Preliminary Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde

DRAFT

May 1985

Risk Analysis Branch
Existing Chemical Assessment Division
Office of Toxic Substances

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Since 1979, when the preliminary results from the Chemical Industry Institute of Toxicology (CIIT) study indicated the formation of nasal cancer in rats, much attention has been focused on the potential human carcinogenicity of formaldehyde (HCHO). However, it was HCHO's acute effects that initially prompted the Federal government's effort to control HCHO exposures from Urea-HCHO foam (UFFI) installations and high HCHO emitting building materials in manufactured homes. Although attention has shifted to the potential human carcinogenicity, HCHO's other effects have the most immediate impact on persons and continue to generate a substantial number of consumer complaints. Consequently, this risk assessment will address HCHO's carcinogenic and noncarcinogenic effects.

1.1. Carcinogenic Effects

Formaldehyde (HCHO) is carcinogenic by inhalation in males and females of one strain of rat and in males of another strain, and there is evidence of its carcinogenicity in mice. In the CIIT study (Kern et al., 1983), HCHO produced tumors of a type with very low background rates after a short latency period and with a dose-response relationship. The same malignant tumors were also seen in the Albert Et al. (1982) and Tobe et al. (1985) studies. Negative studies in other species, in this case the hamster, do not reduce the weight given to the positive findings.

Other data support the bioassay data. HCHO's mutagenic activity has been shown in a number of tests and it has been

shown to be a weak promoter on mouse skin. HCHO has been shown to be capable of eliciting benign tumors at concentrations which fall within human exposure ranges and malignant tumors within an order of magnitude above estimated human exposure. In addition, other aldehydes which are structurally similar to HCHO, such as acetaldehyde, malondialdehyde, and glycidaldehyde, have been shown to have oncogenic potential. Finally, the existing epidemiologic data indicate that HCHO may be a human carcinogen.

The body of epidemiologic data does not demonstrate that HCHO is a human carcinogen because confounding due to exposure to other substances cannot be eliminated; however, the studies do suggest that HCHO may be a human carcinogen. Excess mortality from leukemias and brain cancers have been noted in a group of professionals who use formalin. In addition, two case-control studies show an association between nasal cancer and HCHO and wood dust.

EPA has determined that, based on its proposed Cancer Risk Assessment Guidelines, HCHO can be classified as a Group B1- Probable Human Carcinogen. This classification under the Guidelines means that EPA has determined that there is limited evidence of carcinogenicity to humans from epidemiologic studies and sufficient evidence of carcinogenicity from animal studies.

1.2. Other Effects

Acute effects, irritation of the eyes and upper respiratory system, are responsible for the majority of consumer complaints about HCHO. Most persons experience discomfort within the range

Preliminary Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde

DRAFT

May 1985

Risk Analysis Branch
Existing Chemical Assessment Division
Office of Toxic Substances

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Since 1979, when the preliminary results from the Chemical Industry Institute of Toxicology (CIIT) study indicated the formation of nasal cancer in rats, much attention has been focused on the potential human carcinogenicity of formaldehyde (HCHO). However, it was HCHO's acute effects that initially prompted the Federal government's effort to control HCHO exposures from Urea-HCHO foam (UFFI) installations and high HCHO emitting building materials in manufactured homes. Although attention has shifted to the potential human carcinogenicity, HCHO's other effects have the most immediate impact on persons and continue to generate a substantial number of consumer complaints. Consequently, this risk assessment will address HCHO's carcinogenic and noncarcinogenic effects.

1.1. Carcinogenic Effects

Formaldehyde (HCHO) is carcinogenic by inhalation in males and females of one strain of rat and in males of another strain, and there is evidence of its carcinogenicity in mice. In the CIIT study (Kern et al., 1983), HCHO produced tumors of a type with very low background rates after a short latency period and with a dose-response relationship. The same malignant tumors were also seen in the Albert Et al. (1982) and Tobe et al. (1985) studies. Negative studies in other species, in this case the hamster, do not reduce the weight given to the positive findings.

Other data support the bioassay data. HCHO's mutagenic activity has been shown in a number of tests and it has been

shown to be a weak promoter on mouse skin. HCHO has been shown to be capable of eliciting benign tumors at concentrations which fall within human exposure ranges and malignant tumors within an order of magnitude above estimated human exposure. In addition, other aldehydes which are structurally similar to HCHO, such as acetaldehyde, malondialdehyde, and glycidaldehyde, have been shown to have oncogenic potential. Finally, the existing epidemiologic data indicate that HCHO may be a human carcinogen.

The body of epidemiologic data does not demonstrate that HCHO is a human carcinogen because confounding due to exposure to other substances cannot be eliminated; however, the studies do suggest that HCHO may be a human carcinogen. Excess mortality from leukemias and brain cancers have been noted in a group of professionals who use formalin. In addition, two case-control studies show an association between nasal cancer and HCHO and wood dust.

EPA has determined that, based on its proposed Cancer Risk Assessment Guidelines, HCHO can be classified as a Group B1- Probable Human Carcinogen. This classification under the Guidelines means that EPA has determined that there is limited evidence of carcinogenicity to humans from epidemiologic studies and sufficient evidence of carcinogenicity from animal studies.

1.2. Other Effects

Acute effects, irritation of the eyes and upper respiratory system, are responsible for the majority of consumer complaints about HCHO. Most persons experience discomfort within the range

of 0.1 to 3 ppm HCHO. The eyes are generally the most sensitive. For most persons odor recognition occurs at about 1 ppm HCHO and can be a marker for acute effects. More serious effects occur at exposures above 3 ppm.

In addition to its sensory effect on receptors of the eyes, nose, and throat, HCHO also causes inflammation and cellular and tissue damage. Experiments in rats and monkeys indicate that chronic exposures over 1 ppm causes squamous metaplasia and hyperplasia. Also, subchronic exposures of 2 ppm or greater affect the mucociliary clearance system, causing mucostasis and ciliastasis. Ultrastructural changes to cilia may be occurring below 2 ppm. Possible impairment of the nasal mucociliary system (and other mucociliary systems of tne respiratory system) by HCHO has been linked to increased episodes of respiratory tract infections in children.

A small number of reports associate HCHO with allergic asthma-like symptoms. However, there are no sufficiently well-controlled studies to establish whether HCHO is an inhalant sensitizer.

On the other hand, HCHO is a well-known dermal sensitizer and irritant. After sensitivity is induced, concentrations which elicit allergic response range from as low as 30 ppm in a patch test to 60 ppm HCHO from actual use of formalin. HCHO causes allergic contact dermatitis (Type IV allergy) and probably immunologic contact urticaria (hives or rash) (Type I allergy). Nonallergic contact urticaria has also been reported from multiple exposure.

HCHO has been associated with a number of central nervous system (CNS) disturbances such as memory loss, irritability, and sleep disturbances. However, the human studies linking these CNS effects to HCHO have many technical and design faults which make the results questionable.

A limited number of reports have suggested that HCHO may cause reproductive disorders. However, no clear evidence exists to link HCHO to adverse reproductive outcomes. In addition, based on the available literature it is not likely that HCHO poses a risk as a potential human teratogen.

1.3. Exposure

Two exposure categories are of primary concern: those associated with manufacture of apparel from fabrics treated with HCHO-based resins and those who reside in conventional and manufactured homes containing construction materials in which certain HCHO-based resins are used. Based on the monitoring data available to EPA, the estimated exposure for apparel workers ranges from 0.17-0.64 ppm. The estimated 10-year average exposure to current manufactured home residents is approximately 0.20 ppm, while the 10-year average for manufactured homes under the new Housing and Urban Development (HUD) Manufactured Home Standard is 0.15 ppm. Exposures of conventional home residents are lower, less than 0.1 ppm. However, this segment is not well characterized, and exposures can be higher in new, energy efficient homes.

1.4. Risk Estimates

EPA estimates that there are approximately 800,000 apparel workers, 4,200,000 manufactured home residents, and >100,000,000 conventional home residents exposed to HCHO.

Model-derived 95% upper confidence limits (UCL) and maximum likelihood estimates (MLE) based on squamous cell carcinoma data range from 1×10^{-3} [B1] to 3×10^{-4} [B1] at the UCL and 6×10^{-7} [B1] to 4×10^{-9} [B1] at the MLE for apparel workers, 2×10^{-4} [B1] (UCL) and 1×10^{-9} [B1] (MLE) for manufactured home residents (at the HUD standard), and a minimum of 3×10^{-4} [B1] (UCL) and 7×10^{-12} (MLE) for conventional home residents. Associated maximum likelihood estimates are less than 1×10^{-6} for all catgories of concern. Risks based on polypoid adenoma data are approximately an order of magnitude greater for the exposures of concern.

Attempts to establish definitive dose-response relationships for acute effects have not been successful. Techniques used by the Occupational Safety and Health Administration (OSHA) and HUD have some limited value in determining the percent responding at any given HCHO exposure level. It appears that based on the current human studies only broad response ranges can be described. Consequently, for small differences in concentration, say 0.4 to 0.8 ppm, it is not possible to determine the change in response rates of a given exposed population. However, based on animal data, the NOEL for cellular effects in the nasal cavity is about 1 ppm. Because the mucociliary clearance system of the

nasal cavity is an important bodily defense system, subchronic exposures to HCHO greater than 1 ppm could be harmful. The margins of safety for the cellular and sensory effects at various HCHO exposures were examined. At the OSHA standard of 3 ppm there is no margin of safety. For garment workers small margins of safety exist except for eye irritation. The situation is essentially the same for home residents.

