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# Comparative Hazard Evaluation, an Approach to Regulation: Formaldehyde in Drinking Water

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## EXECUTIVE SUMMARY

Formaldehyde is an important industrial chemical that is ubiquitous to the human environment. The estimated 7 billion pounds of formaldehyde produced annually in the U.S. are consumed in a great diversity of manufacturing and processing applications resulting in occupational exposure of more than 1 million workers and in the nonoccupational exposure of 11 million consumers.

Exposure to formaldehyde can result in a spectrum of adverse health effects depending on the concentration and route of entry into the body. Mild dermal exposure may result in skin irritation that may develop into allergic contact dermatitis in sensitized individuals. More severe dermal exposures can produce a tanning and hardening of the skin due to coagulation necrosis. Ingestion of formaldehyde in aqueous solution results in inflammation of the mucosal linings of the mouth, throat and gastrointestinal tract; ingestion of 1-2 oz. of a 37% solution generally is fatal. Inhalation exposure to formaldehyde at less than 3 ppm airborne concentrations may produce irritation of the eyes, nose and throat and inflammation of the bronchi and lungs. Exposure to 10-20 ppm may cause difficulty in breathing, and pulmonary edema and death may follow exposure to 50 ppm formaldehyde. Because the threshold for odor detection of formaldehyde is generally about 1 ppm or less, and due to its acute irritant properties, voluntary prolonged exposure to harmful atmospheric concentrations is not likely to occur.

Following absorption into the body, formaldehyde is rapidly oxidized to formic acid by enzymes in the erythrocytes and liver. The formic acid is then further oxidized to $CO_2$ and water (and expired as $CO_2$), eliminated in the urine as an excretable sodium salt, or metabolically incorporated into the one-carbon pool for use in biosynthesis of essential amino acids. Formaldehyde is a normal metabolite present in all mammalian cells, and is not generally considered toxic in small amounts.

While formaldehyde has not conclusively demonstrated a potential to cause adverse reproductive effects, its mutagenic potential has been established in several *in vitro* and *in vivo* studies. Possible mutagenic effects include DNA damage, chromosomal aberrations, unscheduled DNA synthesis and DNA-protein crosslink formation.

The carcinogenic potential of formaldehyde was established in a 2-year rodent bioassay conducted in 1978, in which exposure to airborne formaldehyde at 14.3 ppm produced a near 50% incidence of squamous cell carcinoma in the nasal cavity of rats, and a 1% incidence in rats at an exposure level of 5.6 ppm. Only 2 mice exposed to 14.3 ppm developed squamous cell carcinoma, with no tumors resulting from lower exposure levels.

The demonstration of carcinogenicity of formaldehyde in animals evoked a heightened concern that formaldehyde may present a significant carcinogenic risk to humans exposed to airborne formaldehyde in occupational and residential environments. Subsequent mechanistic investigations of the biological effects of formaldehyde indicated that humans are at less risk of cancer from airborne formaldehyde than rodents, obligatory nasal breathers possessing a greater nasal surface area than humans. Also, because carcinogenicity (and possibly mutagenicity) is apparently limited to cytotoxic levels of exposure (greater than 2-3 ppm in animals) humans are not likely to voluntarily endure prolonged exposure to these irritating concentrations. Furthermore, because the carcinogenic dose response was seen to be nonlinear, exposure levels common to the human experience are likely to involve less carcinogenic risk per ppm than exposure at higher levels.

The finding that formaldehyde resins in plumbing fixtures could result in release of formaldehyde into residential drinking water lines prompted a concern that chronic

ingestion via drinking water may present a carcinogenic risk to humans. No national regulations currently exist governing formaldehyde in drinking water, and only two states, New Jersey and California, have proposed regulatory drinking water limits.

This report examines the health risks from chronic exposure to formaldehyde at the low levels found in residential drinking water. Based on a comprehensive analysis of formaldehyde metabolism and biological mechanisms, and comparison of drinking water exposure levels with formaldehyde levels commonly found in foods, it is concluded that low-level drinking water exposure does not constitute a health hazard. By the same oral route of intake, humans typically ingest about 11 mg daily of formaldehyde in foods, a level of intake almost 300 times greater than that from ingestion of formaldehyde as a drinking water contaminant at a concentration of ~20 μg/L. Metabolic studies indicate that the low levels of formaldehyde currently found in drinking water are readily detoxified via normal enzymatic processes already in place for the normal utilization of endogenous formaldehyde.

Investigation of the biological mechanisms of formaldehyde indicate that formaldehyde responses are distinctly nonlinear, resulting in an apparent threshold of effects from formaldehyde exposure. It was also determined that the primary determinant of formaldehyde toxicity is the concentration and not the cumulative dose. Thus small doses that do not overwhelm metabolic detoxification do not result in cumulative toxicity. Furthermore, only cytotoxic levels of exposure appear to be capable of inducing a carcinogenic response, and the subcytotoxic levels found in drinking water are not likely to potentiate carcinogenesis.

A relative potency approach was also used to evaluate the hazard of ingestion of low levels of formaldehyde in drinking water relative to ingestion of other potentially hazardous substances generally regarded as safe. This analysis suggested that the hazard of formaldehyde in drinking water is roughly equivalent to that of the by-products of chlorination and less than the hazard potential of fluoride in drinking water.

This report offered an approach to regulation based on the available information suggesting that formaldehyde is a normal product of metabolism, possesses an apparent threshold of effects, is characterized by a nonlinear dose response (unlike most other carcinogens) and is ingested daily in milligram amounts. Considering ingestion in foods as a surrogate chronic toxicity study, a permissible level of formaldehyde in drinking water was estimated to be about 0.5 ppm, or 500 μg/L. This approach does not rely on linear extrapolation of the carcinogenic dose response from a chronic inhalation study to estimate low-dose risk from ingestion. Such techniques applied to formaldehyde result in an overestimation of low-dose risk and may place an unnecessary, costly burden on regulated sources. The alternate approach offered here attempts to regulate formaldehyde based on a larger, comprehensive body of knowledge incorporating all levels of data instead of restricting the focus to formaldehyde's carcinogenic status. Thus, a comprehensive evaluation of the relative hazard of formaldehyde in drinking water permits a reasonable level of regulation to be determined.

# 1. INTRODUCTION

Formaldehyde (HCHO) is ubiquitous to the human environment. Humans are potentially exposed to formaldehyde from consumer products, in occupational settings and from the ambient environment. The presence of formaldehyde or formaldehyde derivatives in pressed-wood products such as particleboard and plywood, as well as in urea-formaldehyde foam insulation (UFFI), results in the residential exposure of many persons, with higher atmospheric concentrations found in mobile homes and newly constructed dwellings where pressed-wood products and UFFI are commonly used (Gammage and Hawthorne, 1985). Occupational exposure to formaldehyde is common, therefore, in industries engaged in the manufacturing of mobile homes, pressed-wood products and plywood, and in the garment industry, where formaldehyde-containing resins are utilized extensively (Preuss et al., 1985). Formaldehyde in the ambient environment may derive from the photochemical oxidation of airborne hydrocarbons from vehicle exhausts, incomplete combustion of fossil fuels, and microbial decomposition of methane (Squire and Cameron, 1984).

The finding that formaldehyde is carcinogenic in laboratory animals exposed to formaldehyde vapors, at concentrations in slight excess of levels commonly encountered by many humans, has evoked a heightened concern that formaldehyde may present a significant carcinogenic risk to humans. Unlike previously identified carcinogens, however, formaldehyde is also a product of normal human metabolism and is essential in the biosynthesis of certain amino acids (Squire and Cameron, 1984). Normal endogenous tissue levels of metabolically derived formaldehyde range from about 3-12 ng formaldehyde per g of tissue (Hileman, 1984). The normal presence of endogenous formaldehyde suggests to some researchers that low levels of formaldehyde should not be considered toxic (NAS, 1981, as cited in Squire and Cameron, 1984; Carr and Kolbye, 1985), while others consider it as evidence of a practical threshold for low-level formaldehyde effects (Todhunter, 1985).

In assessing the risk of exposure to chemicals identified as carcinogens on the basis of animal testing, as in the case of formaldehyde (Swenberg et al., 1980), the Environmental Protection Agency (EPA) Carcinogen Assessment Group (CAG) commonly invokes the linearized, multistage model in order to extrapolate an estimate of low-dose risk from an analysis of tumor incidence versus administered dose (Anderson, 1983). This process assumes dose-response linearity and lack of a carcinogenic threshold, i.e., that any exposure to a carcinogen, no matter how small, imparts an increment of risk. The validity of using the linearized, multistage model in quantifying the carcinogenic risk of low-dose exposure to formaldehyde has been questioned (Squire and Cameron, 1984; Carr and Kolbye, 1985; Starr et al., 1985). Among other concerns is that the application of linear extrapolation models to nonlinear dose-response data may result in a considerable overestimation of the low-dose response (Todhunter, 1985). Furthermore, risk assessment based on extrapolation modeling of results from one route of exposure does not necessarily address the risk from alternate routes of exposure.

Does ingestion of low levels of formaldehyde in drinking water, for example, involve a similar degree of carcinogenic risk as inhalation of airborne formaldehyde? This is an important question for occupants of residential dwellings where recent investigations have found low levels of formaldehyde ($\sim$20 ppb) as a drinking water contaminant. Are these individuals at an increased risk of cancer from daily ingestion of their residential drinking water?

This report will attempt to provide an answer to this question based on a comprehensive analysis of the available data regarding health effects of formaldehyde exposure, incorporating information on metabolism and biological mechanisms into a framework of comparative hazard evaluation. Integral to this effort will be a comparison of ingestion of formaldehyde in drinking water with ingestion of naturally occurring formaldehyde in foods and other substances generally regarded as safe. The perspective offered by this approach should provide a rational framework enabling regulatory authorities and other concerned individuals to evaluate objectively the potential hazard of ingesting formaldehyde as a low-level contaminant in drinking water.

In order to provide a background for comparative hazard evaluation, a brief overview will examine the nature of residential exposure to formaldehyde from both air and water sources. A discussion of typical dietary sources of formaldehyde will extend the exposure assessment and provide data for later comparisons. In order to provide a better understanding of the health effects of formaldehyde, an overview of the metabolism and biological effects of formaldehyde, including toxic, teratogenic, mutagenic and carcinogenic effects will precede discussion of the potential carcinogenicity of formaldehyde in humans. Then, the comparative hazard evaluation will be followed by a summary and conclusion.

# 2. EXPOSURES

## 2.1 RESIDENTIAL

Formaldehyde is one of the most important and widely used industrial chemicals in the United States today. Current annual production of formaldehyde by U.S. manufacturers has been estimated at 7 billion pounds, resulting in occupational exposure of an estimated 1.4 million workers and nonoccupational exposure of another 11 million consumers of formaldehyde-containing commercial products (Landrigan, 1989).

Approximately half the formaldehyde produced in the U.S. is used in the manufacturing of urea or phenol resins, and most of these are incorporated into housing materials such as urea-formaldehyde foam insulation (UFFI), particle board, plywood and decorative paneling. Degradation of the urea-formaldehyde structural matrix through moisture-induced reactions results in a chronic release of formaldehyde to the ambient indoor air (Gammage and Hawthorne, 1985). The resultant mean air concentrations of formaldehyde typically reach levels of 0.12 ppm in homes with UFFI, compared to a mean concentration of 0.03 ppm in homes without UFFI (Gupta et al., 1982). Among building materials releasing formaldehyde to indoor air, the major contributors are pressed-wood products and UFFI (Matthews et al., 1985).

The use of formaldehyde-containing resins in plumbing fixtures for residential water delivery systems has also resulted in exposures via the oral pathway, due to release of formaldehyde into drinking water. Supplemental to direct ingestion of formaldehyde in drinking water, occupants may also be exposed via inhalation of formaldehyde in vapors generated by bathing or showering. Infants and children, often especially sensitive to the adverse effects of toxic substances, may also be exposed to formaldehyde through use of vaporizers or humidifiers. The following sections will investigate the potential residential exposures deriving from the presence of formaldehyde in drinking water delivery systems.

### 2.1.1 Drinking Water

One of the primary uses of formaldehyde is in the production of polyacetal resins. These resins are commonly used in the manufacturing of appliances, electronics, machinery parts, plumbing hardware and other consumer products (EPA, 1976).

Recent investigations conducted by the Oak Ridge National Laboratory have determined that the use of polyacetal compression fittings in plastic potable water lines can result in the leaching of formaldehyde into residential water delivery systems (Wilson et al., 1989). Normally, an interior protective coating prevents water from contacting the polyacetal resin. However, normal stress on the supply lines may result in a break or fracturing of the coating, permitting water to contact the polyacetal resin directly. This action results in a continuous liberation of formaldehyde into water via hydrolysis of the resin surfaces. The resultant concentrations of formaldehyde in the water vary with the residence time of the water in the pipes, with normal water usage rates in occupied dwellings maintaining the formaldehyde level at about 20 ppb (20 $\mu$g/L). In unoccupied dwellings, or after a few days of no water usage, formaldehyde levels may approach ~100 ppb (100 $\mu$g/L). Fortunately, studies indicate that a simple purging of the water lines by leaving the tap full open for a minute or so is sufficient to reduce elevated formaldehyde levels to the lower concentrations seen in occupied homes.

Formaldehyde in residential water supply lines presents the obvious potential for oral exposure via direct ingestion of drinking water. However, there is also a potential for exposure via inhalation of formaldehyde vapor generated by showering or bathing. Additionally, use of vaporizers or humidifiers could expose children to airborne formaldehyde, placing an often extra-sensitive population at increased risk of adverse health effects due to formaldehyde. The following section of this report provides a estimate of the induced air concentration of formaldehyde expected to result from release of formaldehyde in residential water supplies to ambient indoor air.

### 2.1.2 Inhalation of Vapor from Potable Water

Under steady-state conditions, the concentration of any indoor pollutant is approximately equal to its source strength divided by the product of the building's air exchange rate and volume. It was assumed that the source strength for HCHO could be partitioned into parts attributable to: (1) release from potable water and (2) all other sources. The concentration of HCHO in air attributable to release of HCHO from water is given by:

$$\frac{C_a}{C_w} = \frac{W \cdot e}{i \cdot V,} \qquad (1)$$

where $C_a$ is the concentration of HCHO in air, $C_w$ is the concentration of HCHO in water, W is the daily household use rate of potable water ($m^3$ $person^{-1}$ $h^{-1}$), e is the transfer efficiency of HCHO from water to air, i is the natural infiltration rate ($h^{-1}$), and V is the house volume ($m^3$ $person^{-1}$).

For a worst case analysis, it was assumed that all HCHO entering a house in potable water was released (i.e., e = 1). Nazaroff et al. (1988) have recently summarized the available data on the distributions of W, i, and V in U.S. households. The data for each parameter are well represented by log-normal distributions. Table 2.1 summarizes the geometric means and standard deviations for the data. The ratio, $C_a/C_w$, is a multiplicative function of lognormally distributed parameters and, therefore, it is lognormally distributed. The geometric mean and standard deviation calculated from the values in Table I are 1.18 x $10^{-4}$ and 2.86, respectively. The highest concentration measured to date for water sampled from over 300 homes is about 100 ppb (in an unoccupied home). Based on the expected distribution of air-to-water ratios, there is very little probability the induced air concentration will be greater than 0.1 ppb.

