewed by Consensus Workshop, 1984).

In vivo studies of formaldehyde's mutagenic potential have generally given negative results. Tests conducted include dominant lethal, mouse spot, chromo some aberration, and sister chromatid exchange (Federal Panel, 1984; OSHA, 1985)

Carcinogenicity

Four inhalation studies have demonstrated that formaldehyde is carcinogen at in rodents. A two year inhalation bioassay was conducted for the Chemical Industry Institute of Toxicology by Battelle Columbus Laboratories (CIIT, 1981) Fischer 344 rats and B6C3F1 mice (120 per species per sex per group) were expose to 0, 2, 6 or 15 ppm formaldehyde 6 hours per day, 5 days per week, for two years, followed by a six month observation period. Interim sacrifices took place at 6, 12, 18, 24, 27, and 30 months. Non-carcinogenic effects observed in this study were described above under toxicity. Exposure to formaldehyde produce nasal cancers in both species. In rats, a steep exposure-response curve was served, with no tumors in the low exposure group, two tumors in the intermediate group, and 103 tumors in the high exposure group. Mice were less sensitive formaldehyde than were rats; only two mice, both in the high exposure group, developed nasal tumors.Tumors at sites other than the nasal area were not associated with formaldehyde exposure in either species.

Albert et al. (1982) exposed male Sprague-Dawley rats (100 per group) to a mixture of formaldehyde (14.7 ppm) and hydrochloric acid (10.6 ppm), -6 hours per ,5 days per week, for life. None of the controls

developed nasal tumors, while 28 exposed rats did. In subsequent experiments (Sellakumor et al., 1985), tumors occurred in 38% of rats exposed to formaldehyde (15 ppm, exposure schedule same as above) alone. Coexposure to HC1 did not potentiate formaldehyde's effects, and HC1 alone was not carcinogenic.

Tobe et al. (1985) exposed 4-week-old male Sprague-Dawley rats (32 per group) to 0, 0.3, 2, or 15 ppm. formaldehyde, 6 hours per day, 5 days per week, for 28months (24 months for 15 ppm. group). The formaldehyde was generated from formalin containing 10% methanol. Interim sacrifices were performed at 12, 18, 24 months (5 per group). Controls were exposed to air or 3.3 ppm. methanol. Nassal tumors were seen only at the highest exposure; 14 squamous cell carcinomas 5 squamous cell papillomas occurred among the 32 rats in this group.

Hamsters appear to be less sensitive to formaldehyde than rats (Dawley, 1982). Male Syrian golden hamster, exposed to 10 ppm, 5 hours per day, 5 days week, for life, did not develop nasal tumors. However, exposure to 30 ppm. for hours, 48 hours prior to injection with diethylnitrosamine for 10 weeks, increased the number of tracheal adenomas/tumor bearing animal. This suggest it formaldehyde may act as a cofactor in carcinogenesis.

The mechanism of carcinogenicity by formaldehyde and the possible reasons strain differences in sensitivity have received considerable attention. It has been suggested that the response may relate better to "delivered dose" at the target tissue than to the actual concentration in inspired air (Starr and Gibson, 1985). The "delivered dose" is affected by a number of factors. Depression of respiratory rate in response to irritation by formaldehyde tends to decrease the “delivered dose" relative to the administered concentration, while inhibition of the mucociliary apparatus, stimulation of cell proliferation, and saturation of rural detoxification pathways at high formaldehyde concentrations tend to crease the "delivered dose" relative to the administered dose.

Another important consideration is the difference in the respiratory physiology of rodents and humans. Rodents are obligate nose breathers, while humans lathe through both nose and mouth.

Formaldehyde carcinogenicity by other routes of exposure has been investigated. Two initiation/promotion studies for skin cancer in mice gave negative results (Krivanek et al., 1982; Spangler and Ward, 1982). Administration of hexamethylenetetramine, which is converted to formaldehyde in vivo, in drinking water to mice (1.25 to 12.5 g/kg per day, for up to 60 weeks) or rats (1.5 to 2.5 kg per day for 104 weeks) did not result in treatment related tumors.

Subcutaneous injection of rats with 0.4% formalin (1 ml per week for 15 k) or 9-40% hexamethylenetetramine (1 to 2 ml per week until tumors developed) caused sarcomas at the site of injection, while similar injections of formic acid did not (Watanabe et al., 1954; Watanabe et al., 1955).