2. INTRODUCTION

In November 1979, EPA received information that the interim results of a 24-month bioassay in rats conducted by CIIT showed that a number of the rats had developed nasal cancer after inhalation of HCHO.

In November of 1980, the Federal Panel on Formaldehyde, formed by several Federal agencies under the aegis of the National Toxicology Program, published a report finding that CIIT's bioassay methodology was consistent with accepted testing standards. Using the data available through the 18-month point of the CIIT study, the Federal Panel concluded that "formaldehyde should be presumed to pose a risk of cancer to humans." Also in November 1980, CIIT presented the preliminary results of the full study. CIIT pathologists reported finding statistically significant increases, as compared with controls, in the incidence of malignant tumors in rats exposed to HCHO vapor at the highest of the three levels they tested.

In February 1982, based on its evaluation of the toxicity and exposure data on HCHO then available, EPA decided that, although HCHO had been found to be carcinogenic under the conditions of the test, the available information as to HCHO's cancer risk to humans did not meet the statutory criteria for priority designation under section 4(f) of TSCA.

To assist its evaluation of HCHO the Agency funded the National Center for Toxicological Research to sponsor a Consensus Workshop on Formaldehyde (the Workshop). The Workshop was held

in Little Rock, Arkansas from October 3 through 6, 1983. Over 60 government, industry, university, and public interest organization scientists served on the following eight Panels: (1) Exposure; (2) Epidemiology; (3) Carcinogenicity/ Histopathology/Genotoxicity; (4) Immunology/Sensitization/ Irritation; (5) Structure Activity/Biochemistry/Metabolism; (6) Reproduction/Teratology; (7) Behavior/Neurotoxicity/ Psychological Effects; and (8) Risk Estimation. Each Panel (except the Risk Estimation Panel) was charged with the task of reviewing the major scientific studies relevant to that Panel's area. Also, the Panel members were asked to address a number of discussion topics and prepare a consensus report addressing those topics.

When the Panel deliberations were finished, draft reports were provided to the Risk Estimation Panel. The Risk Estimation Panel was charged with the task of determining how the data could be integrated to make reasonable risk estimates for humans exposed to HCHO at various levels and through different routes.

The decision process of the February 1982 decision under section 4(f) of TSCA generated considerable controversy and formed the basis for a lawsuit by the Natural Resources Defense Council (NRDC) and the American Public Health Association (APHA) (NRDC v. Ruckelshaus, No. 83-2039, filed in the United States District Court for the District of Columbia, July 18, 1983).

In view of public controversy concerning the process and policy issues associated with the Agency's section 4(f) decision

on the cancer hazard of HCHO, EPA announced in the FEDERAL REGISTER of November 18, 1983 (48 FR 52507) its decision to rescind its February 1982 decision, and to ask the public to submit views, arguments, and data relevant to determining whether HCHO should be given priority consideration under section 4(f) of TSCA. Comments were due at EPA by January 17, 1984; EPA announced that it expected to reach a new decision by May 18, 1984.

On May 23, 1984 EPA announced in the Federal Register (49 FR 21898) that two HCHO exposure categories triggered section 4(f) of TSCA (possible widespread cancer risk). The exposures which led to the decision are those associated with manufacture of apparel from fabrics treated with HCHO-based resins and residence in conventional and manufactured homes containing construction materials in which certain HCHO-based resins are used. In addition, EPA also published on the same day an Advance Notice of Proposed Rulemaking (49 fR 21870) announcing the initiation of a full investigation of regulatory options for the two categories.

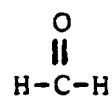
In addition to HCHO's potential cancer risks, HCHO's other effects should be considered in any action to reduce health effects from HCHO. The assessment of the risks from acute respiratory effects was prepared to be considered along with the carcinogenic risk assessment in the overall investigation of HCHO. The hazard discussion of noncarcinogenic effects in the risk assessment is based in part on reports from the Consensus Workshop on Formaldehyde, a report of the Cosmetic Ingredient

Review Expert Panel, a hazard assessment by Ulsamer et al. (1984), and the National Research Council report titled HCHO and other Aldehydes prepared under contract to EPA. The risk assessment focuses on the possibility of determining a dose-response for these noncancer effects because while many of the effects are well documented, the dose-response patterns in the human population are not. Methods used by HUD and OSHA to relate the proportion of the human population responding at particular exposure levels have been analyzed. In addition, EPA has reviewed selected human studies to determine if dose-response relationships can be described.

3. PHYSICAL-CHEMICAL PROPRETIES

HCHO is the simplest member of the aldehyde chemical category. It exists in many different forms. Pure monomeric formaldehyde is a colorless, pungent gas at ordinary temperatures. Aqueous formaldehyde, called formalin, is a clear, colorless solution containing about 37 percent by weight of dissolved formaldehyde in water, usually with 10 to 15 percent methanol added to prevent polymerization. The other forms of formaldehyde are polymers, the best known of which are paraformaldehyde and trioxane (trioxymethylene).

The molecular weight of HCHO is 30. It has the following structural formula:



The chemical name used by Chemical Abstracts Service is formaldehyde, and its Chemical Abstract number is 50-00-0. Synonyms* include formaldehyd; formaldehyde gas; formaldehyde solution; formalin; formalin 40; formalin 100%; formic aldehyde; methaldehyde; methanal; methyl aldehyde; methylene glycol; methylene oxide; oxomethane; oxymethylene; paraform; paraformaldehyde; polyoxymethylene glycols; α-polyoxymethylene; β-polyoxymethylene; tetraoxymethylene; α-trioxane; trioxane; and α-trioxymethylene.

*Includes synonyms for polymeric forms of HCHO.

The boiling and melting points for HCHO are -19°C and -118°C, respectively. Vapor pressure is 400 mm at -33°C. HCHO is soluble in water, acetone, benzene, diethyl ether, chloroform and ethanol (IARC, 1982).

4. HAZARD OF CARCINOGENIC EFFECTS

4.1 Long- and Short-Term Animal Tests

The first long-term study reporting the carcinogenicity of HCHO in animals by the inhalation route was one by Kern et al. (1983) (CIIT-sponsored study performed at Battelle Columbus Laboratories) which reported statistically significant increased levels of squamous cell carcinomas in the nasal cavities of rats at 14.3 parts per million (ppm). In the study, groups of approximately 120 male and 120 female Fischer 344 strain rats and C57BL/6 X $C3HF_1$ strain mice, were exposed by inhalation to 0, 2.0, 5.6, or 14.3 ppm of HCHO gas for 6 hours per day, 5 days per week, for 24 months. Squamous cell carcinomas were observed in the nasal cavities of 103 rats (52 females and 51 males) and 2 male mice exposed to 14.3 ppm of HCHO and in 2 rats (one male and one female) exposed to 5.6 ppm of HCHO gas. The incidence of nasal carcinomas in rats showed a dose-response relationship. See Table 4-1 for a summary of tumor response in rats.

Although the two squamous carcinomas in mice at 14 ppm were not considered by the investigators to be statistically significant in comparison with the incidence in control mice in the study, the finding suggests that the effect is related to HCHO exposure because the natural background rate for such nasal cancers is very low in this strain of mice, with only one neuroepithelioma and one angiosarcoma having been reported by Stewart et al., 1979 (Kern et al., 1983).

Table 4-1.
SUMMARY OF NEOPLASTIC LESIONS IN THE NASAL CAVITY OF FISCHER 344 RATS EXPOSED TO FORMALDEHYDE GAS*

Formaldehyde (ppm)	Sex	No. of nasal cavities evaluated	Squamous cell carcinoma	Poorly Differentiated carcinoma	Adeno-carcinoma	Undifferentiated carcinoma or sarcoma	Carcino-sarcoma	Polypoid adenoma	Osteo-chondroma
0	M	118	0	0	0	0	0	1	1
	F	114	0	0	0	0	0	0	0
2.0	M	118	0	0	0	0	0	4	0
	F	118	0	0	0	0	0	4	0
5.6	M	119	1	0	0	0	0	5	0
	F	116	1	0	0	0	0	0	0
14.3	M	117	51	0	1	2[a]	1	2	0
	F	115	52	1	0	0	0	0	0

*Table adapted from Kern et al. (1983)

[a] A rat in this group also had a squamous cell carcinoma.

The difference in susceptibility of rats and mice may be due, in part, to a greater reduction in respiratory minute volume in mice than in rats during exposure to an irritating agent. In a study by Chang et al. (1983) changes in minute volume, nasal cavity disposition, and cell proliferation were examined. It was found that mice exposed to 15 ppm HCHO for 6 hours experienced an approximately 50% reduction in minute volume. If a "dose" of HCHO is calculated from adjusting for reduction in minute volume and other data, it can be seen that for mice the dose received at 14.3 ppm in the Kern et al. (1983) study is one-half that received by rats at 14.3 ppm (see also Swenberg et al., 1983). Thus, the tumor response in mice at 14.3 ppm is comparable to the response in rats at 5.6 ppm. Interestingly, mice and rats at these exposures showed nearly identical tumor responses, i.e., two squamous cell carcinomas out of approximately 240 mice and rats.

In addition to the squamous cell carcinomas, small numbers of benign tumors characterized as polypoid adenomas were observed in rats at each dose level. These benign tumors did not exhibit a dose-response relationship. However, because this type of benign nasal tumor is rare in control rats it is likely related to HCHO exposure. For a further discussion of these lesions and their use in this risk assessment see Data Selection for Quantitative Analysis after this section.