The odor threshold for HCHO for most people is between 0.05 and 1.00 ppm HCHO in air. Betterton and Hoffmann (1988) have determined the Henry's Law constant to be 2.97 x $10^3$ mole $L^{-1}$ $atm^{-1}$ for dilute aqueous solutions of HCHO at 25°C. Therefore, if the occupant is unable to smell HCHO in drinking water, then the aqueous concentration is likely to be less than 5 to 90 ppm depending on: (1) the individual's odor threshold and (2) how close the water/air/HCHO system comes to thermodynamic equilibrium. It is unlikely that the steady-state air concentrations in homes with such low concentrations in water will exceed 0.5 to 9 ppb.

Another potentially high exposure scenario is use of a humidifier in a small room, such as might be the case of a young child with an upper respiratory infection. Steady-state air concentrations of formaldehyde are proportional to source strength (mole $h^{-1}$) divided by the product of room volume and infiltration. To estimate the impact of this scenario, these assumptions were made:

Table 2.1. Summary of lognormal parameters used in the determination of distribution of $C_a/C_w$

| Variable | Geometric Mean | Geometric SD | Units |
|---|---|---|---|
| Water Use Rate (W) | $7.90 \times 10^{-3}$ | 1.57 | $m^3$ person$^{-1}$ $h^{-1}$ |
| House Volume (V) | $9.87 \times 10^{1}$ | 1.90 | $m^3$ person$^{-1}$ |
| Infiltration (i) | $6.80 \times 10^{-1}$ | 2.01 | $h^{-1}$ |

Room Volume (V): 10' x 10' x 8'(22.65 $m^3$)
Infiltration (i): 1.0 $h^{-1}$
Formaldehyde Release Rate: 100%
Water Use Rate (W): 0.25 gal $h^{-1}$ ($9.46 \times 10^{-4}$ $m^3$ $h^{-1}$)
Formaldehyde Concentration ($C_w$): 100 ppb

and

$$C_a = C_w \cdot W / (i \cdot V).$$

The resulting estimated concentration is much less than 1 ppb.

## 2.2 DIETARY INTAKES

HCHO is a naturally occurring component of many foods in the typical American diet. Rogers (1983) compiled data on the average rates of consumption of foods from various food groups. The U.S. Department of Agriculture (1979) compiled data on beverage consumption. These data are tabulated in Table 2.2. After reviewing the available data, we have estimated the HCHO concentration for each of the same food groups and have estimated the annual HCHO consumption via ingestion of food. Descriptions of estimated HCHO concentrations in each food group are given below.

Meat

Cantoni et al. (1987) reported measurements made earlier in various bovine and porcine meats (Mohler and Denby, 1970) that ranged from .5 mg $kg^{-1}$ for boiled sausage to 52 mg $kg^{-1}$ for ham and bacon. Buckley et al. (1988) measured the HCHO content of fresh muscle tissue of calves fed whey preserved with various levels of formalin. For the control group (i.e., no formalin) the HCHO content was 0.178 mg $kg^{-1}$. Halvarson (1972) measured trace amounts ($\sim$0.01 mg $kg^{-1}$) of HCHO in sausage after storage. The value measured in fresh calf meat was used in this analysis.

Table 2.2. Compilation of annual consumption rate, formaldehyde concentration, and estimated annual consumption of formaldehyde for various food groups

| Item | Food Consumed (kg $y^{-1}$) | HCHO Conc. (mg $kg^{-1}$) | HCHO Consumed (mg $y^{-1}$) | Reference |
|---|---|---|---|---|
| Meat | 68.3 | 0.18 | 12.2 | Buckley et al. (1988) |
| Poultry | 29.1 | 4.00 | 116.3 | Cantoni et al. (1987) |
| Fish | | | | |
| Shell | 1.2 | 0.94 | 1.1 | Radford and Dalsis (1982) |
| Canned | 0.0 | 0.75 | 0.0 | Cantoni et al. (1987) |
| Other | 4.3 | 31.80 | 137.0 | Tsuda et al. (1988) |
| Eggs | 15.1 | 0.70 | 10.6 | Cantoni et al. (1987) |
| Dairy | 135.0 | 0.02 | 2.3 | Buckley et al. (1986) & Cantoni et al. (1987) |
| Animal Fat | | | | |
| Butter | 2.0 | 0.00 | 0.0 | Assumed to be zero |
| Other | 2.9 | 0.00 | 0.0 | Assumed to be zero |
| Vegetable Fat | 22.4 | 0.00 | 0.0 | Assumed to be zero |
| Fruits & Melons | | | | |
| Fresh | 47.9 | 8.13 | 389.2 | IARC Monographs Vol. 29 & Cantoni et al. (1987) |
| Processed | 22.9 | 8.13 | 185.7 | Cantoni et al. (1987) |
| Vegetables | | | | |
| Fresh | 68.4 | 8.17 | 559.0 | Tsuchiya et al. (1975) |
| Canned | 20.7 | 8.17 | 168.9 | Tsuchiya et al. (1975) |
| Frozen | 4.9 | 8.17 | 39.6 | Tsuchiya et al. (1975) |
| Potatoes | 36.0 | 8.17 | 293.8 | Tsuchiya et al. (1975) |
| Legumes | 7.9 | 8.17 | 64.8 | Tsuchiya et al. (1975) |
| Flour & Cereal | 67.8 | 5.60 | 379.7 | Lorenz & Maga (1972) |
| Sugar & sweeteners | 60.7 | 0.75 | 45.6 | Baraniak et al. (1988) |
| Beverages | | | | |
| Coffee | 96.8 | 6.97 | 674.3 | Hayashi et al. (1986) |
| Tea | 44.9 | 6.97 | 313.0 | Assumed to be as coffee |
| Soft Drinks | 61.0 | 8.20 | 500.2 | Lawrence & Iyengar (1983) |
| Juices | 8.8 | 8.13 | 71.2 | Assumed to be as Fruit |
| Beer | 13.9 | 0.60 | 8.3 | Lawrence & Iyengar (1983) |
| Wine | 3.3 | 0.60 | 2.0 | Assumed to be as Beer |
| TOTAL: | | | 3974.8 | |

Poultry — Cantoni et al. (1987) reported measurements made earlier (Mohler and Denby, 1970) that ranged from 2.3 to 5.7 mg $kg^{-1}$. The average of the extremes was used.

Shellfish — Radford and Dalsis (1982) measured HCHO content of fresh shrimp. The mean of four samples collected from different markets was 0.94 mg $kg^{-1}$. This value was used for all shellfish.

Game fish — Cantoni et al. (1987) reported measurements made earlier in fresh water fish (Mohler and Denby, 1970) that ranged from 0.7 to 0.8 mg $kg^{-1}$. The average of the extremes was used for game fish.

Other fish — Tsuda et al. (1988) measured HCHO content in cod after 5 to 8 minutes of boiling and found 31.8 mg $kg^{-1}$. This value was used for other fish.

| | |
|---|---|
| Eggs | Cantoni et al. (1987) reported measurements made earlier (Mohler and Denby, 1970) that ranged from 0.2 to 1.2 mg $kg^{-1}$. The average of the extremes was used. |
| Dairy products | Cantoni et al. (1987) measured HCHO levels in 16 kinds of non-smoked cheeses and three kinds of smoked cheeses. HCHO was absent in seven kinds of cheese, trace amounts were found in seven kinds, and levels ranging from 0 to 18 mg $kg^{-1}$ were found in the others. Buckley et al. (1986) measured HCHO content in milk. Trace amounts below the detection limit (0.017 mg $kg^{-1}$) were found. HCHO content in dairy products was assumed to be equal to the limit of detection reported by Buckley et al. (1986). |
| Fats | Due to its high solubility in water, the HCHO content in fats was assumed to be negligible. |
| Fruits | Tsuchiya et al. (1975) measured the HCHO content of apples using two different measurement techniques. Cantoni et al. (1987) reported measurements made earlier in apples (1.7 to 2.8 mg $kg^{-1}$), pears(6.0 to 8.7 mg $kg^{-1}$), and grapes (2.9 to 3.3 mg $kg^{-1}$) by Mohler and Denby (1970). The six extremes reported by Cantoni et al. (1987) were averaged along with two results from Tsuchiya et al. (1975) and the mean was used for the HCHO content of fruits, fresh, canned, or frozen. |
| Vegetables | Tsuchiya et al. (1975) measured the HCHO content of tomatoes, cabbages, spinach, green onions, carrots, and white radishes using two different measurement techniques. The mean of these results was used for the HCHO content of vegetables. |
| Potatoes and was Legumes | The mean of the vegetable results reported by Tsuchiya et al. (1975) used. |
| Flour & Cereal | Lorenz and Maga (1972) reported 5.6 ppm HCHO in fresh bread. This value was used for all cereal products. |
| Sugar & Sweets | Baraniak et al. (1988) measured HCHO content of maple syrup that had not been contaminated with paraformaldehyde and found 0.75 mg $kg^{-1}$. This value was used for all sweets. |
| Coffee & Tea | Hayashi et al. (1986) measured HCHO content in regular, decaffeinated, and instant coffee. The mean of the three reported values was used for both hot beverages. |
| Soft Drinks | Lawrence and Iyengar (1983) reported the HCHO content of cola drinks to be 8.2 mg $kg^{-1}$. |
| Juices | The HCHO content of fruit juices was assumed to be the same as fruit. |

| | |
|---|---|
| Beer | Lawrence and Iyengar (1983) reported the HCHO content of beer to be 0.6 mg $kg^{-1}$. |
| Wine | The HCHO content of wine was assumed to be the same as beer. |

To develop the estimates of annual HCHO consumption rates for each food group, it was assumed that processing of the food by manufacturers or consumers does not reduce the HCHO content of consumed foods. We believe that cooking (especially boiling in water) will tend to cause rapid evaporation of formaldehyde and lead to lower HCHO concentrations in prepared foods. The reader should note, however, that the highest concentration reported in Table 2.2 is for boiled cod.

# 3. PHARMACOKINETICS

## 3.1 METABOLISM

When formaldehyde is taken up by the body, it is rapidly converted to formic acid (see Fig. 3.1). Dogs injected intravenously with solutions of formaldehyde demonstrated a rapid increase in plasma formic acid with very little detectable formaldehyde (Malorny et al., 1965). The rapidity of conversion of formaldehyde to formic acid was also apparent when either formic acid or sodium formate was injected. The biological half-life of the formic acid thus formed was between 77-90 minutes. In studying methanol poisoning in the monkey, McMartin et al. (1979) observed that intravenously infused formaldehyde had a half-life in the blood of about 1.5 minutes and that formic acid levels promptly increased. In the single reported case of a 41 year old woman who drank 120 ml of commercial formalin (37% w/v formaldehyde, 12.5% w/v methanol), approximately half an hour after ingestion, the blood level of formaldehyde was about 1/50th that of formic acid and continued to fall rapidly, whereas the formic acid levels remained constant for hours (Eells et al., 1981). The formic acid was derived almost totally from formaldehyde, since the blood level of methanol at the time of admission could account for the amount of methanol ingested. Thereafter, the level of methanol fell, presumably due to metabolism first to formaldehyde, then to formic acid. In an attempt to duplicate the results of the case report, the authors gave rats oral doses of formalin equivalent to that ingested by the patient. The results obtained were similar to those observed in the patient, in that equivalent blood levels of formic acid were detected one hour after administration.

When formaldehyde was orally administered to dogs, only formic acid could be detected in the plasma, indicating the rapid metabolism of formaldehyde to formic acid. Human blood *in vitro* was able to quickly oxidize formaldehyde to formic acid via the action of catalase or formaldehyde dehydrogenase (Malorny et al., 1965). The lack of accumulation of formaldehyde in the blood was observed when rats and humans were exposed to air containing formaldehyde. In both rats and humans, blood-formaldehyde concentrations before and after exposure to formaldehyde were similar, i.e., no increase was observed (Heck et al., 1985). A similar study using human subjects showed that the levels of blood formaldehyde measured immediately after exposure were statistically similar to those measured 21 hours later (cited in Heck et al. 1985). When rats were injected with either [$^{14}$C] labeled formaldehyde or formate, the radioactivity in the plasma and packed cells was identical and almost superimposable. This indicated the pharmacokinetics of a single compound which we know to be formate, thus demonstrating the rapid conversion of formaldehyde to formic acid (Heck, 1982; 1983).

The mechanism by which formaldehyde is converted to formic acid is catalyzed by formaldehyde dehydrogenase and glutathione thiol esterases. The first step of this reaction requires nicotinamide adenine dinucleotide (NAD) and reduced glutathione to yield S-formylglutathione, which is subsequently converted to formic acid.

Glutathione thiol esters can be hydrolyzed by a number of enzymes, some which are rather specific in their substrate requirement. In the human liver, Uotila (1973a,b) purified the enzyme glyoxalase II, which acts upon a number of S-2-hydroxyacylglutathione esters, including
S-formylglutathione. A specific enzyme for S-formylglutathione was later purified from human liver by Uotila and Koivulsalo (1974b). The enzyme is specific for S-formylglutathione, demonstrating less than 1% activity toward other substrates tested; as with formaldehyde dehydrogenase, it is mainly a cytosolic enzyme.