The oral mucosa of rabbits was exposed to 3% formalin for a total of 300 hours over an 11 month period by means of an oral tank (Muller et al., 1978), Rabbits exposed to the tank alone developed hyperplasia (proliferation of normal cell types) from mechanical irritation, while two of six formalin treated animals, developed macroscopically visible leukoplakia characterized histologically as carcinoma in. situ. Although this study has a number of shortcomings, including insufficient numbers of animals and lack of detail in reporting, it is of particular relevance to drinking water exposure because it suggests that formaldehyde can cause neoplastic changes orally as well as by inhalation.

QUANTITATIVE RISK ASSESSMENT

Studies Useful for Risk Assessment

Because formaldehyde has been shown to be carcinogenic only at site of entry into the body (e.g. in the nasal area when given by inhalation), it was uncertain whether the inhalation studies are appropriate for risk assessment for drinking water exposures. Muller et al. (1978) have shown that oral exposure of rabbits to formaldehyde causes lesions of the mouth, including carcinoma in situ, However, this study does not contain sufficient data to perform a quantitative risk assessment. Therefore, the rat inhalation study conducted by CIIT was chosen for this assessment. This study was judged most appropriate of the four positive rat inhalation studies because it utilized

the largest number of animals per group, was the only study to demonstrate dose-response, and involved exposure to pure formaldehyde.

Calculation of the Health-Based Maximum Contaminant Level

The incidence of nasal squamous cell tumors in male and female rats reported by CIIT (1981) was fitted to the multistage model using an updated version of GLOBAL82 (Crump, 1986). The daily dose to the animals representing an extra risk of 10^{-6} was calculated for these tumors, and the equivalent human dose was based on a surface area conversion.

The data used in the calculation are shown below.

Dose		Response
(ppm)	(mg/kg per day)	(# animals with tumors/ animals at risk)
0	0	0/157
2	0.33	0/159
5.6	0.93	2/155
14.3	2.40	95/146

Number of animals at risk includes those dying naturally between 0 and 2G months, and those dying naturally or sacrificed at 24 months or later. Those killed during interim sacrifices, prior to 24 months, are not included.

Conversion from ppm to mg/kg per day was as follows:

$$\text{(mg/kg/day)} = \frac{\text{Dose (ppm)} \times 1.22 \frac{\text{mg}}{\text{m}^3} \times \frac{6 \text{ hrs}}{24 \text{ hrs}} \times 0.26 \text{ m}^3 \text{ (breathing rate)} \times \frac{5 \text{ days}}{7 \text{ days}}}{\text{PPM} \quad \text{day} \quad 0.35\text{kg}}$$

The data were fitted to the multistage model, and parameters were estimated e method of maximum likelihood. The likelihood method is used to calculate confidene limits.

The upper 95% confidence limit on the slope, or potency (q_1*) derived from model is 9.19×10^{-3} mg/kg per day . The dose to the test animal, using the stage model,.Which represents the 95% lower bound estimate on excess risk of 10^{-6} 1.09 x 10 mg/kg per day^{-4}.

Because formaldehyde's effects occur through contact at the site of exposure doses were normalized for rats and humans on the basis of surface area. It assumed that the susceptible areas in rats and human are proportional to body e area.

$Da\ (Wa/Wh)^{1/3} = Dh$

1.09×10^{-4} mg/kg/day (.35/70) 1/3 = 1.86×10^{-5} mg/kg/day

Dh = dose to human
Da = dose to rat
Wh = weight of human
Wa = weight of rat

The maximum contaminant level (MCL) that could provide this dose to humans drinking water is calculated by:

MCL (ug/L) = Dh x Wh x 1000 ug/mg

where V = water volume consumed daily

$$\text{MCL} = \frac{1.86 \times 10^{-5} \text{ mg/kg/day} \times 70 \text{ kg} \times 1000 \text{ ug/mg}}{2 \text{ L/day}} = 0.652 \text{ ug/L}$$

Therefore, the drinking water MCL derived from the 95% upper bound on 10^{-6} risk is 0.7 ug/L.

Assumptions and Uncertainties

Several major assumptions were required to perform the risk assessment. One ant assumption is that data on nasal tumors in rodents exposed to formaldehyde inhalation can be used to estimate the risk of tumors in areas of the posed during ingestion of drinking water.

Another assumption is that the same proportion of administered formaldehyde is the susceptible areas during exposure by inhalation and drinking water. assumed that the sizes of the susceptible areas are proportional to the e body surface areas of the rat and the human.