Significant non-neoplastic lesions were also observed. See Figure 4-1 for type, severity, and locations. In rats at 2.0

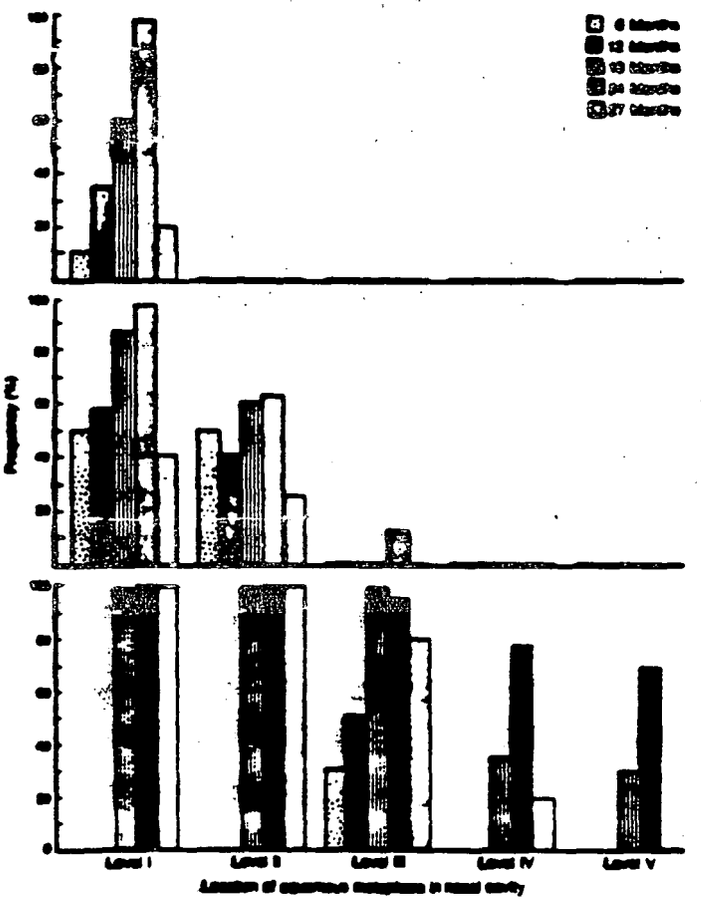


Figure 4-1. Frequency of squamous metaplasia in the nasal cavity of Fischer 344 rats exposed to 2.0 ppm (top), 5.6 ppm (middle), or 14.3 ppm (bottom) of formaldehyde gas for 24 months. Nasal cavity Levels I, II, IV, and V were not evaluated at the 6- and 12-month interim sacrifices in the 14.3 ppm exposure group. Figure taken from Kern et al. (1983).

ppm, purulent rhinitis, epithelial dysplasia, and squamous metaplasia were present in the anterior portion of the turbinates (Level I) at 12 months. The frequency of metaplasia increased up to 24 months and then decreased at 27 months (three months post exposure). In the 5.6 ppm group, purulent rhinitis, epithelial dysplasia, and squamous metaplasia were observed in the anterior and middle portions of the nasal cavity (Levels I, II, and III). Regression of squamous metaplasia was noted at 27 months. Similar lesions were observed in the 14.3 ppm exposure group in all regions of the nasal cavity. Regression of squamous metaplasia was only observed in the posterior portion of the nasal cavity (Levels IV and V).

Inflammatory, dysplastic, and squamous metaplastic alterations of the respiratory epithelium of mice were observed. These lesions were most severe in the 14.3 ppm exposure group (see Figure 4-2). A few mice in the 5.6 ppm group had dysplastic changes at 18 months. At 24 months, there were only a few mice with dysplasia, metaplasia, or serous rhinitis. Mice in the 2.0 ppm group were generally free of significnat lesions with only a few animals with serous rhinitis at 24 months.

One complication noticed during the Kern et al. (1983) study was a spontaneous outbreak in rats of sialodacryeoadenitis. The evidence for this consisted of (a) decreased body weight in all dosed and control rat groups at about the 52nd week of the experiment, followed by prompt recovery of body weight; and (b) histopathologic demonstration of typical lesions in lacrimal and

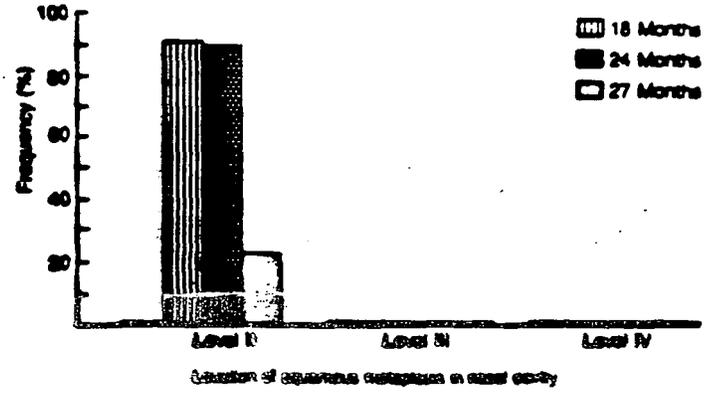


Figure 4-2. Frequency of squamous metaplasia in the nasal cavity of $B6C3F_1$ mice exposed to 14.3 ppm of formaldehyde gas. Figure taken from Kern et al. (1983).

salivary glands of dosed and control rats in the 12-month sacrifice groups. Evidence of sialodacryeoadenitis was not found in rats sacrificed at 6 or 18 months or in those with unscheduled deaths. Virus isolation, viral antigen demonstration, and serologic tests for antibodies were not attempted in rats or mice.

With regard to HCHO in the exposure chamber, a panel of experts reviewed the method of generation of HCHO and monitoring and agreed that "the Battelle approach to HCHO vapor generation was a suitable adaptation of accepted methods and principles and, therefore, was sound and based upon the best available technology. The same type of assessment applied to the chamber air monitoring system, which also combined two well established procedures" (Gralla et al., 1980).

Other studies support the results of the Kern (CIII) study. In two studies reported by Albert et al. (1982) (complete results for one study and preliminary results for the other), rats were exposed for life by inhalation to HCHO alone, mixtures of hydrochloric acid (HCL) and HCHO, or HCL alone.

In the first study, 99 male rats were exposed to a mixture of HCl and HCHO (premixed at high concentrations before introduction into the exposure chamber to maximize the production of bis(chloromethyl) ether (BCME)). This was done because the investigators were studying the hazard associated with the use of HCl and HCHO in close proximity in the workplace. A report had suggested the production of BCME from mixing HCL and HCHO gas. The average concentrations were 10.6 ppm HCL, 14.7 ppm HCHO, and about 1 part per billion (ppb) BCME. Of the 99 animals exposed to the test mixture, 25 developed squamous cell carcinomas of the nose. The contribution by the BCME was thought to be minimal because the expected response to 1 ppb of BCME was estimated to be less than 1.5 percent and there was a 25 percent incidence of nasal tumors in the study. In addition, BCME normally produces neurogenic carcinomas (mainly esthesioneuroepitheliomas), none of which were seen in the study.

The second Albert et al. (1982) study, in which male rats (100 per group) were exposed to HCL alone (10.2 ppm), premixed HCL-HCHO mixture (14.3 ppm HCHO/10.0 ppm HCL), nonpremixed HCHO-HCL mixture (14.1 ppm HCHO/9.5 ppm HCL), or HCHO alone (14.2 ppm), showed statistically significant numbers of squamous cell

carcinomas of the nasal cavity in the rats exposed to HCHO alone and the HCL-HCHO mixtures. A control group of 100 rats was used. No nasal cancers were seen in the HCL-only exposed rats or in the controls. Also, it appeared that the irritant HCL gas did not enhance the carcinogenic response of HCHO because the frequency of tumors was similar in the HCHO alone and HCHO-HCL groups. Table 4-2 displays final results as reported to OSHA by Albert (see OSHA, 1984).

In a study reported by Tobe et al. (1985), groups of 32 male Fischer 344 rats were exposed to HCHO for 6 hours per day, 5 days per week, for 28 months. The five test groups were as follows: colony control, room control, 0.3, 2.0, and 15 ppm HCHO. The significant finding was squamous cell carcinoma (14 cases) and papilloma (5 cases) in the 15.0 ppm group. No tumors were observed in the 0.3 and 2.0 ppm groups. Rhinitis, squamous metaplasia and hyperplasia of the nasal respiratory epithelium were observed in all HCHO exposed groups.

It should be noted that while the carcinoma response was similar between the Kern, Albert and Tobe studies, the benign tumor response was markedly different. In the Kern study only benign polypoid adenomas were observed, whereas in the Albert and Tobe studies benign papillomas were observed. The basis for these differences is difficult to explain. It could represent a strain difference or some unknown factor. (Tobe used the same strain of rats as Kern, Fischer 344, but the small number used at each dose as compared to Kern (32 vs. 240) may explain the

Table 4-2.
SUMMARY OF NEOPLASTIC LESIONS IN THE NASAL CAVITY OF SPRAGUE-DAWLEY RATS*

	Air controls (99 rats)	Colony controls (98 rats)	10 ppm HCL (99 rats)	14 ppm HCHO (100 rats)	Premixed 14 ppm HCHO & 10 ppm HCL (100 rats)	Non-premixed 14 ppm HCHO & 10 ppm HCL (100 rats)
Squamous cell carcinoma	0	0	0	39	45	27
Squamous cell papilloma	0	0	0	10	13	10
Fibrosarcoma	0	0	0	1	1	0
Adenocarcinoma	0	0	0	0	1	2
Esthesioneuroepithelioma	0	0	0	0	1	0
Polyp	0	0	0	0	0	1

*Data from OSHA (1984)

failure of polypoid adenomas to be detected.) Consequently, statements about the significance of these lesions in discussions of human risk must be approached with caution.