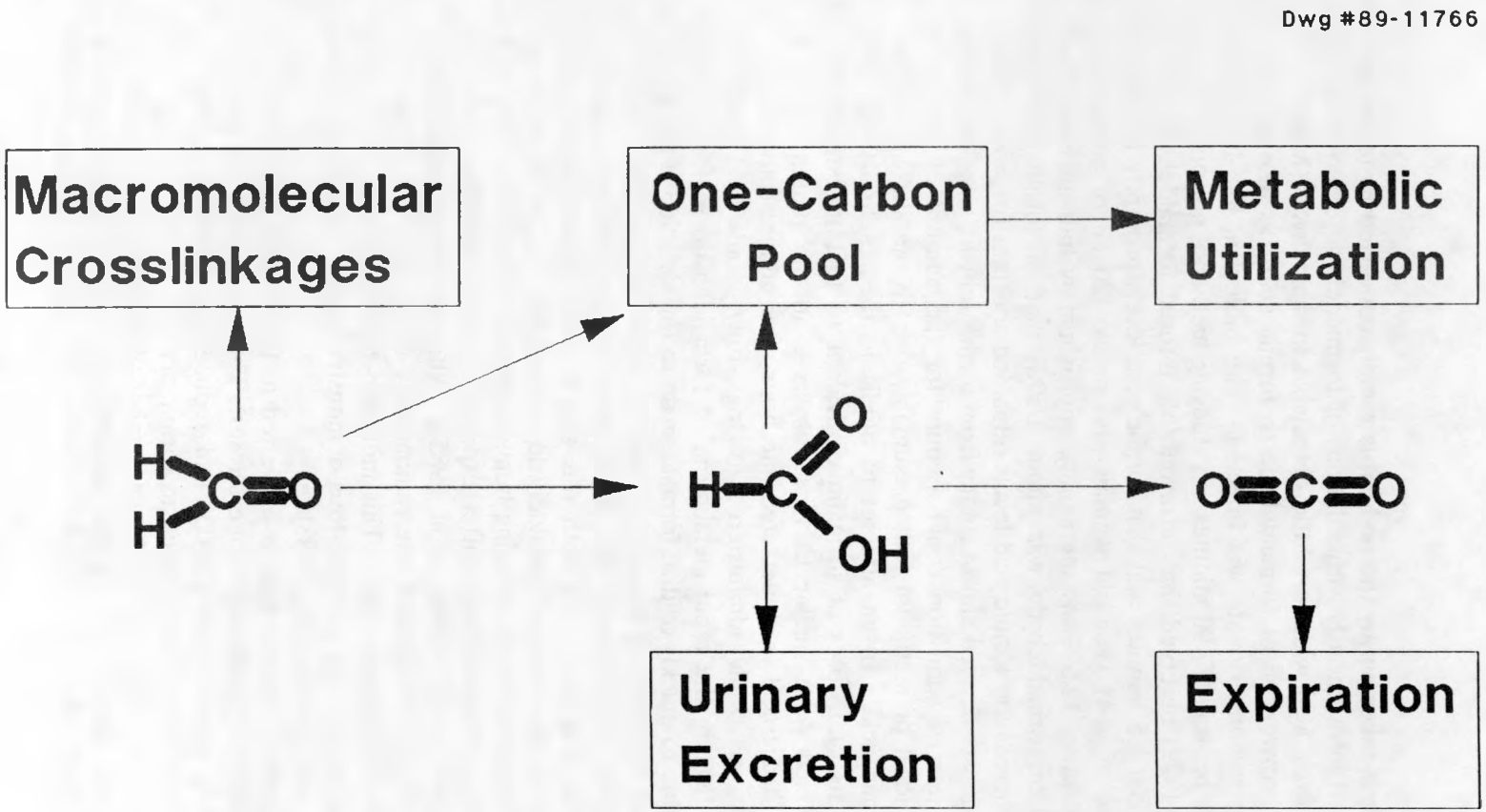


Fig. 3.1 Metabolism of formaldehyde

Rat liver mitochondria contain two NAD-dependent aldehyde dehydrogenases, one with a high, and the other a low $K_m$ for aldehydes (Cinti et al., 1976; Kiovula and Kiovusalo, 1975b; Siew et al., 1976). Only the low $K_m$ enzyme has appreciable activity towards formaldehyde. The high $K_m$ enzyme has properties similar to the microsomal enzyme and, as with the cytosolic enzyme, little or no activity toward formaldehyde (Koivula and Koivusalo, 1975a; 1975b).

Formaldehyde is metabolized via two major pathways, one involving cytoplasmic glutathione-dependent formaldehyde dehydrogenase and the other the low $K_m$ mitochondrial aldehyde dehydrogenase. Dicker and Cederbaum (1984) studied the relative contribution of each enzyme to the overall metabolism of formaldehyde by rat liver, concluding that there was an equal contribution from both. Inhibition studies of formaldehyde metabolism by rat liver led Dicker and Cederbaum (1986) to suggest that under conditions of low formaldehyde concentrations, the cytosolic formaldehyde dehydrogenase predominates, whereas at higher concentrations, the mitochondrial enzyme becomes more important. It has also been estimated that in order for formaldehyde dehydrogenase to become impaired, about 90% of glutathione has to be depleted. At airborne concentrations above 4 ppm, detoxification in the rat via formaldehyde dehydrogenase becomes saturated, resulting in a nonlinear increase in the covalent binding of formaldehyde to DNA in nasal tissue (Swenberg, 1989).

The formate formed by the action of the enzymes discussed above is further oxidized to $CO_2$. This latter step is rate-limiting in the oxidation of formaldehyde to $CO_2$, and requires the participation of two enzymes. The first enzyme, formyltetrahydrofolate synthetase, catalyzes the production of formyltetrahydrofolate from formate and tetrahydrofolate. This intermediate substrate is further acted upon by the second enzyme, tetrahydrofolate dehydrogenase, to yield $CO_2$ (Krebs et al., 1976; Waydhas et al., 1978). A second less important pathway for the oxidation of formate to $CO_2$ is catalyzed by the enzyme catalase, found in rat liver peroxisomes (Oshino et al., 1973; Waydhas et al., 1978).

In summary, upon absorption into the body, exogenous formaldehyde is rapidly converted to formic acid by enzymes in the erythrocytes and liver, with a biological half-life of about 1.5 minutes. The formic acid product is itself then acted upon in any of three ways: 1) it is further oxidized to $CO_2$ (and $H_2O$) and exhaled, 2) it is converted to a soluble sodium salt and excreted in the urine, or 3) it is metabolically incorporated into the one-carbon pool and utilized in the biosynthesis of essential amino acids. The half-life of formic acid participating in either of these pathways is about 80-90 minutes.

## 3.2 SOURCES OF FORMALDEHYDE

The main source of exogenous formaldehyde is derived from the intake of food and exposure to certain occupational environments, discussed in detail elsewhere in this report. Here we will briefly consider some of the chemical precursors of endogeneous formaldehyde.

Formaldehyde is formed when certain methylated xenobiotics (e.g., dimethylnitrosamine, methanol, dihalomethanes) are metabolized by the mixed-function oxidase system of the endoplasmic reticulum. Engelse et al. (1975) studied the metabolism of dimethylnitrosamine in respiratory tissue of the mouse, rat, hamster and human. Although these authors did not measure formaldehyde directly, they measured carbon dioxide which is a direct product of the formaldehyde formed (Montesano and Barlisch, 1976). On the other hand, Jensen et al. (1981), using hamster liver microsomes, demonstrated that formaldehyde formed from dimethylnitrosamine methylates exogenous DNA in a coupled reaction. The distribution of dimethylnitrosamine in the whole body

was studied by Johansson and Tjälve (1978), using the mouse as a model. They inferred from their results that dimethylnitrosamine methylated cellular components via two mechanisms, (a) the breakdown of dimethylnitrosamine, and (b) through the formation of formaldehyde from the one-carbon pool. Several investigations showed that an enzyme fraction from rat liver could metabolize dihalomethanes to yield formaldehyde and the inorganic halide (Heppel and Potterfield, 1948; Ahmed and Anders, 1976; 1978). However, in contrast to the metabolism of dimethylnitrosamine, the mixed-function oxidase system of rat liver does not metabolize dihalomethanes to formaldehyde, but rather to carbon monoxide (Kubic and Anders, 1975). In the intact rat, the production of carbon monoxide was also evident when the animals were injected with halomethanes (Kubic et al., 1974). Dahl and Hadley (1983) studied the metabolism of a number of compounds found in nasal decongestants, solvents, and air pollutants with preparations of rat nasal microsomes. They found that formaldehyde was formed by the action of cytochrome P-450-dependent monooxygenases on these substrates which contain at least one of the functional groups N-methyl, O-methyl or S-methyl. The metabolism of these types of compounds is similar to that of dimethylnitrosamine, which contains an N-methyl-type linkage.

By far, the most common source of formaldehyde in the body results from the catabolism of carbon compounds. The formaldehyde thus formed is reused to synthesize other hydrocarbon molecules. This process, referred to as one-carbon metabolism (see Fig. 3.2), has been extensively reviewed by Huennekens and Osborn (1959). The transfer of one-carbon groups is required in the synthesis of nucleic acid purines, thymine, serine, methionine, choline and in the interconversion between serine and glycine (Huennekeus and Osborn, 1959, and references therein). It is clear from these investigations that free formaldehyde *in vivo* exists in equilibrium with its activated forms, and is utilized only in these activated forms.

Total formaldehyde measured in rat tissues, including liver, lung, kidney, testes, brain, nasal mucosa and plasma, ranged from a concentration of 0.05 to 0.5 μmole/g (1.5-15 μg/g) wet weight (Heck, 1982). The amount of free formaldehyde cannot be measured directly in biological tissue but can be calculated from the reaction of formaldehyde and glutathione catalyzed by formaldehyde dehydrogenase. By this method, Heck (1982) estimated free formaldehyde in rat tissues to be 1-2% of the total formaldehyde measured. Total formaldehyde concentration in rat and human blood have been measured at 2.24 and 2.61 μg/g blood, respectively (Heck et al., 1985), and monkey blood was found to have 2.04 μg/ml formaldehyde. Human blood content is about 73 ml of blood/kg body weight, and the specific gravity of whole blood is 1.06 (FASEB, 1961). Therefore, in a 70-kg man, the total amount of endogenous formaldehyde circulating in the blood would be approximately 14 mg. The liver weight in an average 70-kg man is 1850 g (NAS, 1956) and the total formaldehyde in this organ would range from 2.8 to 28 mg. In the blood and liver, formaldehyde is rapidly metabolized to formate with a half-life of 1.5 mins (McMartin et al., 1979), while the formate product can be metabolized to $CO_2$ in the liver at a maximum rate of 0.4 μmol/min/g wet weight liver (Waydhas et al., 1978). In the whole liver, this capacity translates to about 22 mg of formaldehyde converted to $CO_2$ in a minute.

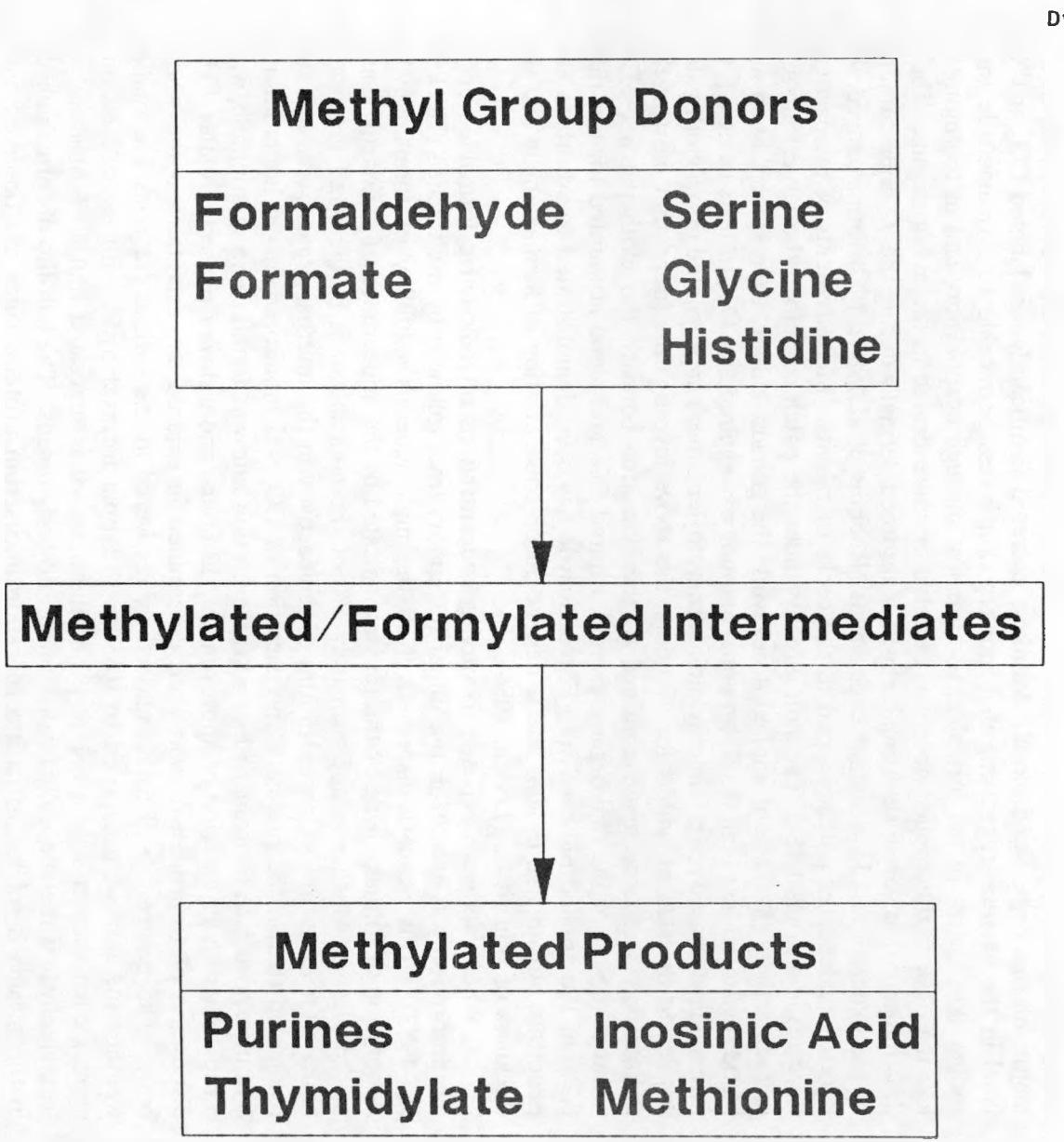


Fig. 3.2 The flow of carbon atoms through the one-carbon pool

## 3.3 ABSORPTION, DISTRIBUTION AND EXCRETION OF EXOGENOUS FORMALDEHYDE

There are three major routes for the uptake of exogenous formaldehyde by humans, i.e., through ingestion, respiration and dermal contact. Jeffcoat et al. (1983) investigated the disposition of formaldehyde after painting an area of dorsal skin of rats, guinea pigs and monkeys with radioactive formaldehyde. The results showed that both rodents were similar in their disposition of formaldehyde in that they excreted about 3% of the total applied dose as $CO_2$ and about 7% in the urine and feces. There was very little radioactivity in the major internal organs and blood. Monkeys excreted significantly less labeled $CO_2$ or [$^{14}$C] label in the excreta, suggesting that monkey skin is less permeable to formaldehyde than rodent skin. Most of the formaldehyde was lost through evaporation, and in the monkey, less than 1% of the applied dose was excreted or concentrated in the major organs. These data indicate that very little formaldehyde is absorbed dermally during the 72 hour duration of the experiment. In a similar experiment (Robbins et al.,1984), [$^{14}$C] formaldehyde was injected under latex patches taped to the backs of rabbits. Measurements of radioactivity were made 4 hours later. The skin directly under the patch contained the largest amount of radioactivity (57-72% of applied dose) while the gonads, kidney, liver, spleen, brain and blood registered less than 0.3%; an equal amount was expired as $CO_2$. In tests using a [$^{14}$C] formaldehyde-based resin (dimethyloldihydroxyethyleneunea) impregnated into a cloth patch applied to the skin of rabbits for 48 hours, the above investigators found that most of the radioactivity was once again confined to the skin area beneath the cloth patch (<3%) whereas the major internal organs, excreta, expired $CO_2$ and blood accounted for less than 0.2% of the applied radioactivity. Formaldehyde has been demonstrated to adsorb to and penetrate human skin *in vitro* and is dependent on concentration of formaldehyde and the thickness of skin tissue (Loden, 1986).