Finally, extensive investigation into the mechanism of carcinogenesis formaldehyde has suggested that the response to the compound may be non-linear, and that several protective mechanisms must be overcome before tumor formation can occur (reviewed by Starr and Gibson, 1985). However, the Risk Estimation Panel of the Consensus Workshop (1984) concluded that this apparent non-linearity does not indicate that a threshold for carcinogenicity from formaldehyde exposure exists. The panel was in general agreement that linear low-dose non-threshold extrapolation is most appropriate for risk assessment.

Finally, it is assumed that the daily water consumption of ar_ adult is liters.

Conclusions

A health-based lifetime maximum contaminant level of 0.7 ug/L was derive. Exposure to this level could result in an excess cancer incidence of no more than 1 in 10^6 individuals.

BIBLIOGRAPHY

Albert, R.E., Sellakumar, A.R., Laskin, S., Kuschner, M., Nelson, N., and Snyder, C.A. 1982. Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J. Nat. Cancer Inst. 68: 597-603.

Ames, B.N. 1985. Testimony to Senate Committee on Toxics and Public Safety Management, State of California.

Ashby, T. and Lefevre, P. 1983. Genetic toxicology studies with formaldehyde and closely related chemicals including hexamethyphosphoramide (HMPA). In: Formaldehyde Toxicity (J.E. Gibson, ed.), Hemisphere Publishing Corp., N.Y., pp 85-97.

Auerbach, C., Moutschen-Dahman, M., and Moutschen, J. 1977. Genetic and cytogenetical effects of formaldehyde and related compounds. Mutat. Res. 39: 317-362.

Beall, J.R. and Ulsamer, A.G. 1984. Formaldehyde and hepatotoxicity: a review. J. Toxicol. Envir. Health 13: 1-21.

Blair, A., Stewart, P., O'Berge, M., Gaffey, W., Walrath, J., Ward, J., Bales, R., Kaplan, S., and Cubit, D. 1986. Mortality among industrial workers exposed to formaldehyde. J. Nat. Cancer Inst. (in press).

Brusick, D. 1983. Genetic and transforming activity of formaldehyde. In: Formaldehyde Toxicity (J.E. Gibson, ed.), Hemisphere Publishing Corp., N.Y., pp 73-84.

Buss, J. Kuschinsky, K., Kewitz, H., and Koransky, W. 1964. Enterale resorption von Formaldehyd. Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak. 247: 380 (cited in Heck and Casanova-Schmitz, 1984).

Casanova-Schmitz, M. and Heck, H. d'A. 1983. Effects of formaldehyde exposure on the extractibility of DNA from proteins in the rat nasal mucosa. Toxicol. Appl. Pharmacol. 70: 121-132.

Casanova-Schmitz, M., Starr, T.B., and Heck, H. d'A. 1984. Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [^{14}C]- and [^{3}H] formaldehyde. Toxicol. Appl. Pharmacol. 76: 26-44.

CIIT. Chemical Industry Institute of Toxicology. 1981. A chronic inhalation toxicology study in rats and mice exposed to formaldehyde. Volume 3. CIIT docket #10922.

Cleveland, W.S. et al. 1977. Atmos. Environ. 11: 357-60.

Consensus Workshop. 1984. Report of the consensus workshop on formaldehyde. Environ. Health Perspec. 58: 323-381.

Crump, K.S. 1986. Quantitative risk assessment for selected volatile organics in drinking water. Prepared by K.S. Crump and Co., Inc. for Office of Science and Research, N.J. Department of Environmental Protection.

Dalbey, W.E. 1982. Formaldehyde and tumors in hamster respiratory tract. Toxicology 24: 9-14.

Della Porta, G., Cabral, J.R., Parmiani, G. 1970. Transplacental toxicity and carcinogenesis studies in rats with hexamethylenetetramine. Tumori 56: 325-334 (cited in Ulsamer et al., 1984).

duVigneaud, V., Vergy, W.G., and Wilson, J.E. 1950. J.Am. Chem. Soc. 72: 2819-2820 (cited in Ulsamer et al., 1984).

Federal Panel. 1982. Report of the Federal Panel on formaldehyde. Environ. Health Perspec. 43: 139-168.

Formaldehyde. In:HSDB, Hazardous Substances Data Bank [Database]. Bethesda, MD: National Library of Medicine, [July 1985]; HSDB number 164. Last revised 4/26/85.