Two other chronic inhalation studies with HCHO designed to investigate possible cocarcinogenic effects of this agent in the upper and lower airways have been reported (Horton et al., 1963, and Dalbey et al., 1982). Since the nasal tissues were not systematically examined histologically, the value of these studies in assessing the carcinogenicity of HCHO is accordingly limited. In spite of these reservations, the studies have some bearing on HCHO carcinogenicity.

In the study reported by Horton et al. (1963), C3H mice were exposed to coal tar aerosol and/or to HCHO at concentrations of 40, 80, 160 ppm. Exposures were carried out for 1 hr/day, 3 days/week for 35 weeks, except for the 160 ppm group which was exposed only for 4 weeks because of toxicity. Only 15 mice survived to 1 year. There is no mention of histopathological evaluation of nasal tissues, so presumably no grossly visible tumors were observed. Coal tar aerosol exposure resulted in lung tumor formation in 5 animals (1 invasive carcinoma), but HCHO exposure did not. No evidence was found for any cocarcinogenic effects of HCHO. The major shortcomings of this study for evaluating the carcinogenicity of HCHO are that too few animals survived past one year, the individual exposures were short, most groups were exposed only for 35 weeks, and histopathology was inadequately reported.

In a study by Dalbey et al. (1982) male Syrian golden hamsters were used to study the chronic effect of HCHO and diethylnitrosamine (DEN). In the first part of the study, 88 hamsters were exposed to 10 ppm HCHO, 5 times/week for lifetime. There were 132 untreated controls. The second part of the study examined HCHO's promotional potential. For the second part of the study the hamsters were divided into 5 groups: 50 untreated controls; 50 hamsters exposed to 30 ppm HCHO, 5 hrs/day, 1 day/week for life; and 3 groups receiving DEN injections of DEN (0.5 mg, once per week for 10 weeks). Of the three groups receiving DEN, one consisted of 100 hamsters receiving only DEN, a second group of 50 hamsters were exposed to 50 ppm (5 hrs) of HCHO 48 hours prior to each injection of DEN, and the third group was exposed to 30 ppm HCHO (5 hrs/day, 5 days/week) for life, beginning 2 weeks after the last DEN injection.

In the hamsters exposed to 10 ppm HCHO for life there was no evidence of carcinogenic activity. Toxic effects of HCHO in the nasal cavity were limited to hyperplastic and metaplastic areas in 5% of the hamsters. No hyperplasia or metaplasia was observed in the controls. The incidence of rhinitis was similar in both control and exposed hamsters, and was not considered to be related to exposure of HCHO.

Caution must be exercised when comparing this part of the Dalbey et al. (1982) study with the Kern et al. (1983) study. One factor that should be considered is that the pathological

evaluation in the Dalbey et al. (1982) study was less rigorous. Only 2 sections of the nasal turbinates were examined as compared to sections taken from 5 anatomical levels of the nasal cavity of rats in the Kern et al. (1983) study.

Also, the Kern et al. (1983) study used three HCHO exposure levels (2.0, 5.6, and 14.3 ppm) whereas only 10 ppm of HCHO was used in the Dalbey et al. (1982) study. If one compares the ppm-hrs/week received by rats at 5.6 ppm in the Kern study and hamsters at 10 ppm, one sees that the ppm-hrs/week for the hamster is equivalent to a hypothetical dosing regimen of 8.3 ppm for rats (5.6 ppm X 6 hr/days X 5 days = 168 ppm-hrs/week vs. 10 ppm X 5 hr/days X 5 days = 250 ppm-hrs/week; this is equivalent to $\frac{250 \text{ ppm-hrs}}{6\text{h/d} \times 5\text{d/wk}}$ = 250 ppm-hrs/wk ÷ 6 hr/day X 5 d/wk = 8.3 ppm). Since only two squamous cell carcinomas were seen in the Kern et al. (1983) study out of 240 rats at 5.6 ppm, the likelihood of detecting a tumor in the Dalbey et al. (1983) study, which used 88 hamsters, is poor. In fact, there is a 30% probability that the absence of tumors is due to chance.

Finally, it is well established (Kane et al., 1979 and Buckley et al., 1984) that many sensory irritants decrease the respiratory rate of exposed animals. For rats the RD50 (concentration required to reduce respiratory rate by 50%) is approximately 32 ppm and for mice it is 3.1 ppm. If one assumes that the sensory irritant response is found in hamsters (little data have been developed on the hamster in this regard) (see Alarie, 1985), it is possible that the hamsters in the Dalbey et

al. (1982) study reduced their respiratory rate at the 10 ppm level by some percentage, say 20 percent. This would be the equivalent of a hypothetical exposure of 6.6 ppm in the Kern et al. (1983) study which would further lessen the chance of detecting a tumor response.

Although an RD50 value has not been reported for hamsters, a study by Feron et al. (1978) comparing the responses of hamsters, rats, and rabbits to acrolein vapor indicates that hamsters may resemble mice more in their respiratory response to HCHO than rats. The hamsters were slightly affected (nasal cavity lesions) at 1.4 ppm and severely affectd at 4.9 ppm by the acrolein. In contrast, rats were slightly affected at 0.4 ppm and were more severely affected at 1.4 and 4.9 ppm. This response is similar to the difference in response (nonneoplastic lesions) between rats and mice in the Kern et al. (1983) study where rats were affected at all dose levels whereas mice, because of a lower RD50 value for HCHO, were affected only slightly at 5.6 ppm and more seriously at 14.3 ppm. Since the mouse RD50's for acrolein and HCHO are 1.7 ppm and 3.13 ppm respectively (Kane et al., 1977), which indicates that acrolein is a more potent sensory irritant, one would expect that rats would experience more severe lesions fron acrolein at exposure levels below those of HCHO that evoked responses in the Kern et al. (1983) study. This is in fact the case. In a study by Rusch et al. (1983), rats were unaffected at 1.0 ppm HCHO, whereas in the Feron et al. (1978) study rats were affected at 0.4 ppm (acrolein). Thus, it seems, plausible that

hamsters are more like mice in their response to certain sensory irritants.

In the second part of the Dalbey et al. (1982) study no tumors were observed in untreated hamsters or those hamsters receiving only HCHO. However, 77% of the DEN-treated controls had a tumor (adenomas) at ten or more sites in the respiratory tract. Although HCHO exposure concurrent with or after DEN treatment did not increase the number of tumor-bearing animals (TBA), the number of tumors/TBA (tracheal tumors) was nearly doubled over DEN-only controls when HCHO was administered concurrently with DEN treatment, whereas post-HCHO treatment had no measurable effect. Thus, under conditions of the test, HCHO appears to be able to act as a cofactor in chemical carcinogenesis. However, there was a corresponding decrease in lung tumors in hamsters exposed to both agents, this suggests that the effect on the trachea may be within the limits of experimental variability (Consensus Workshop on Formaldehyde, 1984).

In a study by Rusch et al. (1983) groups of 6 male Cynamologus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Syrian golden hamsters were exposed to 0, 0.20, 1.0 and 3.0 ppm HCHO for 22 hrs/day, 7 days/week, for 26 weeks. The most significant finding was squamous metaplasia/ hyperplasia in rats and monkeys at 3.0 ppm, little or no response was seen at the lower exposure levels. Hamsters did not show any significant responses at any exposure level. The results from

this study indicate that concentration may be more important than total dose if squamous metaplasia/hyperplasia is the response measured when the results are compared to those of the Kern et al. study. In the Kern study squamous metaplasia was found in rats in the 2.0 ppm exposure group during the course of the exposure (2.0 ppm 6 hr/day, 7 days/week, for life). However, in the Rusch et al. (1983) study rats exposed to 1.0 ppm HCHO had no squamous metaplasia even though they received a total dose 2.5 times that received by the rats at 2.0 ppm in the Kern et al. (1983) study. However, this study was inadequate to show a neoplastic response because of the small number of animals and its short duration.

The carcinogenicity of HCHO also has been tested by a variety of other routes of administration including subcutaneous injection in rats (Watanabe et al. 1954, 1955), ingestion by mice and rats (Della Porta et al. 1968, 1970), and application to the buccal mucosa in rabbits (Meuller et al., 1978). Because of shortcomings in experimental protocols, none of these studies permits firm conclusions regarding HCHO carcinogenicity. Nonetheless, some of the studies give definite clues that HCHO may be carcinogenic to a variety of target tissues as well as to a variety of animal species (and not only to the nasal epithelium of rats).

The most revealing study in this regard is that by Meuller et al. (1978) who applied a solution of 3% formalin to the oral mucosa of rabbits, using an "oral tank." Each exposure lasted

for 90 minutes and was repeated 5 times per week for a period of 10 months. As a result, 2 out of 6 rabbits developed grossly visible leukoplakias that, according to the authors, showed histological features of carcinoma *in situ*. Unfortunately, the information given on the histomorphology of the lesions is very scanty.

Other experiments which suggest that HCHO produces carcinogenic effects are those by Watanabe et al. (1954, 1955), who injected rats (strain unknown) subcutaneously with formalin and with hexamethylenetetramine (HMT, from which HCHO is liberated *in vivo*).

However, several other studies carried out with HMT by Brendel (1964) who administered HMT by gavage to rats and Della Porta et al. (1968, 1970) who administered HMT in drinking water to mice and rats, resulted in negative findings. The significance of these finding must be tempered by the fact that chemicals often give disparate results by different routes of exposure. For example, hexamethylphosphoramide (HMPA) is a potent nasal carcinogen by inhalation, but was not carcinogenic in rats fed HMPA for 2 years (Lee et al., 1984).