When rats were exposed to varying concentrations of radioactive formaldehyde in air, absorption was greater in the upper respiratory tract followed by the trachea (Heck et al., 1983). This result is expected given the high aqueous solubility of formaldehyde. Absorption of formaldehyde by the rat was indicated by the appearance of radioactive label in the plasma, which was approximately 4% of the concentration in the nasal mucosa 6 hours after exposure . Concentrations of radioactivity in the internal organs were low and resembled that in the plasma. The excretion of $CO_2$ was monitored for 70 hours after a 6 hour exposure to formaldehyde, and the excretion rate was found to be multiphasic, with a rapid phase over a period of approximately 12 hours, and a slower phase thereafter. The disposition of formaldehyde was then determined in expired air, excreta, and the whole body. The percentage of total radioactivity recovered in the various fractions was similar whether the rats were exposed to 0.63 or 13.1 ppm formaldehyde, with expired air and carcass each accounting for about 4% of the dose. It is suggested that 40% of absorbed formaldehyde is metabolically incorporated into body tissues. The half-life of formaldehyde in the plasma is related to its incorporation into serum proteins since the observed half-life of 55 hours compares well with that of serum proteins (Esumi et al., 1979). Similarly, formaldehyde incorporation into erythrocytes is indicated with a turnover time of several weeks. The deposition of airborne formaldehyde (15 ppm) in the nasal mucosa is rapid during the first 30 minutes of exposure and then decreases. However at a lower formaldehyde concentration (2 ppm), the initial rate is much faster. This observation can be explained by the decrease in the respiratory minute volume following exposure at the higher concentration. After 6 hours of exposure, the concentration of formaldehyde in the nasal mucosa is proportional to the airborne concentration up to about 15 ppm (Heck, 1982).

The major route for the labeling of nucleic acids in tissues after rats have been exposed to airborne radioactive formaldehyde is through metabolic incorporation, while labeling of protein in the respiratory mucosa is due to covalent binding (Casanova-Schmitz et al., 1984; Casanova and Heck, 1987). Rats exposed to formaldehyde via inhalation did not show increased blood levels of formaldehyde measured immediately after exposure (Heck et al., 1985). Inhaled formaldehyde is therefore not expected to react with nucleophilic compounds at sites distant from the nasal mucosa. It is not unexpected that formaldehyde cross-links with cellular macromolecules occur only in the nasal mucosa and not in the bone marrow (Casanova and Heck, 1987).

The fate of ingested formaldehyde in rats and mice was studied by Galli et al. (1983) who fed the animals cheese made from milk spiked with [$^{14}$C] formaldehyde. Both rats and mice excreted (urine and feces) 63-67% and exhaled as $CO_2$, 24-28% of the radioactivity. The half-lives of the elimination phase are 27.8 and 26.4 hours for mice and rats, respectively. The authors concluded that [$^{14}$C] activity does not accumulate in any of the tissues of either species since after 8 days no radioactivity could be detected. It should be noted that formaldehyde in milk processed to make cheese is linked to milk proteins and lipids, and probably does not undergo the same type of metabolism in the body as inhaled or injected formaldehyde. It is suspected that the radioactivity in the blood is in the form of methylated amino acids.

## 3.4 CHEMICAL REACTIVITY

Formaldehyde is a gas at room temperature but reacts readily with water to give methylene glycol. In more concentrated solutions, polymerization of formaldehyde molecules occurs (NRC, 1981). In the laboratory, formaldehyde can be made to undergo many types of chemical reactions, but only interactions with biomolecules will be discussed here.

Formaldehyde can react with proteins, nucleic acids, alcohols and hydrochloric acid (Ulsamer et al., 1984). The latter reaction yields the product bis(chloromethyl)ether, which has found to be carcinogenic in both mice and rats (DHEW, 1968-1969). However, the reaction is not a problem in aqueous solutions due to rapid hydrolysis of the ether; the small amounts of bis(chloromethyl)ether possibly formed in aqueous solutions are below the limit of detection (Kitchens et al., 1976). Perhaps the most important interaction of formaldehyde with biomolecules is the reaction with nucleic acids and proteins. The functional groups involved would be amines, hydroxyls and sulfhydryls, but the most likely reaction to occur with biological molecules would probably involve the amino groups. The possibility exists for the formation of many types of derivatives arising from the reactions with formaldehyde of Schiff bases, mono and dimethylol, and methylene compounds (Feldman, 1973; Auerbach et al., 1977). Thus the purine and pyrimidine bases of nucleic acids, DNA and RNA are methylated, with the possible formation of methylene bridges between aminopurines, e.g., adenine and guanine bases, to give rise to methylene bis-compounds.

Under physiological conditions, amino groups from proteins can react with formaldehyde to give the methylol derivative; higher concentrations of formaldehyde will give rise to the dimethylol derivative. A slower secondary reaction involving the monomethylol derivative results in stable condensation methylene products. Methylene cross-links are also likely to occur between the protein monomethylol derivative and the amino groups of amino acids or nucleic acids.

Cross-linkages between formaldehyde and nucleic acids and proteins in chromosomes can also occur; special attention has been paid to the histones. Even under mild conditions (24h., 0°C, pH 7.8) the nucleohistones are completely linked to DNA when chromatin from pea buds is treated with formaldehyde (Brutlag et al., 1969). Yet no cross-linking of DNA strands was detected under comparable conditions (Freifelder and Davison, 1963). Later work confirmed the occurrence of cross-linkages between DNA and amino acids or histones when treated with formaldehyde (Siomin et al., 1973).

Formaldehyde can react with alcohols to yield acetal, although the importance of this reaction in the body is not known. However, reaction with sulfhydryl groups is well documented based on evidence of adduct formation with cysteine and glutathione.

Reactive oxygenated compounds such as peroxides and free radicals have been implicated in certain disease processes. These highly reactive oxygenated species can be formed by radiation or chemicals. In the presence of oxidizing molecules, formaldehyde can form reactive hydroxyperoxides and free radicals, and thus present a biological hazard (Auerbach et al., 1977).

# 4. STUDIES OF BIOLOGICAL EFFECTS OF FORMALDEHYDE EXPOSURE

The biological effects of exposure to formaldehyde have been extensively investigated in laboratory animals and humans. This section presents an overview of these effects focusing on: 1) acute and chronic toxicity in animals and humans following oral, inhalation and dermal exposure to formaldehyde; 2) reproductive and/or teratogenic effects of formaldehyde in animals and humans; 3) mutagenicity based on in vitro and in vivo tests; 4) evidence of carcinogenicity in animals; 5) implications of such evidence for assessment of human carcinogenic risk, and 6) epidemiologic evidence of carcinogenicity in humans.

## 4.1 TOXICITY

### 4.1.1 Experimental Systems

#### 4.1.1.1 Acute

The acute effects of formaldehyde administration to animals vary as a function of species, concentration and route of exposure. According to Ulsamer et al. (1984), oral exposures are slightly less toxic than intravenous and subcutaneous injection, possibly as a result of the reaction of formaldehyde with intestinal chyme resulting in less formaldehyde available for absorption. Acute oral exposure have been employed in lethality studies to determine the $LD_{50}$ concentration (lethal dose to half the exposed population) among several species. Based on administration of formalin (~37% aqueous formaldehyde), the rat oral $LD_{50}$ is 800 mg/kg, compared to the guinea pig oral $LD_{50}$ of 260 mg/kg (Smyth and Seaton, 1941), illustrating the species-dependent nature of formaldehyde toxicity.

In an analysis of the acute toxicity of formaldehyde based on various findings, Goode (1985) regards the rat oral $LD_{50}$ of 800 mg/kg as indicative that formaldehyde is "slightly toxic" to rats. A dermal $LD_{50}$ of 270 mg/kg (in rabbits) is considered to indicate moderate toxicity. Moderate toxicity is also indicated by a 4-hour inhalation $LC_{50}$ value (lethal concentration to half the exposed animals) of 482 ppm in rats. Results of eye irritation testing in rabbits indicate that formaldehyde (formalin) is a severe eye irritant, with a score of 8 on a scale of 10. Skin sensitization studies were performed using guinea pigs by administration of a challenge dose one week following a two-week initial exposure period. Results of sensitization studies indicate that formaldehyde "is a skin sensitizer, but not via the airborne route" (Goode, 1985).

#### 4.1.1.2 Chronic (including subchronic)

Subchronic tests usually employ an exposure duration of about 30-90 days and provide a clinical and pathological profile of adverse effects. Subchronic tests also permit selection of "no-effect" levels and provide guidance for defining optional levels for subsequent chronic toxicity testing (Goode, 1985).

A subchronic oral toxicity study of formaldehyde in rats was conducted by Til et al. (1988). These investigators exposed groups of 10 male and 10 female Wistar rats to formaldehyde in drinking water at dose levels of 5, 25 and 125 mg/kg body weight/day (equivalent to drinking water concentrations of 35.7, 178.6 and 892.9 ppm formaldehyde at normal rat intake levels of 0.049 L/day) for 4 weeks. Animals were observed daily; body weights were recorded weekly. At the end of 4 weeks, urinalysis, hematology and clinical chemistry evaluations were performed. Histopathological evaluation of tissue samples from

the liver, kidney, tongue, pharynx, esophagus, stomach and nose were conducted following sacrifice early in the fifth week. In the high-dose group, males demonstrated decreased total protein and albumin levels in the blood plasma, and females demonstrated a slight increase in the relative weight of the kidneys. Other effects noted in the high-dose group rats included a thickening of the limiting ridge of the forestomach, hyperkeratosis of the forestomach, and slight focal atrophic gastritis. One high-dose female also demonstrated moderate papillomatous hyperplasia of the stomach. No histopathological changes were observed in the stomachs of the lower dose group animals. No morphological changes related to treatment were observed in the kidneys or livers of rats at any dose, even though the decreased plasma protein and albumin observed in high-dose males suggested the possibility of decreased albumin synthesis in the liver. It was concluded on the basis of these results that 25 mg/kg body weight/day (178.6 ppm formaldehyde at a normal rat intake of 0.049 L/day) represented a no-observed-adverse-effect level in rats exposed to formaldehyde in drinking water.

In contrast to the experiment of Til et al. (1988), dogs and rats exposed orally to formaldehyde for 13 weeks revealed no stomach effects (Johannsen et al., 1986). In this study, groups of 4 male and 4 female pure-bred beagle dogs were fed formaldehyde in the diet at concentrations to approximate 0, 50, 75, or 100 mg/kg body weight/day for 90 days. (The equivalent dosage in drinking water would be 0, 28.7, 43.0 and 57.4 ppm formaldehyde at normal dog intake levels of 0.61 L/day.) Groups of 15 male and 15 female Sprague-Dawley rats were similarly given formaldehyde in their drinking water at concentrations approximating intake levels of 0, 50, 100 or 150 mg/kg body weight/day (equivalent to drinking water concentrations of 0, 357.1, 714.3 and 1071.1 ppm at normal intake levels of 0.049 L/day) for 90 days. Body weights and food and water consumption in all animals were monitored at intervals throughout the study. Complete gross necropsy of all animals followed terminal sacrifice. Significant reductions in weight gain were observed in both genders of dogs in the 100 mg/kg body weight/day group, in both genders of rats in the 150 mg/kg weight/day group and in male rats in the 100 mg/kg body weight/day group. These depressions in body weight gain were considered to be a manifestation of the systemic toxicity of orally ingested formaldehyde (Johannsen et al., 1986). Other results from this study indicate no differences in absolute or relative organ weights, urinalysis results or hematological parameters among exposed animals and their controls. No pathological tissue changes attributable to formaldehyde exposure were observed in this study; the gastric mucosa appeared normal in both rats and dogs, with no evidence of irritation (in contrast to the study of Til et al., 1988, discussed previously). As interpreted by the authors, the findings of the present study indicate that oral intake of relatively large amounts of formaldehyde is well tolerated, and that formaldehyde possesses a low order of toxicity following repeated oral exposure (Johannsen et al., 1986).

Subchronic inhalation studies have also been performed. As reported by Goode (1985), rats demonstrated no adverse effects when exposed to 1.6 ppm formaldehyde, 22 hours/day for 90 days, or 4 ppm for 6 hours/day, 5 days/week for 13 weeks. Exposure of rats to 3.8 ppm, 22 hours/day for 90 days resulted in lung inflammation. Rats exposed to 39 ppm, 6 hours/day, 5 days/week for 2 weeks demonstrated nasal ulceration. Exposure of mice to 82 ppm, 1 hours/day, 3 days/week for 35 weeks resulted in squamous cell metaplasia. Exposure to 161 ppm, 1 hour/day, 3 days/week for 11 weeks resulted in mortality. Thus, subchronic inhalation of formaldehyde results primarily in respiratory effects of increasing severity with increasing concentration, and in fatality at high concentrations.

A 26-week inhalation toxicity study was performed in multiple species to investigate formaldehyde effects under conditions approximating an environmental exposure of the general public (Rusch et al., 1983). In this study, groups of 6 male cynomologus monkeys, 20 Fischer 344 rats of each gender, and 10 Syrian Golden hamsters of each gender were exposed to formaldehyde at target concentrations of 0, 0.2, 1.0 and 3.0 ppm for 22 hours/day, 7 days/week for 26 weeks. Actual concentrations were later determined to be 0, 0.19, 0.98, and 2.95 ppm. Hamsters demonstrated no significant effects at any exposure level. Hoarseness, congestion and nasal discharge were increased in all high-dose group monkeys and were considered related to formaldehyde exposure. Body weights of monkeys and hamsters were unaffected by formaldehyde exposure. However, both genders of high-dose rats demonstrated significant reductions in body weight (considered to be exposure-related) beginning from week 2 and continuing throughout the study. The only effect on organ weights noted was in the livers of high-dose group rats, in which depressions of 26% in males and 12% in females were apparent. Alterations in liver weight were not substantiated by remarkable histopathological findings.

In this study, significant effects were noted in the nasal turbinates of rats and monkeys. Microscopic examination of the central portion of the turbinate revealed an increase in the incidence of squamous metaplasia and basal cell hyperplasia in high-dose rats (23/37 and 25/37 vs 3/39 and 4/39 in controls, respectively). The incidence of these lesions in rats was not increased at lower exposure levels. In monkeys, all animals (6/6) in the high-dose group, and none in the control group, demonstrated squamous metaplasia and hyperplasia. In this study, the demonstration of squamous metaplasia at 3 ppm, but not at 1 ppm, was suggestive of a threshold (Clary, 1985).