Gibson, J.E. 1984. Comments on "Formaldehyde and hepatotoxicity" by Beall and Ulsamer. J. Toxicol. Environ. Health 14: 465-467.

Goldmacher, V.S. and Thilly, W.G. 1983. Formaldehyde is mutagenic for cultured human cells. Mutat. Res. 116: 417-422.

Halperin, W.E., Goodman, M., Stayner, L., Elliott, L.J., Keenlyside, R.A., and Landrigan, P.J. 1983. Nasal cancer in a worker exposed to formaldehyde. J. Am. Med. Assoc. 249: 510-512.

Hayes, R.B., Raatgever, J.W., deBryyn, A., and Gerin, M. 1986. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. Int. J. Cancer 37: 487-492.

Heck, H. d'A. and Casanova-Schmitz, M. 1984. Biochemical toxicology of formaldehyde. Rev. Biochem. Toxicol. 6: 155-189.

Heck, H. d'A., White, E.L., and Casanova-Schmitz, M. 1982. Determination of formaldehyde in biological tissues by gas chromotography/mass spectrometry. Biomed. Mass. Spectrom. 9: 347.

Heck, H. d'A., Chin, T.Y., and Schmitz, M.C. 1983. Distribution of 14C formaldehyde in rats after inhalation exposure. In: Formaldehyde Toxicity (J.E. Gibson, ed.) Hemisphere Publishing, Washington, pp 26-37.

Heck, H. d'A., Casanova-Schmitz, M., Dodd, P.B., Schachter, E.N. Witek, T.J., and Tosun, T. 1985. Formaldehyde (CH_2O) concentrations in the blood of humans and Fischer 344 rats exposured to CH_2O under controlled conditions. Am. Ind. Hyg. Assoc. J. 46: 1-3.

Hurni, H. and Ohder, H. 1973. Reproduction study with formaldehyde and hexamethylenetetramine in beagle dogs. Food Cosmet. Toxicol. 11: 459-462.

Infante, P. and Kang, H. Nasal sinus, pharyngeal, and buccal cavity cancer and formaldehyde exposed workers. OSHA Internal Document, cited in Consensus Workshop, 1984.

IARC. International Agency for Research on Cancer. 1982. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Industrial Chemicals and Dyestuffs. Volume 29. Formaldehyde, pp. 345-398.

Johannsen, F.R., Levinskas, G.J., and Tegeris, A.S. 1986. Effects of formaldehyde in the rat and dog following oral exposure. Toxicol. Letters 30: 1-6.

Kitchens, J.F., Casner, R.E., Edwards, G.S., Harward, W.E. III, and Macri, B.J. 1976. Investigation of Selected Potential Environmental Contaminants: Formaldehyde (EPA-560/2-76-009) U.S. E.P.A., Office of Toxic Substances (IARC, 1982). (Cited in Formaldehyde, Hazardous Substances Databank, 1985).

Krivanek, N.D., McAlack, J.W., and Chromey, N.C. 1982. Skin initiation/promotion study with formaldehyde in CD-1 mice. In: Formaldehyde: Toxicology-Epidemiology-Mechanisms (Clary, J.J. et al., eds). Dekker, N.Y.

Liebling, T., Rosenman, K.D., Pastides, H., Griffith, R.G., and Lemeshow, S. 1983. Mortality in relation to occupation: a study of workers at the Monsanto-Springfield Chemical Plant. Am. J. Ind. Med. 5: 423-428.

Marks, T.A., Worthy, W.C., and Staples, R.E. 1980. Influence of formaldehyde and Sonacide (potentiated acid glutaraldehyde) on embryo and fetal development in mice. Teratology 22: 51-58.

Mashford, P.M. and Jones, A.R. 1982. Formaldehyde metabolism by the rat: a re-appraisal. Xenobiotica 12: 119-124.

Morgan, K.T., Jiang, X-Z, Starr, T.B., and Kerns. W.D. 1986. More precise localization of nasal tumors associated with chronic exposure of F-344 rats to formaldehyde gas. Toxicol. Appl. Pharmacol. 82: 264-271.

Muller, P., Raabe, G., and Schumann, D. 1978. Leukoplakia induced by repeated deposition of formalin in rabbit oral mucosa. Exp. Path., Bd. 16: 36-42.

National Research Council. 1979. Emergency Response Report on Formaldehyde. National Academy of Sciences, Washington.