A study by Klenitzky (1940) in which "formol oil" was applied 50 times to the cervix uteri of mice resulted in no tumors.

Finally, a study by Spangler et al. (1983) has been interpreted as showing weak promoting activity of HCHO on mouse skin. However, in another study by Krivanek et al. (1983) no

promotion was observed when nonirritating applications of HCHO were used (Consensus Workshop on Formaldehyde, 1984).

4.2. Data Selection for Quantitative Analysis

As discussed above, there are a number of studies available which indicate the carcinogenic potential of HCHO. For the purpose of Quantitative Risk Assessment, the Agency generally chooses a well-designed and conducted study that uses the most sensitive species of animal.

In the case of HCHO, only one multidose, long-term study is available, the Kern et al. (1983) study (CIIT study). This study has been reviewed by a number of panels (IRMC, 1984; Consensus Workshop on Formaldehyde, 1984) and has been found to be of sufficient quality for risk estimation purposes. The selection of the Kern et al. (1983) is consistent with EPA's proposed Carcinogen Risk Assessment Guidelines (EPA, 1984a). Since squamous cell carcinomas were the only statistically significant malignant tumors observed in the study, they will be used for quantitative risk assessment. A small number of benign tumors, were also observed. The Guidelines state that benign tumors should be combined with malignant tumors for risk estimation unless the benign tumors are not considered to have the potential to progress to the associated malignancies. The following discusion explores this question.

4.2.1. Polypoid Adenomas/Other Tumors Observed

In the Kern et al. (1983) study, a small number of polypoid adenomas were reported in the rats: 1, 8, 6, and 5 adenomas in

the 0, 2.0, 5.6, and 14.3 ppm groups, respectively. Because a number of questions were raised about the accuracy of the diagnosis of these lesions, they were reexamined by a pathology working group (PWG) (Boorman, 1984; Consensus Workshop, 1984). The results of the PWG reexamination are as follows: 1, 8, 5, and 2 adenomas in the 0, 2.0, 5.6, and 14.3 ppm groups, respectively. However, two adenomas diagnosed at 2.0 ppm and one at 5.6 ppm were borderline calls between focal hyperplasia and small benign tumors. See Table 4-3 for a breakdown by dose and sex. In addition, two lesions originally diagnosed as nasal carcinomas were rediagnosed as adenocarcinoma and poorly differentiated carcinoma which were thought to be morphologically related. This has relevance to the following discussion of the potential of polypoid adenomas to progress to a cancer.

Table 4-3.
INCIDENCE OF POLYPOID ADENOMA AS REPORTED BY PWG

Sex	DOSE (ppm) 0	2.0	5.6	14.3	Total	Statistically Significant[a]
M	1	4*	5**	2	12	No
Nasal cavities evaluated***	(118)	(118)	(119)	(117)		
F	0	4	0	0	4	No
Nasal cavities evaluated	(114)	(118)	(116)	(115)		
Combined	1	8	5	2	16	Yes at 2.0 ppm
Nasal cavities evaluated	(232)	(236)	(235)	(232)		

[a]One tailed Fisher exact test.
*Two tumors in this group were judged to be borderline lesions between small benign tumor and focal hyperplasia.
**One tumor in this group was judged to be a borderline lesion between small benign tumor and focal hyperplasia.
***From Kern et al. 1983.

The PWG was asked to speculatea about the possible progression-of the polypoid adenomas. The consensus of the PWG was that there was no evidence that polypoid adenomas progressed to squamous cell carcinomas and that they should not be combined with squamous cell carcinomas for statistical purposes (Boorman, 1984). This recommendation was accepted by the Risk Estimation Panel of the Consensus Workshop on Formaldehyde (1984). However, a small number of other cancers were seen in the Kern et al. (1983) study. These included one adenocarcinoma, one poorly differentiated carcinoma, one carcinosarcoma, and two poorly differentiated carcinoma/sarcoma. The Carcinogenicity/ Histopathology/Genotoxicity Panel of the Consensus Workshop on Formaldehyde (1984) stated that "[T]he polypoid adenomas can be evaluated separately and in combination with the nonsquamous carcinomas that were observed in the 14 ppm rats." It is possible that one of these lesions may represent the malignant counterpart of polypoid adenoma. However, the nature and progression of benign nasal tumors is not well understood.

Studies by Lee et al. (1984), Takano et al (1982), and Reznik et al. (1980) have examined the morphology of nasal tumors in rats caused by exposure to hexamethylphosphoramide (HMPA), 1,4-dinitrospiperazine, and 1,2-dibromo-3-chloropropane, respectively. In the Reznik et al. (1980) study, 78% of the tumors in males and 66% in females in the low dose group were benign (adenomas and squamous-cell papillomas). However, in the high dose group 89% and 76% of the tumors in males and females,

respectively, were malignant (adenocarcinomas and squamous-cell carcinomas). It does not appear that the shift from primarily benign tumors at the low dose to primarily malignant tumors at the high dose means that the benign tumors were progressing to their malignant counterparts. Most of the benign tumors were located in the anterior part of the nasal cavity, while most of the malignant tumors were located in the region of the ethmoturbinates and the posterior part of the nasal septum. Adenomas and adenocarcinomas were often seen in rats at the same time and dose, but in different parts of the nasal cavity.

In the Takano et al. (1982) study, 5 different proliferative lesions were seen: simple hyperplasia, papillary hyperplasia, nodular hyperplasia, papilloma, and carcinoma (mostly adenocarcinomas). Papillary hyperplasia and papilloma were mainly located in the anterior regions of the nasal cavity. Nodular hyperplasia and adenocarcinoma, on the other hand, were found in the posterior regions. Also, these pairs of lesions often coexisted in their respective locations. The conclusion of the authors was that papillary hyperplasia progresses to papilloma and that nodular hyperplasia progesses to adenocarcinoma.

The studies by Lee et al. (1982, 1984) showed that HMPA caused mainly epidermoid (squamous cell) carcinomas (71%), adenoid squamous carcinoma (15%) and squamous cell papilloma (8.2%). (A small number of adenomatous polyps were seen with adenoid squamous carcinomas.) The squamous cell papillomas were

mostly exophytic, which may indicate that they may not represent the benign counterpart of the epidermoid carcinomas for two reasons. First, in the Takano et al. (1982) study, nodular hyperplasias rather than papillomas seemed to progress to adenocarcinomas. Second, the papillomas and nodular hyperplasias are similar to human exophytic and inverted papillomas, respectively. In humans, carcinomas apparently arise from inverted papillomas rather than exophytic papillomas.

The experience with other chemicals (see Lee et al., 1982) and the foregoing illustrate the variability of the types and locations of the tumors found. In addition, except in limited cases, the progression of preneoplastic and benign neoplasms to malignant neoplasms is not known with any assurance. Also, although some studies of chemicals show a tumor profile that is predominantly benign at low doses and malignant at high doses (NTP, 1982a; NTP, 1982b) other studies, such as of HMPA, show primarily malignant tumors at all dose levels eliciting a response. This may be the result of a speed-up of the carcinogenic process at higher doses in the former case or as in the latter one the chemical may be so potent that even at low doses progression is completed before termination of the study.

In the Kern et al. (1983) study, two main types of tumors were seen: polypoid adenomas and squamous cell carcinomas. In discussing these two lesions the Consensus Workshop on Formaldehyde (1984) recommended that they not be combined "for risk estimation because of differences in the cell type of

origin." However, the Conference did recommend that they be evaluated separately and in combination with the nonsquamous carcinomas. Since an adenocarcinoma and a morphologically similar carcinoma were seen in the study, the polypoid adenomas may represent the benign counterpart of these lesions. However, the PWG stated that these lesions might arise de novo, originate from submucosal glands, arise in polypoid adenomas, or a combination of the above. Also, the PWG stated that "not enough information was available about nasal cavity tumors to predict the possibility of benign tumors progressing to carcinomas." As for the possibility that the polypoid adenomas may be the benign counterpart of carcinosarcomas, this seems unlikely due to different tissue type. Added to this are the lack of dose-response, diagnostic uncertainties (3 of the 12 tumors were borderline calls), and the poor statistical significance of these lesions.

Finally, as discussed earlier, in the Albert et al. (1982) and the Tobe et al. (1985) studies papillomas rather than polypoid adenomas were observed and in the Kern et al. (1983) study only polypoid adenomas were observed. This intraspecies (and intrastrain since Tobe et al. and Kern et al. used Fischer 344 rats) difference also adds weight to the uncertainty in using the polypoid adenoma data for risk estimation purposes. Whether the difference in benign tumors observed is due to a strain difference is not clear. However, the separate appearance of two distinct types of benign tumors further calls into question the

significance of these lesions regarding their ability to progress to squamous-cell carcinomas and their relevance in estimating human risk.

Consequently, because there are so many uncertainties associated with the polypoid adenoma data, it is recommended that (1) they not be combined with squamous cell carcinomas (pooling) for statistical purposes, and (2) risk estimates should be generated separately using the polypoid adenoma data (see Sections 7.2 and 7.4).

4.3. Short-Term Tests: Mutagenicity/Genotoxicity

HCHO has been shown to produce mutations in a wide range of test systems. Mutagenic activity of HCHO has been demonstrated in viruses, Escherichia coli, Psendomonas pluonescens, Salmonella typhimurium, and certain strains of yeast, fungi, Drosophila, grasshopper, and mammalian cells (Ulsamer et al., 1984). HCHO's ability to cause single strand breaks in DNA, DNA-protein cross-links, sister chromatid exhanges (SCE), and chromosome aberrations has been demonstrated (Consensus Workshop on Formaldehyde, 1984).