### 4.1.2 Humans

#### 4.1.2.1 Acute

Ingestion of formalin (a 37% aqueous solution of formaldehyde) results in immediate inflammation of the linings of the mouth, throat, and gastrointestinal tract (Wartew, 1983), and eventual ulceration and coagulation necrosis of the mucous lining of the gastrointestinal tract (Gaál, 1931, as cited in Kitchens et al., 1976). The eventual outcome is kidney damage and circulatory collapse leading to death (Kitchens et al., 1976). Death from ingestion of as little as 1 oz of formalin (within 3 hours) and recovery from ingestion of up to 4 oz has been reported; the fatal dose in humans is generally considered to be 1-2 oz of formalin (Kitchens et al., 1976). Expressed in units of ppm, this intake would be approximately equivalent to ingestion of 500-1000 liters of water containing 20 ppm formaldehyde. Furthermore, as discussed in a later section, formaldehyde toxicity is not cumulative, thus, in appproximating a fatal dose, this amount would need to be drank nearly at once. Other effects associated with formalin ingestion are pneumonia, hemorrhagic nephritis and abortion (Newell, 1983).

The ingestion of formaldehyde, generally as poisoning or attempted suicide, (first reported in 1899), has resulted in death from intake of as little as "a few drops" to as much as 120 ml of concentrated formaldehyde solution. Autopsy of fatal cases has revealed effects in the esophagus and stomach ranging from a simple hardening of tissue to extreme corrosion, frequently coincident with marked congestion, edema and hemorrhage (Kline, 1925, as cited in Kitchens et al., 1976).

The primary response to airborne formaldehyde is sensory irritation of the eyes, nose and throat. Irritation has been reported from exposure to as little as 0.25 ppm in chamber studies and 1 ppm or higher under normal conditions (Hileman, 1984). Effects are

generally dose-related, although development of tolerance and normal individual variation in sensitivity to formaldehyde tend to obscure definition of the dose response. The threshold of formaldehyde odor detection has been estimated to be 1 ppm or less for most individuals (Wartew, 1983). Anderson and Mølhave (1983) report that the lowest threshold of formaldehyde odor detection for a cross-section of the population is about 0.05 $mg/m^3$ (0.041 ppm), and about half the population can detect formaldehyde at about 0.21 $mg/m^3$ (0.17 ppm). No acute effects have been observed to result from exposure to formaldehyde at 0.030 ppm (Scheuplein, 1985). Mucus flow-rate reduction of 10-50% has been reported in humans exposed to formaldehyde at 0.38 to 1.63 ppm for up to 5 hours; no impairment of mucociliary function was observed (Swenberg et al., 1983a). Most persons report eye, nose and throat irritation at formaldehyde levels of about 2-3 ppm (Wartew, 1983), although symptoms of eye irritation at 0.05 ppm and throat irritation at 0.1 ppm have been reported (Squire and Cameron, 1984). At concentrations less than 1 ppm, irritation is mild and adaptation occurs in minutes (Gamble, 1983). Above 3 ppm irritation increases; exposures to 4-5 ppm for 30 minutes evoke lachrymation and discomfort (IARC, 1982). At 10-20 ppm, difficulty in breathing accompanies increasingly severe symptoms. Exposure at 50 ppm and above may cause severe injury to the respiratory tract such as pneumonitis and pulmonary edema, and death (IARC, 1982; Wartew 1983).

In a controlled study of human exposure to formaldehyde, parameters measured were mucus flow rate, airway resistance, odor threshold, performance and discomfort (Anderson and Mølhave, 1983). Exposures were 0.3, 0.5, 1.0 and 2.0 mg formaldehyde/$m^3$ air (equivalent to 0.24, 0.41, 0.82 and 1.63 ppm formaldehyde), for up to 5 hours. Among effects noted was a reduction in mucus flow rate, primarily in the anterior two-thirds of the nose, with further reductions not increasing above 0.41 ppm. No significant airway resistance was demonstrated at any concentration tested. At exposures to 1.63 ppm, an increased odor threshold for the detection of ethyl valerate was observed; no threshold shifts occurred at lower concentrations. Exposure to $\geq$0.82 ppm resulted in discomfort (characterized as conjunctival irritation and dryness of the nose and throat) within the first hour, with evidence of tolerance development after 3 hours exposure. No discomfort was reported with exposures at 0.24 ppm and 0.41 ppm during the first 2 hours of exposure. Performance (measured as speed and accuracy in addition, multiplication and transfer of numbers to punch cards) was not affected at any exposure.

In a study of 33 subjects exposed to formaldehyde at 0.03-3.2 ppm for a total of 35 minutes, and 48 others exposed to 0.03-4.0 ppm for 1.5 minutes, responses of eye, nose and throat irritation, increased lachrymation and odor detection were, in general, linearly related to exposure concentration over the range tested (Weber-Tschopp, et al., 1977, as cited in Newell, 1983). A different study by Schuck et al. (1966) examined eye irritation in 12 subjects exposed to 0.01 to 1.0 ppm formaldehyde for 5 minutes. The irritation response was linear above 0.3 ppm (Newell, 1983).

Formaldehyde is a primary irritant to the skin, eyes and mucous membranes, and is ranked among the 10 most prominent skin contact sensitizers (Jass, 1985). Acute effects from topical exposure include conjunctivitis, corneal burns, urticaria and dermatitis (Plunkett, 1976). Dermal exposures can produce either an acute inflammatory reaction or acute contact allergic dermatitis characterized by edema, erythema, papules, vesiculation and oozing (Gupta et al., 1982). In occupational groups, dermatitis resulting from formaldehyde exposure is a well-recognized problem. The rate of skin sensitization in occupational groups has been estimated at 4-6% (Hileman, 1984). As reviewed by Kitchens et al. (1976), effects from dermal exposure to formaldehyde vary as a function of concentration. Repeated mild exposures may result in allergic contact dermatitis in sensitized persons; more severe exposures may result in a tanning and hardening of the skin due to coagulation.

Most cases of dermatitis are caused by contact with aqueous formaldehyde solutions or fabrics containing formaldehyde, although exposure to formaldehyde vapors may also result in dermatitis.

Eye contact with aqueous solutions of formaldehyde produces concentration-related effects. Transient ocular effects have been reported to result from accidental splashing with a 4% solution, but permanent corneal damage has resulted from eye contact with formalin (~37% aqueous solution) (Wartew, 1983).

#### 4.1.2.2 Chronic

Chronic oral exposure to formaldehyde occurs from the daily ingestion of low levels of formaldehyde in foods (see Section 2.2). Formaldehyde in foods may be naturally occurring or the result of contamination (Kitchens et al., 1976). It has been reported that chronic ingestion of 22-200 mg/day for 13 consecutive weeks has not resulted in toxic effects in humans (Zurlo, 1971, as cited in Kitchens et al., 1976), but no other details were reported.

Chronic inhalation exposure of humans to formaldehyde vapors is common in both occupational and residential environments. The use of urea-formaldehyde, phenol-formaldehyde or melamine-formaldehyde resins by workers engaged in the manufacture of plywood or particleboard may result in exposure to as much as 10 ppm formaldehyde vapor (Newell, 1983). Most industrial and environmental exposures are generally 3 ppm or less (Gamble, 1983). Other occupational environments where employees are exposed to formaldehyde include hospitals, the rubber industry, and in the manufacture of nitrogenous fertilizers, disinfectants, preservatives, deodorizers, paper and medicines (Anderson and Mølhave, 1983; Maibach, 1983). Certain of these industries have been evaluated in epidemiologic investigations of formaldehyde carcinogenicity (see Section 4.4.3 of this report).

The potential for non-occupational exposure to formaldehyde is great because of its widespread use in many types of consumer products. Potential sources, according to Wartew (1983), include "adhesives, shampoo, curtains, carpeting, urea-formaldehyde foam insulation, motor-car exhaust fumes, tobacco smoke and plywood." The principle source of formaldehyde exposure for smokers is tobacco smoke (~40 $mg/m^3$); for non-smokers, the home environment may provide exposures to as much as 1.16 $mg/m^3$ from off-gassing from modern building and insulation materials (Wartew, 1983).

Despite the great potential for human exposure to formaldehyde, no controlled human inhalation studies have been reported which employ exposures exceeding a 5-hour duration. Nevertheless, reports from industry generally provide an indication of the types of health effects associated with chronic inhalation and/or dermal exposure to formaldehyde. Respiratory effects reported include occupational asthma (accompanying formalin exposure) and chronic airflow obstruction, although evidence supporting the latter is inconclusive (Gamble, 1983). Chronic, low-level dermal exposure to formaldehyde has been reported to result in allergic contact dermatitis (Wartew, 1983).

## 4.2 REPRODUCTIVE EFFECTS/ TERATOGENICITY

### 4.2.1 Experimental Systems

The available data on the potential teratogenicity of formaldehyde in experimental animals has been reviewed extensively by Staples (1983), from the perspective that a teratogenic response "consists of an alteration that occurs during the course of development to result in a permanent structural or functional defect" (Staples, 1983). Teratogenic endpoints of interest were external malformations among fetuses, macroscopic structural changes in internal organs or skeleton, and persistent and significant biochemical alterations in offspring. In general, anticipated reproductive effects would include alterations in pregnancy rate, maternal weight gain, length of gestation, number and average weight of fetuses per litter, incidence of implants, and sex ratio.

The data set evaluated by Staples consisted of reports by Puskina et al. (1968), Ritter et al. (1971), Godmekler (1968), Guseva (1972), Kalmykova (1979), Ranstroem (1956), Isaacson and Chaudhry (1962), Hurni and Ohder (1973) and Marks et al. (1980). Staples (1983) emphasized that many of the studies were flawed by incomplete reporting of data, very small numbers of animals tested (in both experimental and control groups) and lack of documentation regarding the integrity of test chemical and the sensitivity and accuracy of chemical/biochemical analyses performed. In consideration of the available data, then, Staples (1983) concluded that none of the studies presented convincing evidence of the teratogenicity or potential for adverse reproductive effects of formaldehyde in experimental animals. He further noted that data are lacking to convincingly demonstrate "that formaldehyde or its toxic metabolites ever reach the conceptus after administration by the oral, dermal, or inhalation route...."

### 4.2.2 Humans

Data regarding the reproductive effects and teratogenicity of formaldehyde in humans have been reviewed by Wartew (1983). Among the studies reviewed was an investigation of workers exposed to formaldehyde in a cotton mill (Shumilina, 1975) and in a plywood factory (Avdeeva et al., 1980), and effects of formaldehyde in the home environment (Garry et al., 1980). In none of these studies was formaldehyde proven conclusively to be responsible for adverse reproductive or teratogenic effects in the exposed populations.

Thus, based on the available data, formaldehyde has not been demonstrated to result in adverse reproductive effects or teratogenicity in any exposed animal or human population.

## 4.3 MUTAGENICITY

### 4.3.1 *In Vitro*

Formaldehyde has been tested for mutagenicity in a variety of *in vitro* assays, with conflicting results. Early studies demonstrated that formaldehyde was mutagenic to *Pseudomonas fluorescens* (Englesberg, 1952) and weakly mutagenic to *Escherichia coli* (Demerec et al., 1951). For some investigators formaldehyde did not demonstrate mutagenicity in *Salmonella typhimurium*, either with or without metabolic activation, at concentrations up to $1.3 \times 10^3$ nmol/plate (De Flora, 1981) and 1000 $\mu$g/plate (Brusick, 1983), although other investigators have reported positive results in *Salmonella typhimurium* (IARC, 1982). Mutagenic activity of formaldehyde has also been demonstrated in

*Saccharomyces cerevisiae* (Chanet and von Borstel, 1979, as cited in IARC, 1982). As reported in IARC (1982), formaldehyde has also induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells and cultured human lymphocytes (Obe and Beek, 1979), unscheduled DNA synthesis in HeLa cells (Martin et al., 1978), and DNA-protein crosslinks in mouse L1210 cells (Ross and Shipley, 1980) and Chinese hamster V79 cells (Swenberg et al., 1982). It has been observed that cells deficient in DNA repair enzymes are generally more susceptible to the lethal effects of formaldehyde than DNA repair-proficient cells (IARC, 1982).

#### 4.3.2 *In Vivo*

The *in vivo* mutagenic activity of formaldehyde has been studied in several species. When administered to *Drosophila* (fruit fly) larvae in food, formaldehyde has produced a variety of mutagenic effects including dominant and recessive lethals, inversions and translocations (chromosomal aberrations) (Auerbach and Moser, 1953). Exposure of *Drosophila* larvae to sublethal concentration of formaldehyde vapor for up to 2 hours, or adult flies for up to 1 hour, produced no mutations (Auerbach, 1949). Injection of formaldehyde into adult male flies has, however, induced mutations (Auerbach, 1952). Intraperitoneal injection of formaldehyde at 16-40 mg/kg body weight in Swiss (ICR/Ha) mice failed to induce dominant lethal mutations (Epstein et al., 1972). Spermatocytes from treated male Q strain mice revealed no chromosomal abnormalities following administration of 50 mg/kg body weight formaldehyde via intraperitoneal injection (Fontignie-Houbrechts, 1981; IARC, 1982).

Although the evidence is somewhat contradictory, formaldehyde has been demonstrated to be capable of inducing DNA damage, chromosomal aberrations, unscheduled DNA synthesis and DNA protein crosslinks in a variety of *in vitro* and *in vivo* systems. It is significant to note that the appearance these effects may be contingent upon administration of formaldehyde at cytotoxic concentrations (Squire and Cameron, 1984).

### 4.4 CARCINOGENICITY

#### 4.4.1 Experimental Systems

The carcinogenicity of inhaled formaldehyde in rodents was established in a chronic two-year bioassay conducted by Battelle Columbus Laboratories (Columbus, Ohio) in June, 1978, under sponsorship of the Chemical Industry Institute of Technology (CIIT) (Swenberg et al., 1980). In this study, 120 $B6C3F_1$ mice and Fischer 344 rats of each gender were exposed to formaldehyde (generated by the heating of paraformaldehyde) at airborne concentrations of 0, 2.0 $\pm$ 0.6, 5.6 $\pm$ 1.2, or 14.3 $\pm$ 2.8 ppm for 6 hours/day, 5 days/week for 24 months. Body weights, clinical signs and mortality were followed throughout the study; blood and urine samples were periodically obtained for measurement of hematological parameters, clinical chemistry and urinalyses. At preselected intervals (6, 12, 18, 24, 27 and 30 months) animals were subjected to a complete gross pathologic examination, tissue histopathological evaluation and determination of selected organ weights. Some female mice were held for a 3 month postexposure observation period before necropsy; some rats of each gender were observed postexposure for 3 and 6 months before sacrifice.

The results of the bioassay indicated that rats were more susceptible than mice to the toxic consequences of formaldehyde exposure. Survival of both genders of rats was affected by formaldehyde exposure at 14.3 ppm; mouse survival was unaffected at any exposure concentration. Evaluation of neurofunctional parameters revealed no

formaldehyde-related abnormalities in either gender of rats or mice. Transient depressions in body weight were noted in both genders of rats and mice; body weights returned to control levels during an observation period of no exposure. Both genders of rats exposed to 14.3 ppm formaldehyde demonstrated a significant ($p<0.01$) incidence of dyspnea (difficulty in breathing), considered to be exposure-related. Clinical chemistry, hematology and urinalysis revealed no formaldehyde-related abnormalities. Male rats in the 14.3 ppm exposure group demonstrated a decrease in the absolute weight of kidney and liver possibly as a result of formaldehyde exposure. Organ weight changes observed in mice, unsubstantiated by clinical chemistry or histopathological findings, were not considered to be a result of formaldehyde exposure.