National Research Council. 1981. Formaldehyde and other aldehydes. National Academy Press, Washington.

Natvig, H., Andersen, J. and Rasmussen, E. W. 1971. A contribution to the toxicological evaluation of hexamethylenetetramine. Food Cosmet. Toxicol. 9: 491-500.

Nazarenko, I.V. 1960. Limit of allowable formaldehyde concentration in water basins. In: Cherkinskii, S.N., ed., Limits of Allowable Concentrations of Deleterious Substances in Water Basins. Book 4. Moscow. (Translated by Levine, B.S. 1962). U.S.S.R. Literature on Water Supply and Pollution Control, Volume 3., Washington, D.C., U.S. Dept. of Commerce.

Neely, W.B. 1964. The metabolic fate of formaldehyde-14C intraperitoneally administered to the rat. Biochem. Pharmacol. 13: 1137-1142.

Occupational Safety and Health Administration. 1985. Occupational exposure to formaldehyde; proposed rule and notice of hearing Fed. Reg. 50: 50412-50499.

Olsen, J.H., Jensen, S.P., Hink, M., Faurbo, K., Breum, N.O., and Jensen, O.M. 1984. Occupational formaldehyde exposure and increased nasal cancer risk in man. Int. J. Cancer 34: 639-44.

Rusch, G.M., Clary, J.J., Rinehart, W.E., and Bolte, H.F. 1983. A 26-week inhalation toxicity study with formaldehyde in the monkey, rat, and hamster. Toxicol. Appl. Pharmacol. 68: 329-343.

Sellakumar, A.R., Snyder, C.A., Solomon, J.J., and Albert, R.E. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharamcol. 81: 401-406.

Spangler, E.F. and Ward, J.M. 1982. Skin initiation/promotion study with formaldehyde in Sencar mice. In: J.J. Clary et al., ed. Formaldehyde Toxicity-Epidemiology-Mechanisms. Dekker, N.Y. (cited in Ulsamer et al., 1984).

Starr, T.B. and Gibson, J.E. 1985. The mechanistic toxicology of formaldehyde and its implications for quantitative risk estimation. Ann. Rev. Pharmacol. Toxicol. 25: 745-767.

Stayner, L., Smith, A.B., Reeve, G., Blade, L., Elliott, L., Keenlyside, R., and Halperin, W. (1985). Proportionate mortality study of workers in the garment industry exposed to formaldehyde. Am. J. Ind. Med. 7: 229-240.

Stayner, L.T., Elliott, L., Blade, L., Keenlyside, R., and Halperin, W. 1986. A retrospective cohort mortality study of workers exposed to formaldehyde in the garment industry (in press).

Tobe, M. et al. 1985. Studies of the inhalation toxicity of formaldehyde. National Sanitary and Medical Laboratory Service Toxicity Department of the Organism Safety Research Center. pp. 1-94. (cited in OSHA, 1985; Crump, 1985).

Ulsamer, A.G., Beall, J.R., Kang, H.K., and Frazier, J.A. 1984. Overview of health effects of formaldehyde. Hazard Assessment of Chemicals: Current Developments 3: 337-400.

U.S.EPA. United States Environmental Protection Agency. 1975. Preliminary assessment of suspected carcinogens in drinking water. Office of Toxic Substances, Washington, D.C.

U.S.EPA. United States Environmental Protection Agency. 1985. Preliminary assessment of health risks to garment workers and certain home residents from exposure to formaldehyde. Office of Toxic Substances, Washington, D.C.

Verschueren, K. 1983. Handbook of environmental data on organic chemicals. Van Nostrand Reinhold, New York.

Watanabe, F., Matsunaga, T., Soejina, T. and Iwata, Y. 1954. Study on aldehyde carcinogenicity. Communication I: Experimentally induced rat sarcomas by repeated injection of formalin. Gann 45: 451-452 (cited in Consensus Workshop, 1984).

Watanabe, F. and Sugimoto, S. 1955. Studies on the carcinogenicity of aldehydes. Part II. Seven cases of transplantable sarcomas of rats developed in the area of repeated subcutaneous injections of urotropin (hexamethylenetetramine). Gann 46: 365-367 (cited in Consensus Workshop, 1984).

Weikman, F.F., Lehman, A.T., Pfeiffer, C.C., and Chase, H.F. 1941. A study on the possible effects of prolonged formaldehyde ingestion. J. Pharmacol. Exp. Ther. 72: 46.