In vitro studies have shown HCHO's ability to transform BALB/c 3T3 mouse cells, BHK 21 hamster cells, and C2H-10T1/2 mouse cells and to enhance the transformation of Syrian hamster embryo cells by SA7 adenovirus, and to inhibit DNA repair (Consensus Workshop on Formaldehyde, 1984). HCHO also causes increases in the frequencies of observed mutations in the presence of other mutagens, such as X-rays, ultraviolet

radiation, and hydrogen peroxide. Compared to strains of E. coli and Saccharomyces cerevisiae with normal repair mechanisms, HCHO caused greater lethal and mutagenic effects in excision repair-deficient strains (Ulsamer et al., 1984).

In reviewing much of the above literature, the Consensus Workshop on Formaldehyde (1984) "found that the recent work is more likely to find HCHO a mutagen than earlier studies, and is also more likely to show a dose-response relationship. These results are most probably attributable to the greater sophistication in the way the later assays were carried out. It should be noted that in the above studies, the relationship between the cytotoxicity induced by HCHO and mutagenicity or transformation induced by this agent is typical of most mutagens/carcinogens that are positive in these assays. The data we have reviewed are consistent with HCHO acting as a weak mutagen (i.e., less than a ten-fold increase over background)."

In a study by Grafstrom et al. (1983) using cultured bronchial epithelial and fibroblastic cells, HCHO's ability to cause the formation of cross-links between DNA and proteins, cause single-strand breaks in DNA, and inhibit the resealing of single-strand breaks produced by ionizing radiation has been shown. HCHO also inhibited the unscheduled DNA synthesis that occurs after exposure to ultraviolet irradiation or to benzo-[a]pyrene diolexepoxide, but at doses substantially higher than those required to inhibit the resealing of X-ray induced single-strand breaks.

As a follow-up to the above study, Grafstrom et al. (1984) investigated the repair of DNA damage caused by HCHO in human bronchial epithelial cells and fibroblasts, skin fibroblasts, and DNA excision repair-deficient skin fibroblasts from donors with exeroderma pigmentosum. Exposure of these cell types to HCHO caused similar levels of DNA-protein cross-links (DPC) and DPC removal in all cell types. The half-life for DPC's was about 2-3 hours. An examination of the induction and repair of DNA single-strand breaks (SSB) showed that the production of SSB was dose dependent, and that the removal of SSB occurred at rates similar to the removal of DPC. In addition, the results indicate that exposure to HCHO causes SSB without the involvement of excision repair, and that excision repair of HCHO damage may increase the SSB frequency. HCHO also enhanced cytotoxicity of ionizing radiation and N-methyl-n-nitrosaourea in normal bronchial epithelial cells and fibroblasts. The authors speculated that the inhibition of DNA-repair probably involves the interaction of HCHO with cellular proteins of importance in DNA repair. They noted that the repair of DNA lesions caused by ultraviolet radiation has been shown to be inhibited by alkylating agents.

In a related study, Grafstrom et al. (1985) investigated the effect of HCHO on the repair of O^6-methylguanine and the ability of HCHO to potentiate the mutagenicity of N-methyl-N-nitrosourea (NMU) in normal human fibroblasts. When rate of DNA repair was measured for NMU-treated cells that were incubated with HCHO, a significantly lower rate of DNA repair was observed compared to

NMU-treated cells. The authors proposed that HCHO inhibits DNA repair by binding to the active site of O^6-alkylguanine DNA alkyltransferase. Also, although NMU and HCHO are weak mutagens, addition of HCHO to NMU-treated cells resulted in a significantly higher mutation frequency than was found with HCHO or NMU alone. The increase may be due to HCHO inhibiting O^6-methylguanine repair (Grafstrom et al., 1985).

A recent study by Casanova-Schmitz et al. (1984) has reported the difference between metabolic incorporation and covalent binding in the labelling of macromolecules in rat nasal mucosa and bone marrow by inhaled [^{14}C]- and [^{3}H] HCHO. Rats were exposed to labelled HCHO at concentrations of 0.3, 2, 6, 10, or 15 ppm for 6 hrs, one day following a single pre-exposure to the same concentration of unlabelled HCHO. The principal finding reported by the authors was the apparent nonlinearity in the amount of covalent binding of HCHO to DNA of the respiratory mucosa. The amount of HCHO covalently bound to mucosal DNA at 6 ppm was reported to be 10.5 times higher that at 2 ppm, whereas covalent binding to protein increased in a linear manner with increases in HCHO concentration. No covalent binding was noted in tissues from the olfactory mucosa or bone marrow. The apparent nonlinear covalent binding of DNA between 2 and 6 ppm has been used as an input in quantitative estimation of risk from HCHO exposure (Starr et al., 1984).

The interpretation of the results from the Casanova-Schmitz et al. (1984) study have been intensively reviewed (Cohn et al., 1985) The principal conclusions of the reviewers are as follows:

1. The implication that the number of DNA-protein cross-links is important to risk assessment must be viewed in light of the facts that the mechanism of formaldehyde carcinogenesis is presently unknown, and that formaldehyde may contribute to carcinogenesis in more ways than directly damaging the genome (Cohn, 1984). The relationship between DNA-protein cross-links and carcinogenesis has not been defined for formaldehyde or other chemical carcinogens.

2. The assertion that the measurement made "is a direct measure of the dose of formaldehyde that reacts with DNA" requires proof that the parameter measures the result of all agent reactions with DNA, including DNA adducts, reactions with cellular nucleic acids (Beland et al., 1984; Feldman, 1975; Wilkins and MacLeod, 1976), and possible DNA small molecule cross-links, etc. Approximately 80% of DNA-protein cross-links are eliminated in one hour (Wilkins and McLeod, 1976), a fairly rapid repair which may not be characteristic of all formaldehyde DNA damage, such as stable DNA-formaldehyde adducts (Beland et al., 1984). Also, there is no reason to expect that short-term exposure is representative of chronic exposure. In fact, there is evidence to the contrary since cell proliferation decreases after 9 days (Swenberg et al., 1983), and squamous cells eventually replace respiratory epithelial cells (CIIT, 1981), processes which occur long after the experiment terminates.

3. The assertion that the authors are measuring DNA-protein cross-links needs to be validated by actual characterization of the DNA fractions by sensitive analytical techniques. In this regard, other work has shown that the great majority of radiolabel associated with DNA after exposure of either "naked" DNA or tissue culture cells to radiolabeled formaldehyde, in the absence of the use of $NaBH_4$, is noncovalently bound HCHO (Beland, 1983). If $NaBH_4$ is used, the adduct profile is not altered (F.A. Beland, personal communication).

4. Caution is indicated when attempting to estimate isotope ratios due to metabolic incorporation. For example, if the isotope ratios observed in olfactory mucosal interfacial DNA rather than those in respiratory mucosal aqueous DNA are used to indicate the ratios resulting from metabolism, similar to what is done for proteins by the authors, the relationship of administered dose, and "covalently bound" DNA is not demonstrably nonlinear throughout the entire dose range, especially when the

"nonlinearity" between 6 and 2 ppm referred to by CIIT is examined. The authors indicate that olfactory mucosal interfacial DNA contains no DNA-protein cross-links, and since it is isolated by the same method as respiratory mucosal interfacial DNA, it is likely to be more structurally similar to respiratory mucosal interfacial DNA and may therefore be the more appropriate control for the endpoint of DNA-protein cross-links. The result also demonstrates the sensitivity of the experiment.

5. The paper as published cannot be adequately evaluated because it excludes the specific activity of the administered doses, and actual counts. Using these data (provided to us separately by the authors), the specific activity for the administered dose is much lower than doses usually used for in vivo studies. The resultant "DNA binding" is, however, quite high. For example, at 6 ppm, the binding is approximately one adduct per 10,000 nucleotides, approximately 10 to 100 times higher than that observed in "naked" DNA or in tissue culture for formaldehyde binding (Beland, 1984) or cross-links (Wilkins and MacLeod, 1976); it is also very high when compared to binding of even chronically administered "strong" carcinogens with an intense biological effect (Poirier et al., 1983; Swenberg et al., 1984). These facts again urge caution in interpretation of the measurements as DNA-protein cross-links. Also, the (dpm - background) values for a number of points, especially those at the lower doses, are low (151, 176 for ^{3}H, and 121, 123 for ^{14}C at 0.3 and 2.0 ppm, for example), necessitating special care in measurement and interpretation.

Various studies have been undertaken to determine whether HCHO has genotoxic effect in vivo. In mice, the dominant lethal test was found to be negative (doses up to 40 mg/kg, IP). However, in a more recent dominant lethal assay using higher doses (50 mg/kg, IP) and a different mouse strain, marginally positive results were obtained, but only in the first and third week of the seven weeks studied (Consensus Workshop on Formaldehyde, 1984). However, the positive response obtained may not be indicative of a mutagenic change for the following reasons:

1. The week to week variation in implantations data are common in dominant lethal studies. Therefore, concurrent controls should be included in each weekly mating. It is not clear from the paper how the control matings were conducted; the control value is shown as a mean with no indication of the extend of weekly variation in control population.

2. The index of implantation deaths should probably be analyzed on the basis of "per pregnant female" and not on the total numbers as done in the paper.

3. Preimplantation losses as shown in week 1 and 3 should be viewed as an index of dominant lethal effect only if the losses were found to be due to death of preimplants and not due to failure of oocytes to become fertilized.