The observation of nonneoplastic lesions included epithelial hyperplasia, dysplasia and metaplasia of the respiratory epithelium in rats at 2.0, 5.6 and 14.3 ppm, and in mice at 5.6 and 14.3 ppm. Also, benign polypoid adenomas were observed in 3.4, 2.6 and 2.2% of rats exposed to 2.0, 5.6 and 14.3 ppm formaldehyde respectively. This lesion, also noted in one male control rat, was not observed in mice. Interestingly, regression of metaplasia was observed in both rats and mice in the 2.0 and 5.6 ppm groups in the three months observation period following the termination of exposure.

Of primary interest was the observation of squamous cell carcinoma of the nasal cavity, a very rare form of cancer in rodents (Wartew, 1983). The incidence of this carcinogenic lesion was much lower in mice than in rats. Only two male mice exposed to 14.3 ppm formaldehyde displayed squamous cell carcinoma, detected after 24 months of exposure. Female mice remained cancer-free. In rats exposed to 14.3 ppm, 51 males and 52 females displayed squamous cell carcinoma after 12 months exposure, as did one rat of each gender at 5.6 ppm. This exposure group also displayed a carcinoma, an undifferentiated sarcoma, an undifferentiated carcinoma, and two carcinomas of the respiratory epithelium. Thus, the incidence of squamous cell carcinoma in rats was ~50% at 14.3 ppm and 1% at 5.6 ppm, suggesting a nonlinearity of carcinogenic response to inhaled formaldehyde. A ~50% incidence of squamous cell carcinoma was also observed in Sprague-Dawley rats exposed to ~14 ppm formaldehyde in a New York University study which confirmed the carcinogenicity of formaldehyde in a second strain of rats (Albert et al., 1982).

### 4.4.2 Implications for Assessment of Carcinogenic Risk to Humans

Certain findings of the CIIT chronic bioassay have been evaluated from the perspective of their possible relevance to the assessment of the carcinogenic risk of inhaled formaldehyde to humans. Among these are the localized nature of the effect (squamous cell carcinoma of the nasal cavity), the greater magnitude of the carcinogenic response observed in rats when compared to mice, and the apparently nonlinear nature of that response. Considered as a whole, these investigations suggest that humans are at much less risk from formaldehyde-induced cancer than are rodents.

In this section are reviewed a series of investigations into the nature of the biological response to formaldehyde exposure. The body of knowledge deriving from these studies provides insight to evaluate the conditions likely underlying the carcinogenicity of formaldehyde. While these studies employ inhalation exposures, their primary contribution is to the elucidation of biological mechanisms and they are not included here to simply profile a generalized response to inhaled formaldehyde.

Several factors suggest that formaldehyde effects would likely be limited primarily to the area of initial deposition. First, formaldehyde is highly water-soluble and very reactive; virtually none of an inhaled dose reaches the lungs except at very high exposure

levels (Squire and Cameron, 1984). Because the mucous layer covering the respiratory epithelium of rats is approximately 95% water (Swenberg et al., 1983), formaldehyde inhaled nasally would readily dissolve in this mucus layer, which would then mediate the effects of formaldehyde to the underlying respiratory epithelium. Second, tumors at remote sites would be the result of absorption of inhaled formaldehyde into the circulatory system and subsequent distribution to distant target tissues. Evidence that systemic absorption of inhaled formaldehyde does not occur is provided by several investigators. Studies by Heck et al. (1983) suggest that the primary absorption site of inhaled formaldehyde is the nasal mucosa, based on the observation that following inhalation exposure of rats to radiolabeled formaldehyde, the concentration of the radiolabel in the nasal mucosa was 1-2 orders of magnitude higher than that observed in the plasma or internal organs. These investigators also examined the effect of inhaled formaldehyde on the blood formaldehyde concentration immediately after exposure in humans ($1.9 \pm 0.1$ ppm for 40 minutes) and rats ($14.4 \pm 2.4$ ppm for 2 hours)(Heck et al., 1985). In humans, the blood formaldehyde concentrations before and immediately after exposure were $2.61 \pm 0.14$ $\mu$g formaldehyde/g blood and $2.77 \pm 0.28$ $\mu$g formaldehyde/g blood, respectively. In unexposed rats, the blood formaldehyde concentration was $2.24 \pm 0.07$ $\mu$g formaldehyde/g blood; the concentration in rats immediately following exposure was $2.25 \pm 0.07$ $\mu$g formaldehyde/g blood. Thus, it is evident that inhaled formaldehyde does not contribute to the blood formaldehyde concentration and is unlikely to produce effects remote from the site of deposition.

Additional evidence supporting this conclusion is provided by Casanova-Schmitz et al. (1984). These investigators reported that following the exposure of rats to 15 ppm formaldehyde, no cross-linkages with DNA, RNA or proteins, or adduct formation, were detected in the bone marrow of exposed animals. However, at a 2 ppm exposure concentration, protein cross-linkages were observed in rat nasal mucosa. It was emphasized that the rapidly dividing cells of the bone marrow should be an especially sensitive system for the detection of covalent binding of formaldehyde at distant sites, if indeed it did occur. Thus, the available evidence suggests that inhaled formaldehyde would not likely produce toxic effects at tissues other than those exposed directly to the airborne chemical.

Another finding of the CIIT chronic bioassay was the enhanced tumorigenicity noted in rats relative to mice. As previously stated, squamous cell carcinoma was observed in ~50% of rats exposed to formaldehyde at 14.3 ppm and in ~1% of rats exposed to 5.6 ppm formaldehyde. Only two male mice in the 14.3 ppm group demonstrated squamous cell carcinoma. This apparent species variation in susceptibility to tumor induction has been explained from the perspective that the critical factor determining tissue effects from formaldehyde is the actual tissue dose achieved and not simply the vapor concentration characterizing the exposure (Squire and Cameron, 1984). In the case of inhaled formaldehyde, the dose to the target tissue is determined by airflow to surface relationships, mucociliary activity and nasal deposition of inspired formaldehyde, factors which vary among species as a function of nasal anatomy, physiology and response to sensory irritation. The disproportionate response of rats and mice to the effects of inhaled formaldehyde has been explained on the basis of a greater sensitivity of mice to the effects of sensory irritants (such as formaldehyde) than is observed in rats. Chang et al. (1981, as cited in Swenberg et al., 1983) determined that at equal levels of exposure (15 or 6 ppm formaldehyde) $B6C3F_1$ mice demonstrated a 40-70% reduction in minute ventilation compared to the 10-20% reduction observed in rats. Therefore, among equally exposed rats and mice, the uptake and deposition of inhaled formaldehyde would be less in mice than in rats. This conclusion supports the observation of greater numbers of tumors in rats than in mice in the CIIT chronic bioassay. But it is significant to note that rodents (rats and mice) are obligatory nasal breathers, whereas humans employ oronasal breathing. Thus compared to

humans, rodents have greater nasal exposure to material in inspired air resulting in increased deposition in the nasal cavity and a greater dose to the target tissue. Rodents also possess atrioturbinates in their nasal cavities that act as baffles to deflect large amounts of inspired air. Humans lack these structures and therefore, have proportionally only about one-half the nasal surface area as rodents for filtering inspired air. Thus, at similar exposure concentrations, humans would be expected to receive a smaller dose to the target tissue than rodents (Squire and Cameron, 1984).

Evidence that the tumorigenic response of rats and mice to formaldehyde in the CIIT chronic bioassay is apparently nonlinear is based on the observation of a 50-fold increase in tumor incidence resulting from a 3-fold increase in the air concentration of formaldehyde. The basis of nonlinearity of response to formaldehyde is suggested by the studies of Casanova-Schmitz et al. (1984, as cited in Squire and Cameron, 1984). These investigators determined that the extent of covalent binding of formaldehyde to respiratory mucosal DNA in the rat was 10.5-fold higher at 6 ppm than at 2 ppm. As previously stated (Section 3.), the process of enzymatic detoxification by formaldehyde dehydrogenase becomes saturated at airborne concentrations above 4 ppm, resulting in a nonlinear increase in binding of formaldehyde to DNA. Thus, nonlinear detoxification offers an explanation for the nonlinear covalent binding observed by Casanova-Schmitz and colleagues. Additional insight explaining the nonlinearity of response to formaldehyde is provided by Swenberg et al. (1983). In studies of the effect of formaldehyde on cellular proliferation in the nasal cavities of rodents, a 10 to 20-fold increase in cell replication was observed to result from exposure of rats to 6 or 15 ppm formaldehyde (or mice to 15 ppm formaldehyde); exposures of rats at 2 ppm or less (or mice at 6 ppm or less) resulted in no increase in cell proliferation. Thus, mechanisms involved in the nonlinear response to formaldehyde exposure include covalent binding to DNA, metabolic detoxification and cellular replication, as well.

As discussed by Hoel et al. (1983) and Starr et al. (1985), there are several nonlinear kinetic processes that may play a role in determining the tumorigenic response of cells in the target tissue. Among these are metabolic activation and detoxification, covalent binding to DNA and proteins (as discussed above), and repair of DNA adducts. These saturable processes, assumed to be governed by Michaelis-Menten kinetics, determine the actual tissue dose expected to result from an administered dose. Additional nonlinear functions of formaldehyde response include inhibition of the respiratory depression reflex (Chang et al., 1983) and inhibition of mucociliary clearance (Morgan, 1983). Each of these factors influence the relationship between administered dose and delivered dose. Models employed in quantitative risk assessment that assume a strictly linear relationship between the concentration of formaldehyde in inspired air and formaldehyde in the target tissue can produce erroneous risk estimates that greatly overestimate the low-dose response (Swenberg et al., 1983a).

It should be noted at this point that the critical factor determining the toxic response to formaldehyde is the concentration and not the total cumulative dose, based on evidence from several studies. In acute studies of formaldehyde effects on cell replication (Swenberg et al., 1983, as cited in Swenberg et al., 1983a), rats were exposed to the same daily dose of formaldehyde, but under different regimens of concentration and exposure duration, i.e., 12 ppm for 3 hours, 6 ppm for 6 hours and 3 ppm for 12 hours (all totaling 36 ppm-hours/day). In the central portion of the respiratory epithelium (the primary site of squamous cell carcinoma observed in the CIIT chronic bioassay), cell replication was seen to be strictly concentration-dependent. The percentage of labeled cells resulting from exposure to 3, 6 and 12 ppm was $1.73 \pm 0.63$, $3.07 \pm 1.09$ and $9.00 \pm 0.88\%$, respectively.

If cell replication were dependent on cumulative dose rather than concentration, the percentage of labeled cells would have been similar for all exposure protocols.

Evidence of the greater importance of concentration over total cumulative dose in determining formaldehyde effects is also provided by a comparison of the results of the chronic inhalation study of Rusch et al. (1983) with findings of the CIIT chronic bioassay. Rusch and colleagues exposed monkeys, rats and hamsters to formaldehyde vapor concentrations of 0, 0.2, 1.0, and 3.0 ppm for 22 hours/day, 7 days/week, for 26 weeks. In this study, the incidence and severity of inflammatory, hyperplastic and metaplastic lesions was much lower in rats exposed to 3 ppm formaldehyde for 22 hours/day, 7 days/week (462 ppm-hours/week) than in rats exposed to 14.3 ppm formaldehyde for 6 hours/day, 5 days/week (450 ppm-hour/week) in the CIIT chronic bioassay. Thus, available data indicate that the concentration of formaldehyde, rather than cumulative dose, is of primary importance in formaldehyde toxicity. This sentiment was also expressed by Heck (1982) in stating that a prolonged exposure to a low concentration of formaldehyde would probably entail less risk than a shorter exposure to a higher concentration, even though the same cumulative dose were achieved.

The final point of discussion in this section is that increased cell proliferation seems to be a critical event in formaldehyde carcinogenesis (Jones et al., 1983; Farber, 1982, as cited in Squire and Cameron, 1984). As noted by Swenberg et al. (1983), compensatory cellular proliferation is a prominent response to cytotoxicity. Furthermore, increased replication (10 to 20-fold) was observed in rats exposed to 6 or 15 ppm formaldehyde and in mice exposed to 15 ppm formaldehyde. Increased cell turnover was not associated with exposure of rats to 2 ppm or less, or mice exposed to 6 ppm or less. The CIIT chronic bioassay demonstrated squamous cell carcinoma in rats at 5.6 and 14.3 ppm, and in mice at 14.3 ppm formaldehyde, the same exposure levels characterized by increased cellular replication. As stated by Swenberg et al. (1983). "The fact that only exposure concentrations associated with squamous cell carcinoma in rats and mice resulted in increased cell proliferation lends strong support to the hypothesis that increased cell proliferation is a critical event in formaldehyde carcinogenesis." Also, as stated in the International Association for Research on Cancer (IARC) Monograph (IARC, 1982), "Levels of formaldehyde that cause nasal tumors also cause acute degeneration, necrosis, inflammation and increased cell replication in the nasal mucosa of rats and mice following inhalation exposure." Thus, it may be reasonably stated that... "such observations may provide useful markers for apparent no-effect levels which may impact on carcinogenesis risk assessment" (Squire and Cameron, 1984).

The observation of tumors only at cytoxic levels of exposure is reasonable from the perspective that formaldehyde does not react with double-stranded DNA, and it is likely that unwinding of the double helix, as occurs during cell division, may be necessary before formaldehyde can form DNA adducts (Singer and Kusmierik, 1982, as cited in Squire and Cameron, 1984). Further insight is offered by Todhunter (1985), who notes that alterations in the genome serve as initiating events which must become "fixed" into the cells prior to neoplastic transformation. The cellular repair of such mutational insults prior to DNA replication during cell division effectively results in loss of the initiating event. If, however, cytotoxicity results in an increased rate of cell division accompanying compensatory cellular proliferation, the likelihood is increased that the initiating event will become "fixed" and the mutational event will be expressed (Jones et al., 1983). Thus, at cytotoxic doses, the dose-response curve would be much steeper than at subcytotoxic doses, and this is apparently true in the case of formaldehyde. The effect is seen as a nonlinear increase in tumor yield as the dose is increased.

In summary, based on the available biological data, certain conclusions may be derived regarding the potential carcinogenicity of formaldehyde to humans. First, if airborne formaldehyde were carcinogenic to humans, the manifestation of that carcinogenicity should appear as nasal cancer or, possibly, lung cancer, because of the apparent lack of toxicity at sites distant from the point of deposition. Therefore, epidemiologic evidence supporting an association between formaldehyde and cancer should disclose an elevated incidence of nasal or lung cancer (the following section of this report will investigate whether or not this has happened). Second, based on anatomical differences between humans and rodents, humans are at less risk of cancer because the delivered dose to the target tissues is less, at equal exposures. Third, regardless of route of exposure, the intake "dose" would have to be of sufficient magnitude to overwhelm the process of metabolic detoxification, and induce compensatory cellular proliferation in response to cytotoxicity. If via inhalation, that dose would have to exceed 4 ppm to overwhelm metabolic detoxification if humans received the same tissue dose as rats, but humans receive much less. An oral dose to humans would have to overwhelm liver detoxification, which can convert 22 mg of formaldehyde to $CO_2$ every minute (see Section 3.). Based on the natural content of formaldehyde in foods (see Section 2.2), that oral dose would certainly have to be much greater than the ~11 mg/day normal dietary intake level, or stomach cancer from formaldehyde would be rampant. Fourth, based on considerations of nonlinearity at all levels of biological response to formaldehyde, the concentration, and not the cumulative dose is the primary determinant of formaldehyde toxicity. The carcinogenic risk per ppm of formaldehyde is thus greater at high exposure than at low exposure concentrations. Chronic human exposures at low dose should not present a hazard.

### 4.4.3 Humans--Review of Epidemiologic Studies

The determination that airborne formaldehyde exposure produced nasal carcinoma in animals (Swenberg et al., 1980), coupled with the widespread industrial and commercial use of formaldehyde, has heightened concern that formaldehyde may contribute to the incidence of cancer in humans (Blair et al., 1985). Epidemiological investigations have attempted to establish this association. Among the epidemiological methods used to study the relationships between exposure and disease are the case-control study and the cohort study. The case-control study is appropriate in evaluating the relationship between an uncommon disease and a common exposure. The cohort study is more useful in situations where the disease is common, but the exposure is not (Squire and Cameron, 1984).

Both methods have been used to study the carcinogenicity of formaldehyde in humans, focusing on a potential increased incidence of tumors of the nasal or nasopharyngeal epithelium, based on the observed 80% correlation between sites of chemically induced cancer in test animals and humans (Tomatis et al., 1978, as cited in Squire Cameron, 1984). It should be noted that nasal cancer in humans is rare; the annual incidence rate is about 8 cases per 1,000,000 males in the United States (AMA, 1989). Because of the combined oronasal breathing of humans, as opposed to the strictly nasal breathing of rodents, the effects of formaldehyde in humans may possibly extend to the lung, as well. Tumors at distant body sites do not appear likely due to the high solubility and reactivity of formaldehyde at the site of initial deposition and because of other considerations discussed elsewhere in this report (see Section 4.4.2).

Most epidemiological investigations to date have involved two groups: employees in industries where formaldehyde is used or produced and professionals who are occupationally exposed to formaldehyde, such as morticians, embalmers, anatomists and pathologists. Case-control studies by Tola et al. (1980), Brinton et al. (1984), Hardell et al. (1982) and

Hernbert et al. (1983) (all as cited in Blair et al., 1985) have investigated the possible association between formaldehyde and disease among industrial workers. Cohort studies by Levine et al. (1983), Harrington and Shannon (1975) and Stroup et al. (1984) (all as cited in Blair et al., 1985), are among those investigating formaldehyde exposure and disease relationships among embalmers, pathologists and occupational groups. Epidemiologic evidence has been contradictory. Among the case-control studies, only the study of Hardell et al. (1982) suggested a possible association between nasal cancer and formaldehyde (Blair et al., 1985). This study reported a relative risk of about 4 based on findings in the particle board manufacturing industry, although the results were possibly confounded by co-exposure to wood dust.

Among the cohort studies, the only condition associated with a consistently elevated mortality was brain cancer among professional groups (embalmers, pathologists and anatomists). Even accounting for diagnostic bias, the association of brain cancer and these occupational groups persists. However, these workers are routinely exposed to many different chemicals (phenols, dyes, glycerols, etc.) in addition to formaldehyde, and identification of the specific risk factor responsible for brain cancer is not possible (Blair et al., 1985). Furthermore, there is no defensible scientific hypothesis to explain how formaldehyde, a highly reactive and easily detoxified substance, could reach the brain or any other sites in the body not directly exposed to formaldehyde (Swenberg, 1989).

Several studies show an elevated incidence of leukemia among the professional groups. Although diagnostic bias may be responsible for some of the excess, exposure to benzene or other chemicals may have confounded the specific association of leukemia with formaldehyde (Blair et al., 1985).

Two more recent epidemiologic investigations are of particular interest. In a National Institute for Occupational Safety and Health (NIOSH) study of 256 deaths in three garment industry plants (the initial phase of a two-part study) (Stayner et al., 1985), deaths from respiratory cancer were evident. However, a statistically significant increase in incidence was noted for malignant neoplasms of the buccal cavity, biliary ducts and liver, and other lymphatic and hematopoietic sites (AMA, 1989). Because of the small numbers of deaths and the lack of concordance with earlier studies, these finding were regarded as being inconclusive.

The second phase of the NIOSH investigation focused on 11,030 workers in permanent-press garment factories and found excesses in mortality due to cancers of the buccal cavity, tonsils and connective tissue. No deaths from nasal cancer were found, but increased mortality was observed from neoplasia of the lung, trachea and bronchi, and from bronchitis and leukemia. The authors of the study considered the mortalities from lymphopoietic neoplasms, leukemia and cancers of the buccal cavity to be related to formaldehyde exposure. An independent review of the data by the Environmental Protection Agency (EPA) disclosed a statistically significant trend between duration of exposure to formaldehyde and cancer of the buccal cavity.

Finally, the study of Blair et al. (1986), sponsored by the National Cancer Institute (NCI), examined cancer mortality among 26,561 workers in formaldehyde-producing or -using plants, the largest cohort of any formaldehyde study. In contrast to earlier studies, excess mortality from cancers of the brain or from leukemia was not apparent. Deaths from pharyngeal and buccal cavity cancer were not in excess. However, excess mortality from oropharyngeal and nasopharyngeal cancer was evident. Because the incidence rates for these latter cancers were apparently not related to dose, the authors concluded the results to be inadequate to support a specific association between formaldehyde exposure and cancer. A later reevaluation of this study by the NCI (Blair et al., 1987, as cited in AMA, 1989) considered that the occurrence of oropharyngeal and nasopharyngeal cancers could

have been affected by exposure to particulate matter associated with dusty formaldehyde resin-molding compounds.

Thus, while selected sets of epidemiological data may suggest a marginal association between formaldehyde exposure and cancer of the buccal cavity, nasal cavity or lung, it should be emphasized that these findings are not consistent across the many studies completed to date (Swenberg, 1989).

## 5. STATUTES AND GUIDELINES

Presented with contradictory epidemiologic data, but compelled by law to issue environmental health standards even in the absence of conclusive data, the EPA issued its health risk assessment of formaldehyde on April 16, 1987. Based on "limited" evidence from 9 of 28 studies reviewed, and corroborative evidence from 6 of 25 earlier studies, the EPA classified formaldehyde as a Group B1 "probable human carcinogen", implicating an association between formaldehyde exposure with the occurrence of respiratory site-specific cancers. Echoing the same sentiment that formaldehyde is a "probable human carcinogen", the Occupational Safety and Health Administration (OSHA), under pressure from labor unions and others, issued its final rule on formaldehyde (under court order) on November 21, 1987. The new standard set an eight-hour time-weighted average exposure limit for formaldehyde of 1.0 ppm and a short-term (15 minute) exposure limit not to exceed 2.0 ppm. The formaldehyde industries responded by taking legal action to block promulgation of the new standard, which should have become effective on February 2, 1988. The controversy surrounding the EPA and OSHA rulings that formaldehyde is a probable human carcinogen shows no signs of relenting (AMA, 1989).

No national drinking water standards regulating formaldehyde in drinking water currently exist. However, two states have independently proposed a drinking water regulation for formaldehyde. Based on a safety factor of 10 applied to the finding of stomach irritation resulting from ingestion of formaldehyde at 300 ppb, California has proposed a regulation limiting formaldehyde in drinking water to 30 ppb (DHS, 1987). New Jersey has proposed a more restrictive limit of 0.65 ppb based on a linear extrapolation of the carcinogenic dose-response curve generated the CIIT bioassay (Sullivan, 1987).

# 6. RELATIVE HAZARD

This section will present a dual perspective from which to evaluate the low-level ingestion of formaldehyde as a contaminant in drinking water. The first approach (Section 6.1) will compare intake of formaldehyde as a drinking water contaminant with the daily ingestion of formaldehyde as a normal component of foods. This approach is straightforward and offers a direct comparison of oral formaldehyde intake from two separate sources. The second approach (Section 6.2) is less direct, but necessarily so, for the focus here has shifted from a straightforward comparison of formaldehyde intake levels to an evaluation of the hazard resulting from that intake. Each approach offers insight into the issue at hand, and together provide a rational framework from which to evaluate the ingestion of formaldehyde as a low-level contaminant in drinking water.

## 6.1 INGESTION OF FORMALDEHYDE AS A DRINKING WATER CONTAMINANT RELATIVE TO CONSUMPTION OF FORMALDEHYDE IN FOODS.

Section 2.2 of this reports presents a compilation of the annual consumption rate, formaldehyde concentration and estimated annual consumption of formaldehyde, based on the levels of formaldehyde commonly found in specific food groups (see Table 2.2). The data reflect the formaldehyde content of the typical American diet; it seems likely that we are all exposed to dietary formaldehyde at some level.

Based on Table 2.2 the annual consumption of dietary formaldehyde results in an intake of about 4000 mg/year, equivalent to approximately 11 mg/day, the target value for comparison with intake levels of formaldehyde as a drinking water contaminant. The typical human ingests approximately 2 liters of water per day from all sources (ICRP, 1975). Thus, ingestion of 2 liters of drinking water containing formaldehyde at a concentration of ~20 ppb (20 $\mu$g/liter) would result in an intake of only 40 $\mu$g formaldehyde daily, constituting an increase of only about 0.3% over endogenous levels (~14 mg, see Section 3.2). This value may be regarded as an overestimate, because part of the 2 liter daily intake of water is considered to derive from water in fruit juices, soft drinks, etc.

In any case, a 40 $\mu$g daily intake of formaldehyde in drinking water is less than the normal daily intake from foods (11 mg) by a factor of ~275. If metabolic detoxification protects us from the much greater intake of formaldehyde in foods, which it obviously does, then it is certainly protective at an additional intake level of only 40 $\mu$g daily. As stated in Section 3 of this report, the liver has the capacity to convert 22 mg of formaldehyde to $CO_2$ every minute, so the additional burden of detoxifying 40 $\mu$g of formaldehyde, whether all at once or over the period of one day, is negligible. Also from Section 3.2 we see that, in the average human, 14 mg of endogenously produced formaldehyde is circulating in the blood. This level is greater than 40 $\mu$g by a factor of 350.

If the residence were unoccupied or water was not used for a few days, the formaldehyde concentration could approach ~100 ppb (100 $\mu$g/L). In this case, daily ingestion of 2 L of drinking water would result in an intake of ~200 $\mu$g formaldehyde. Intake of formaldehyde in drinking water in this "worst case" scenario would still be a factor of about 55 less than the normal dietary intake of formaldehyde. The value of 200 $\mu$g is also a factor of 70 less than the level of endogenous formaldehyde circulating in the blood.

Alternately, one may calculate the formaldehyde concentration in drinking water required to result in an intake level equal to that from foods. If half the daily intake of water derived from drinking water, i.e., if only 1 liter were ingested, that water would have to contain formaldehyde at a concentration of ~11 ppm (11,000 ppb) to result in an intake level equivalent to the normal dietary intake of formaldehyde. Of course, one could

calculate the intake level of drinking water, at the normally measured concentration of 20 ppb, that would be required to result in a 11 mg daily intake. At a concentration of 20 $\mu$g/L, one would have to ingest 550 gallons of water daily to equal the daily dietary intake of formaldehyde. Such comparisons may seem absurd if extended too far, but they do tend to illustrate the point.

## 6.2 COMPARISON OF HAZARD FROM FORMALDEHYDE INGESTION WITH INGESTION OF SUBSTANCES GENERALLY REGARDED AS SAFE.

In an effort to avoid the confusion and uncertainty of using unvalidated mathematical extrapolation models to derive risk estimates for hazardous substances, researchers at Oak Ridge National Laboratory have developed a relative potency methodology (Jones et al., 1985; 1988). The technique makes maximal use of toxicological data to derive an array of relative potency values characterizing the potential toxicity of a substance relative to one or several reference compounds. All chemicals may be evaluated on a unitless common scale, regardless of their prior designation as carcinogen or noncarcinogen (as seen in the case of formaldehyde, such a designation is subject to change as scientific evidence accumulates) and has been used to estimate relative potencies (RPs) for nearly 300 diverse substances thus far (Jones et al., 1988). The relative potency methodology is well documented and the interested reader should consult Jones et al. (1985; 1988) for further details.

Chlorination of drinking water is generally regarded as safe by most persons and is desirable for the control of pathogenic (disease-causing) microorganisms that may transmit water-borne diseases such as typhoid fever and cholera. However, the reaction of chlorine with existing organic matter naturally occurring in water may result in the eventual formation of compounds referred to as trihalomethanes (THMs). One such THM is chloroform, a known animal carcinogen (IARC, 1982).

Based on the frequency of distribution of the THMs detected in the National Organic Reconnaissance Survey for Halogenated Organics (Symons et al., 1975), the theoretical finished water with the median concentration of each compound would contain about 21 $\mu$g/L of chloroform ($CHCl_3$), 6 $\mu$g/L of bromodichloromethane ($CHBrCl_2$) and 1.2 $\mu$g/L of chlorodibromomethane ($CHBr_2Cl$). Based on the application of Finney's harmonic mean formula (Finney, 1952), the relative potency of drinking water based on this THM content, can be derived from the following equation:

$$RP_{dw} = \Sigma_i f_i \bullet RP_i \qquad \text{(Jones and Owen, 1989)}$$

where $f_i$ = the fractional contribution (by weight) of each of the THMs to the weight of 1 L of water ($10^9$ $\mu$g) and $RP_i$ = the relative potency of each of the THMs based on comparisons to benzo[a]pyrene as the reference standard, from Jones et al. (1988).

Therefore, the relative potency of drinking water based on its THM content is derived by the calculation

$$RP_{dw} = \frac{21\ \mu g}{10^9\ \mu g} CHCl_3\ (0.005) + \frac{6\ \mu g}{10^9\ \mu g} CHBrCl_2\ (0.0065) + \frac{1.2\ \mu g}{10^9\ \mu g} CHBr_2Cl\ (0.021)$$

$$= \frac{0.105 + 0.039 + 0.025}{10^9}$$

$$= 1.7 \times 10^{-10}.$$

The small calculated value suggests a very weak composite toxicity of chlorinated drinking water relative to benzo[a]pyrene, the reference standard used in calculating the individual RP values (a value of 1 would indicate toxicity equal to that of benzo[a]pyrene).

In another example, fluoridation of drinking water (at target levels of 1 mg/L) is commonly employed to enhance the dental health of children. No adverse effects have been associated with fluoride intake at this level in the world's temperate zones; fluoridation of drinking water is also generally regarded as safe. Based on its fluoride content alone, the relative potency of drinking water can be calculated according to the formula

$$RP_{dw} = RP_f \cdot \text{concentration/liter}$$
$$= 0.046 \cdot \frac{1 \text{ mg}}{10^6 \text{ mg}}$$
$$= 4.6 \times 10^{-8}.$$

This value is also quite small, indicating a weak toxicity relative to benzo[a]pyrene.