(IRMC Report on Systemic Effects, 1984)

Negative results were obtained when the induction of micronuclei or chromosomal aberrations were used as an endpoint. A small increase in SCE's has been reported in the bone marrow of mice exposed to high (>25 ppm) HCHO concentrations. Unfortunately, technical problems were encountered during the HCHO exposures, and the actual concentrations required to elicit this effect are not known (Consensus Workshop on Formaldehyde, 1984). In a recent study by Ward Jr. et al. (1984) measuring changes in sperm morphology, mice were treated by gavage with five consecutive daily doses of formalin (100 mg/kg; 10 animals). No increase in abnormal sperm morphology was obseved in the treated mice.

The possibility of genetic effects in humans caused by inhalation of HCHO has been investigated by a number of persons.

In an unpublished study by Spear (1982), significant numbers of SCE's in eight students exposed to HCHO during an anatomy laboratory class were found. Mean HCHO levels were 1 ppm during dissections. However, no genetic effects in humans were seen in

studies by Fleig et al. (1982), Ward Jr. et al. (1984), and Thomson et al. (1984).

In the study by Fleig et al. (1982), 15 employees exposed to HCHO during HCHO manufacture and processing were studied. The employees had 23 to 35 years of exposure. Mean HCHO levels did not exceed 5 ppm before 1971 and 1 ppm after that date, with most workers exposed to a maximum of 0.25 ppm (post 1971). No increase in chromosome aberrations was observed as compared to controls. Similarly, in a study of pathology staff exposed to HCHO by Thomson et al. (1984), no difference in chromosome aberrations induction and SCE frequencies was seen between the exposed and control groups (6 exposed and 5 controls). Time-weighted average levels of HCHO ranged from 1.14 to 6.93 mg/m^3, with peaks greater than 11.0 mg/m^3. The pathology workers were generally exposed to HCHO for 2-4 hours per day, 2-3 days per week. Finally, in the Ward Jr. et al (1984) study, sperm count, morphology, and fluorescent body frequency in 11 autopsy service workers exposed to HCHO and 11 controls were evaluated. Time-weighted average HCHO levels ranged from 0.61 to 1.32 ppm (weekly exposure range 3-40 pm hours). No significant differences in the endpoints studied were observed between exposed and control groups.

4.4. Other Effects/Defense Mechanisms

4.4.1. Introduction

The cancer response observed in the Kern et al. (1983) study was very nonlinear, 1% of the rats responded at 5.6 ppm while 50%

responded at 14.3 ppm. A number of hypotheses have been developed which attempt to explain this response and the different responses seen in rats and mice in that study. These hypotheses are based on the noncarcinogenic effects of HCHO. Although these noncarcinogenic effects are not easily separated, it is possible to discuss them in three subject areas: sensory irritation; cell-proliferation; and the mechanics of the mucous layer "defense" system.

4.4.2. Sensory Irritation

In the Kern et al. (1983) study, the response observed in mice as compared to rats is markedly different, 2 mice responding at 14.3 ppm versus 103 rats responding at this concentration. Also, in studies using hamsters (Dalbey et al., 1982), no tumor response was seen. One of the reasons given for the difference between rats and mice is the observation that mice exposed to 14.3 ppm reduce their breathing rate in response to the irritant properties of HCHO. Such an effect may be occuring in hamsters at the doses tested, but experimental evidence is lacking. How reduction in breathing rates (which is an effective defense mechanism at certain concentrations) is weighed in terms of HCHO cancer risk assessment is discussed below.

It is well established that sensory irritants evoke responses by stimulating the free nerve endings of the afferent trigeminal nerve located in the corneal, nasal, and oral mucosa. Besides burning sensations, sensory irritants cause a number of physiological reflex responses, one of which is a

decrease in respiratory rate. A number of chemicals have been studied in this regard and have RD50's established for them. The RD50 value is that concentration of an irritant that causes a 50% reduction in respiratory rate. A proposal to use RD50's to establish concentration standards for human exposure to sensory irritants has been made (see Kane et al., 1979; and Buckley et al., 1984). A number of chemicals have been investigated and RD50 values established, including HCHO and hydrogen chloride. Consideration of this effect may be important in interpreting inhalation bioassays because a doubling of a nominal concentration to which an animal is exposed may not result in a doubling of the dose actually received by the animal. For instance, the RD50 value of HCHO for Swiss-Webster mice is 3.13 ppm. Consequently, results from a study using a dosing regimen with concentrations above and below this number should be interpreted in the light of the fact that the dose actually received by the test animals does not increase in the same proportion as the nominal concentration.

In the case of the Kern study, experimental data (Chang et al., 1981; 1983) indicate that mice exposed to 14.3 ppm HCHO reduced their breathing rate to such an extent that an adjusted exposure concentration would show the mice being dosed with approximately the same amount of HCHO as rats at 5.6 ppm, where the same cancer response was observed. If this factor is wholly responsible for the difference in response between rats and mouse, then adjusted doses can be used to calculate risks from

mouse data. Thus, it can be postulated that if mice could be exposed to levels of HCHO that would approximate the amount rats received at 14.3 ppm, then the response in mice would be similar and estimated risks would parallel those estimated from rat data. If mice are less sensitive than rats to HCHO's carcinogenic potential, then the risk would be less. However, experimental data in this regard are lacking, and there is no evidence that mice would be more or less sensitive to HCHO on a dose received basis. Since experimental data regarding the respiratory response of hamsters to sensory irritants is lacking, one can only surmise from the bioassay data that hamsters are less sensitive to HCHO's carcinogenic properties. EPA's proposed guidelines address this point by stating, "Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations." It should be noted that all the rat inhalation studies of HCHO (Kern et al., 1983; Albert et al., 1982; and Tobe et al., 1985) had comparable response rates at 14 ppm HCHO. If one looks at the cancer data for acetaldehyde, one sees roughly comparable responses in hamsters and rats at similar dose levels, although the anatomical location of the effects are different. This raises the possibility that the carcinogenic response of hamsters and rats

to closely related aldehydes may be similar. However, much data needs to be developed in this regard.

In conclusion, the weight of the evidence indicates that mice are more sensitive to the sensory effects of HCHO than rats, and it may be this response which accounts for the different carcinogenic response observed in rats and mice in the Kern et al. (1983) study. Adjusting dose levels for this response shows that mice may be as sensitive as rats to the carcinogenic potential of HCHO. Hamsters, on the other hand, appear to be less sensitive to HCHO, although the response of hamsters and rats to acetaldehyde is similar, which presents the possibility of comparable responses to HCHO (as discussed in the section on animal tests, two factors may account for the absence of an observed effect in hamster; pathology, and the lack of a multi-dose test). Consequently, as provided for in the Guidelines, the selection of the rat data for risk estimation purposes is justified.

Finally, although a reduction in respiratory rates is a defense mechanism at certain concentrations and above, its practical importance to low-dose risk estimation is nil provided that when quantitative risk estimation is done, dose levels are adjusted, if necessary, to reflect the actual dose received thereby ensuring an accurate dose-response. This defense mechanism is not indicative of a threshold or nonlinearity at low doses.

4.4.3. Cell Proliferation, Cytotoxicity, and the Mucous Layer

Another important consequence of HCHO's irritant properties is its effects on cell proliferation and damage it can cause to the mucociliary clearance system (respiratory and olfactory epithelium) of the nasal cavity. These effects have been cited (Starr et al., 1984) as important factors in HCHO induced carcinogenicty from the standpoint of their impact on the mucociliary clearance system, as a prerequisite for HCHO induced cancer, and in understanding the importance of concentration versus cumulative exposure. These factors have an important impact on the model chosen for quantitative risk assessment and the weighing of noncarcinogenic effects as a cancer risk factor.

4.4.3.1. Cell Proliferation and Cytotoxicity

Studies by Swenberg et al. (1983) and Chang et al. (1983) have reported the relationship between HCHO concentration and cumulative exposure on cell turnover in the nasal cavity of rats and mice. A diagram indicating the coding of the nasal cavities of rats and mice for the test data discussed below is provided in Figure 4-3.

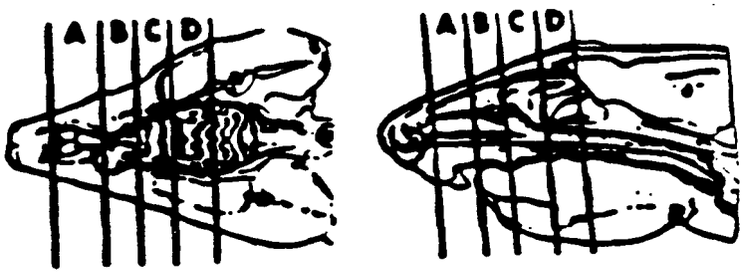


Figure 4-3. Drawing indicating the level of sections from the nasal passages of rats and mice. Figure taken from Swenberg et al. 1983.

In one test, rats and mice were exposed to 0, 0.5, 2, 6, and 15 ppm HCHO 6 hrs/day for 3 days, and then to ^{3}H-thymidine 2 hours after the end of exposure. As illustrated in Table 4-4, increased cell proliferation as measured by increased incorporation of labelled thymidine into cells was evident in rats at 6 and 15 ppm and in mice at 15 ppm.