To compare the risk of exposure to any hazardous substance with the risk from ingestion of drinking water, the following equation is used:

$$\frac{Risk_{test}}{Risk_{dw}} = \frac{(\text{concentration } \mu g/L)(1 \text{ L}/10^9 \mu g)(RP_{test})}{RP_{dw}}$$

where $RP_{dw} = 1.7 \times 10^{-10}$, if based on chlorination by-products, or $4.6 \times 10^{-8}$ based on fluoride content.

The risk of ingestion of drinking water contaminated with low levels of formaldehyde (20 $\mu g/L$) may be calculated as

$$\frac{Risk_{test}}{Risk_{dw}} = \frac{(20 \ \mu g/L)(1L/10^9 \ \mu g)(0.033)}{1.7 \times 10^{-10}}$$

$$= \frac{\frac{0.66}{10^9}}{1.7 \times 10^{-10}}$$

$$= \frac{6.6 \times 10^{-10}}{1.7 \times 10^{-10}}$$

$$= 3.9, \text{ based on THM content.}$$

Substitution of $4.6 \times 10^{-8}$ in place of $1.7 \times 10^{-10}$ as the denominator above, results in a value of 0.014, based on fluoride content alone.

Therefore, using relative potency arguments, the hazard from ingestion of formaldehyde at 20 $\mu g/L$ in drinking water, is about four times greater than the hazard from ingestion of chlorinated drinking water, but about 100 times less than the hazard from fluoridated drinking water. It should be emphasized that deviations by a factor of 4 are not considered significant in dealing with such small numbers, i.e., a value of $6.6 \times 10^{-10}$ is hardly

different from the value $1.7 \times 10^{-10}$. Thus, the hazard from ingestion of formaldehyde at 20 ppb in drinking water is little different from the hazard from chlorination by-products (THMs) and probably less than for fluoride.

It should be noted that the relative potency approach utilized here generally assumes linearity of dose response. However, formaldehyde is known to be nonlinear with regard to cancer incidence vs administered dose. The RP value for formaldehyde was derived from fairly high-dose, $LD_{50}$-type data. The net effect is that the above risk calculations effectively overestimate formaldehyde risk, yielding a net conservatism (overestimate) in subsequent comparisons with chlorination by-products and/or fluoride in drinking water.

At this point the relative hazard evaluation presented above permits a determination that chronic ingestion of formaldehyde as a low-level drinking water contaminant does not constitute a significant human health risk. By comparison with the level of formaldehyde normally ingested in foods, the additional intake via drinking water is negligible. Also, relative potency considerations indicate that the hazard of formaldehyde in drinking water is roughly equivalent to that of chlorination by-products and less than the hazard potential of fluoride in drinking water; both are generally regarded as "safe".

Additional evidence is provided by studies of metabolism and biological mechanisms of formaldehyde. Metabolic investigations indicate that low levels of exogenous formaldehyde are effectively detoxified via normal enzymatic processes already in place for disposition and utilization of endogenous formaldehyde. If routes of exposure were equivalent, and assuming 100% absorption, then ingestion of greater than 4 ppm (4000 $\mu$g/L) would be required to overwhelm normal metabolic detoxification. However, oral intake is likely to be less hazardous than an equivalent inhalational exposure, because reaction of ingested formaldehyde with stomach residues would reduce the amount of formaldehyde available for subsequent absorption. Investigations of biological mechanisms of formaldehyde indicate that the primary factor influencing toxicity is the concentration encountered and not the cumulative dose over a period of time. Thus, repeated low-level exposure via formaldehyde in drinking water does not evoke cumulative toxicity. Mechanistic investigations also provide evidence that carcinogenicity of formaldehyde is apparently contingent upon induced cellular proliferation in response to cytotoxicity. Ingestion of formaldehyde at 20 $\mu$g/L does not likely constitute a cytotoxic "dose".

Section 2.1.2 of this report presents an estimate of the induced air concentration of formaldehyde expected to result from volatilization of formaldehyde in drinking water at a concentration of 100 ppb, the maximum measured concentration. The resultant induced air concentration is likely to be much less than 1 ppb, a concentration well below the threshold for detection of any acute health effects. At this small concentration, no acute or chronic health effects are likely to occur.

Based on the above considerations, formaldehyde in drinking water at a concentration of 20 $\mu$g/L apparently does not constitute a hazard to human health. What, then, is an appropriate regulatory level for formaldehyde in drinking water, acknowledging that no federal drinking water regulation currently exists for formaldehyde? The following sections provide necessary insight into formulation of a reasonable answer to that question.

## 6.3 DERIVATION OF GUIDANCE CRITERIA--STANDARD METHODS

The historical approach to regulation of potentially harmful substances has relied on an initial determination that the substance of interest has human carcinogenic potential. This determination is made through an evaluation of the "weight of evidence" for carcinogenicity provided by the available toxicological, biological and chemical data for the substance.

This approach to regulation of toxic chemicals is guided conceptually by assumptions that suggest noncarcinogens exert effects through mechanisms that demonstrate thresholds (Anderson et al., 1983). Subthreshold doses are considered to be pharmacologically ineffective and elicit no adverse response. Thus, regulations for threshold chemicals or substances (noncarcinogens) attempt to limit exposures to levels that are of low enough concentration to be considered "safe", as characterized by such indices as acceptable daily intake (ADI) for the general population, or threshold limit value (TLV) for occupational groups.

In the absence of human data, the U.S. Environmental Protection Agency (EPA) derives ADIs for noncarcinogens based on adjustments to "no observed adverse effect levels", or NOAELs, from animal experiments. These NOAELs are modified by incorporation of large, chemical-specific safety factors to predict essentially safe levels of exposure in the human population (Anderson et al., 1983). These factors are numerical modifiers used to compensate for such uncertainties as extrapolations from subchronic to chronic exposure, inter- and intraspecies variability, or use of a "lowest observed adverse effect level" (LOAEL) if a NOAEL is unavailable (Dourson and Stara, 1983). Safety factors commonly ranging from 100 to more than 5000 are used to compensate for deficiencies in toxicological data with the intent of ensuring that calculated values will indeed be protective of human health. However, the choice of specific factors to ensure an adequate margin of safety may be subjective and their application may be inconsistent.

The current approach to regulation of carcinogens is guided by the assumption that carcinogens act through nonthresholded mechanisms. Accordingly, any degree of exposure to a carcinogen, no matter how small, is assumed to impart some increment of risk. From this perspective, the EPA has restricted derivation of ADIs to noncarcinogens.

Human risk estimates for carcinogens are most credibly derived from epidemiologic data in which well-documented exposures elicit a statistically significant increase in cancer incidence as a function of increasing dose. However, due to inadequate documentation of exposure levels, confounding by multifactorial exposures, lack of appropriates control groups, and other shortcomings of epidemiologic data, many studies are rendered unsuitable for risk assessment (NAS, 1983).

In the absence of suitable human data, the EPA Carcinogen Assessment Group (CAG) typically derives risk coefficients by (1) selecting the best or most appropriate animal experiment, (2) fitting a linearized, multistage model to the data, (3) deriving the upper 95% confidence interval of the maximum-likelihood value, and (4) extrapolating from the test animal to 70-kg man (Anderson et al., 1983). However, valid extrapolation from test animal data to humans is undermined by a lack of understanding of the basic mechanisms of carcinogenesis, the relationship of cancer to aging and life-span, species differences in metabolism and pharmacokinetics and human heterogenicity (Ames et al., 1987).

In the case of formaldehyde, both threshold and nonthreshold approaches have been used in an attempt to derive regulatory criteria, due in part to earlier considerations that it was not a carcinogen. As reported by Scheuplein (1985), the FDA has calculated an ADI for formaldehyde in foods on the basis of a NOAEL from a chronic fetotoxicity investigation in dogs that demonstrated no adverse effects from an intake of 15 mg/kg body weight/day. Application of a safety factor of 100, commonly used to adjust NOAELs from animal studies, yields an ADI for humans of 0.15 mg/kg body weight/day, or about 10 mg/day.

Similarly, an ADI may be calculated on the basis of a study reported by Zurlo (1971), in which no adverse effects were demonstrated in humans ingesting up to 200 mg formaldehyde daily for 13 consecutive weeks. In this case, appropriate safety factors (each with a value of 10) accommodating extrapolation from subchronic to chronic exposure and

accounting for human variability, would yield an ADI of ~2 mg/day (or 20 mg/day if only one safety factor of 10 is applied). Thus a human ADI may be calculated to be 2, 10 or 20 mg/day, depending on which study is used and choice of safety factors.

In contrast with the safety factor approach for calculating ADIs, quite different numbers may be generated through attempts to regulate formaldehyde as a carcinogen. New Jersey is one of few states that has proposed a drinking water standard for formaldehyde (Sullivan, 1987). The maximum contaminant level recommended by the New Jersey Drinking Water Quality Institute is 0.65 μg/L, equivalent to an intake of only ~1.3 μg/day. This recommendation was made on the basis of the linearized, multistage model applied to the carcinogenesis bioassay dose-response from the CIIT study (Swenberg et al., 1980). The intake level of ~1.3 μg/day generated through carcinogenesis dose-response modeling is a factor of about 1500 more restrictive than the lowest value of 2 mg/day deriving from safety factor calculations of ADI. Thus, a great disparity exists among potential guidance criteria for formaldehyde, depending on which approach to regulation is chosen. Naturally, the issue to be resolved centers on determining which value is more correct--the 2-20 mg/day based on an ADI approach, or the 1.3 μg/day based on extrapolation modeling of formaldehyde as a carcinogen.

The obvious move is to accept that formaldehyde has the potential to be a human carcinogen and regulate it accordingly, dismissing ADI-type calculations as inappropriate. The problem then becomes one of how to reconcile the regulated intake of formaldehyde in drinking water of 1.3 μg/day with the normal dietary intake of 6.5 mg/day (see Section 2.2). Based on a formaldehyde content of 8.13 mg/kg (or 8.13 μg/g) for fresh fruit, ingestion of a single gram would exceed the New Jersey recommended drinking water daily intake limit by a factor of ~6. One may conclude that while extrapolation modeling may ensure protection of human health, the cost may include an unrealistic margin of safety.

## 6.4 AN ALTERNATE APPROACH TO FORMALDEHYDE REGULATION

The traditional approaches discussed in the preceding section rely on a prior evaluation of the "weight of evidence" that formaldehyde has human carcinogenic potential. Indeed, formaldehyde has been shown to induce nasal squamous cell carcinomas in rodents exposed to airborne formaldehyde at 14.3 ppm (Swenberg et al., 1980). However, it was seen that the carcinogenic response was undeniably nonlinear (in opposition to standard assumptions regarding carcinogenic mechanisms), with no carcinomas seen at exposures below 5.6 ppm. Therefore, application of standard extrapolation models that assume linearity of dose response does not seem appropriate in the case of formaldehyde, and it is likely that such models would overestimate the low-dose response. Thus, the New Jersey drinking water regulation of formaldehyde at 0.65 μg/L, based on a linear extrapolation of the carcinogenic dose response, may be considered overly restrictive if not plainly impractical, since that concentration of formaldehyde is probably below the analytical limit of detection. Furthermore, the New Jersey drinking water regulation assumes equivalence of formaldehyde exposure whether via inhalation or ingestion. From the information presented in the preceeding sections, an oral dose would be less hazardous than an equivalent inhalation dose due to reaction of the ingested formaldehyde with stomach chyme, resulting in less formaldehyde available for potential absorption.

Based on the consideration that formaldehyde is a normal metabolite in the human body that has demonstrated a practical threshold for carcinogenicity in the animal bioassay, this report concludes that formaldehyde is effectively noncarcinogenic at similarly low levels of exposure. Formaldehyde drinking water regulations need not be as restrictive as those

for more "traditional" carcinogens, and should incorporate available information on metabolism, biological mechanisms and normal dietary intake levels to derive a reasonable drinking water regulatory limit.

Because no truly chronic human ingestions studies of formaldehyde currently exist, an approach suggested in this report is to consider normal dietary intake of formaldehyde to be a surrogate for chronic ingestion. On that basis, no adverse effects are associated with dietary intake of formaldehyde at ~11 mg/day. Based on a 2 liter daily ingestion of water, an equivalent level in drinking water would be around 5.5 mg/L, or 5.5 ppm. Due to uncertainty in the dietary estimate and in consideration of human variability, this value may be reduced by a factor of 10 to yield a recommended drinking water level of 0.5 ppm (500 ppb), or 0.5 mg/L. This level of intake is not likely to overwhelm normal metabolic detoxification of formaldehyde, nor is it below the analytical limit of detection. Daily ingestion of 2 liters of drinking water containing formaldehyde at 0.5 mg/L yields an intake of 1 mg, a factor of ~10 below normal dietary intake levels. Thus formaldehyde intake from both food and water sources would be ~12 mg daily, within the range of normal variation centering on a 11 mg daily dietary intake.

## 7. SUMMARY AND CONCLUSIONS

This report has evaluated the potential hazard of chronic ingestion of low levels of formaldehyde in drinking water. Current information regarding metabolism and biological mechanisms was incorporated into a framework of comparative hazard evaluation to permit the determination that low-level ingestion of formaldehyde in drinking water is not a significant threat to human health. Compared to the normal ingestion of formaldehyde in foods, additional intake via drinking water at current residential levels is negligible. From a relative potency perspective, the hazard of low-level ingestion via drinking water is comparable to the hazard potential of chlorination by-products and less than that of fluoride.

Additional evidence from studies of metabolism indicate that normal enzymatic detoxification can effectively process low levels of ingested or inhaled formaldehyde; rapid conversion to formic acid is followed by either further oxidation to $CO_2$ and water, excretion in the urine as the sodium salt, or metabolic incorporation into the one-carbon pool. Mechanistic investigations suggest that the biological responses to formaldehyde are nonlinear, resulting in less carcinogenic risk per ppm at low exposures than at higher exposures. Mechanisms also indicate that the concentration, rather than the cumulative dose, is the primary determinant of toxicity, and if the concentration is a subcytotoxic level, no compensatory cellular proliferation results to enhance the potential for carcinogenicity.

In regard to standard setting, this report offered an alternative approach based on the common daily ingestion of formaldehyde in foods. This approach avoids the uncertainty attendant the use of linear extrapolation models applied to an inhalation dose-response curve to estimate low-dose risk via a different route of exposure.

This report does not suggest that such an approach is valid when applied to regulation of most carcinogens. However, formaldehyde is atypical in that it is a normal product of metabolism, and it has demonstrated an apparent threshold of effects, resulting from a cascade of nonlinear mechanisms underlying its manifestations of toxicity. Thus, a reasonable level of exposure may be permitted through regulations that consider a more comprehensive view of formaldehyde than the narrow focus provided by linear, no-threshold assumptions generally applied to carcinogens.

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