Table 4-4.
EFFECT OF FORMALDEHYDE EXPOSURE ON CELL PROLIFERATION IN LEVEL B OF THE NASAL PASSAGES*

Exposure*	% of Labelled Respiratory Epithelial Cells***	
	Rat	Mouse
Control	0.22 ± 0.03	0.12 ± 0.02
0.5 ppm	0.38 ± 0.05	0.09 ± 0.04
2 ppm	0.33 ± 0.06	0.08 ± 0.04
6 ppm	5.40 ± 0.82	0.15 ± 0.06
15 ppm	2.83 ± 0.81	0.97 ± 0.04

*Table taken from Swenberg et al. (1983).
**All animals exposed for 6 hrs/day for 3 days.
***Mean ± standard error.

When the labelled thymidine is administered 18 hours after the last exposure, a greater increase in cell turnover is seen as illustrated in Table 4-5. The increase in cell labelling may be because 2 hours post exposure may not be the most sensitive time for DNA synthesis due to initial inhibition by HCHO (Swenberg et al., 1983).

Table 4-5.
EFFECT OF THE TIME OF ^{3}H-THYMIDINE PULSE ON CELL REPLICATION AFTER HCHO EXPOSURE TO RAT*

Post-Exposure Time of Pulse	% Labelled Cells**	
	0/ppm	6 ppm***
2 hours	0.26 ± 0.03	1.22 ± 0.17
18 hours	0.54 ± 0.06	3.07 ± 1.09

*Table taken from Swenberg et al. (1983).
**Mean ± standard error.
***6 ppm, 6hr/day for three day.

To determine whether concentration is more important than cumulative dose, a series of concentration time products were tested. Each product equaled 36 ppm-hrs of exposure. The results of this test, which appear in Table 4-6, indicate that, at least for the effect measured, concentration has a greater affect in level B of the rat nasal cavity.

Table 4-6.
EFFECT OF HCHO CONCENTRATION vs. CUMULATIVE EXPOSURE ON CELL TURNOVER IN RATS (Level B)*

Exposure	% Labelled Cells**	
	3 days + 18 hrs	10 days + 18 hrs
Control	0.54 ± 0.03	0.26 ± 0.02
3 ppm X 12 hrs	1.73 ± 0.63	0.49 ± 0.19
6 ppm X 6 hrs	3.07 ± 1.09	0.53 ± 0.20
12 ppm X 3 hrs	9.00 ± 0.88	1.73 ± 0.65

*Table taken from Swenberg et al. (1983)
**Mean ± standard error.

However, the amount of labeling measured in the most anterior region of the nasal cavity indicates the opposite. The extent of labeling was essentially the same at each HCHO exposure level. See Table 4-7 for details.

Table 4-7.
EFFECT OF HCHO CONCENTRATION vs. CUMULATIVE EXPOSURE ON CELL TURNOVER IN RATS (Level A)*

Exposure	% Labelled Cells After 3 Days Exposure**
Control	3.00 ± 1.56
3 ppm X 12 hrs	16.99 ± 1.50
6 ppm X 6 hrs	15.46 ± 10.01
12 ppm X 3 hrs	16.49 ± 2.07

*Table taken from Swenberg et al. (1983)
**Mean ± standard error.

Whether this difference in cell proliferation between levels A and B is due to differences in mucocillary clearance in the respective regions, to HCHO-laden mucous flowing from posterior to anterior regions (Swenberg et al., 1983) or simply that the "capture" capacity of Level A is exceeded which allows pass-by of HCHO to Level B and beyond, or some other reason, is unknown.

The data developed on mice regarding cell proliferation are not as clear. In a test to measure differences between concentration and cumulative exposure there was an inverse response as illustrated in Table 4-8.

Table 4-8.
EFFECT OF HCHO CONCENTRATION vs. CUMULATIVE EXPOSURE ON CELL TURNOVER IN MICE (Level A)*

Exposure	% of Labelled Cells After 10 Days Exposure**
Control	1.24 ± 0.57
3 ppm X 12 hrs	10.14 ± 3.20
6 ppm X 6 hrs	4.72 ± 1.61
12 ppm X 3 hrs	1.76 ± 0.49

*Table taken from Swenberg et al. (1983).
**Mean ± standard error.

The difference between rats and mice has not been adequately explained, except that there appears to be a significant species difference regarding cell proliferation.

A study by Rusch et al. (1983) supports the concept that concentration may be more important than cumulative exposure, at

least for rats. In the study, five groups of 6 male Cynomologus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Syrian golden hamsters were exposed to 0, 0.2, 1.0, and 3.00 ppm for 22 hrs per day, 7 days per week for 26 weeks.

The most significant finding was squamous metaplasia/ hyperplasia in rats and monkeys at 3.0 ppm. Hamsters were not affected at any dose level. However, the most significant finding is that even though rats at 1.0 ppm in the Rusch et al. (1983) study received a cumulative exposure 2.5 times greater than rats at 2.0 ppm in the Kern et al. (1983) study, which experienced squamous metaplasia, they were largely free of squamous metaplasia. This strengthens the conclusion of the Swenberg et al. (1983) study which indicates that, at least for rats, concentration is more of a factor than cumulative exposure.

In the Kern et al. (1982) study, significant levels of noncarcinogenic lesions were noted in rats at all dose levels. The severity and extent of these lesions were concentration and time dependent and seem to be correlated with the cancer response, i.e., these lesions preceded the appearance of squamous cell carcinomas and their severity increased with increasing cancer response. This observation, tied with the data showing increases in cell proliferation due to HCHO exposure and a threshold for squamous hyperplasia/metaplasia of between 1 and 2 ppm, leads some to the hypothesis that there is a threshold for HCHO's carcinogenicity or that the dose-response is nonlinear at low doses. Another factor suggested to contribute to the

possibility of a threshold between 1 and 2 ppm HCHO, is the role of the mucous layer in trapping and removing HCHO in this range. This hypothesis is that when its removal capacity is exceeded, HCHO can then impact the respiratory epithelium, thus causing the noncarcinogenic effects noted above. A discussion of the role of the mucous layer follows this section.

As noted previously, there was a 50 fold increase in cancer response due to a slightly more than a doubling of the dose in the Kern study (5.6 to 14.3 ppm). What was the change in response of the noncarcinogenic effects? Using data developed for the incidence of squamous metaplasia in rats in the Kern study, a comparison can be made. The incidence of squamous metaplasia in level 2 of the rat nasal cavity was chosen because it showed a positive correlation with concentration rather than cumulative dose, moreover, it is in the middle of the anterior part of the nasal cavity where the squamous cell carcinomas were observed, and it is of the same cell type as the carcinomas. If one compares the percentage incidence of squamous metaplasia in the three dose groups at the sacrifice points in Table 4-9, one sees a clear dose-response, but not a 50 fold increase between 5.6 and 14.3 ppm; there appears to be only a 2 fold increase or less. While increased cell turnovers could lead to greater interaction of HCHO and single-strand DNA, and thus an enhancement of the cancer response, the data on the incidence of squamous metaplasia alone do not appear to explain the extreme nonlinearity observed.

Table 4-9.
FREQUENCY OF SQUAMOUS METAPLASIA IN LEVEL 2 OF THE RAT NASAL CAVITY*

Dose (ppm)	Incidence (Percent) of Squamous Metaplasia Month of Sacrifice				
	6	12	18	24	27
5.6	50	45	60	65	30
14.3	75	90	98	100	100

*Estimated from Figure 4-1.

Other chemicals such as acetaldehyde, hexamethyphosphoramide (HMPA), are cytotoxic and cause cancer in rats. What can the data on these chemicals tell us?

If one examines the incidence and severity of the noncarcinogenic lesions seen in the Feron et al. (1984) acetaldehyde study and the tumor response, one sees a roughly dose-related response, i.e., a doubling of dose doubles the response seen (cancer and noncancer). Although the olfactory epithelium was severely affected at the highest dose, the cancer response is hardly increased over the next lower dose (see the section on Structure Activity Relationships for a full discussion of the data on acetaldehyde).

An anatamical region that had a high incidence of noncancer lesions that were dose-related was the larnyx (mostly squamous metaplasia). Table 4-10 illustrates this response. However, only one tumor was observed in the larnyx.

Table 4-10.
INCIDENCE OF LESIONS OTHER THAN TUMORS
IN THE LARNYX OF RATS EXPOSED TO
ACETALDEHYDE [NUMERIC]*

	Dose (ppm)			
	0	750	1500	3000/1000
Number of Male Rats	50	50	51	47
Squamous metaplasia	3	6	23	41
Hyperkeratosis	1	4	13	32

*Data from Feron et al. (1984)

Finally, the relationship between the noncancer and cancer response seen in rats exposed to HMPA is unremarkable. As Table 4-11 indicates, an increase in dose did not lead to a many fold increase in the cancer response although HMPA severely damaged the nasal mucosa of the rats.

Table 4-11.
INDICENCE OF EPIDERMOID AND ADENOID SQUAMOUS
CARCINOMAS IN RATS EXPOSED TO
HEXAMETHYLPHOSPHORAMIDE*

Dose (ppb)	0	10	50	100	400	4,000
No. of Rats Examined	396	200	194	200	219	215
	Tumor Incidence (%)					
Epidermoid carcinoma	0	0	12.4	29.5	62.6	55.8
Adenoid squamous carcinoma	0	0	2.1	2.5	9.6	19.1

*Data from Lee et al. (1982)

As a general matter, it appears that there is no clear relationship between cell proliferation/cytoxicity and tumor response. It is clear that there is much variation in the way tissues respond to carcinogens, and no firm conclusions can be drawn. The appearance of noncancer lesions is not surprising given the acute toxicity of many carcinogens. However, it is impossible at this time to clearly link the noncancer effects in the Kern study to the appearance of cancers and the nonlinearity of the response. On the other hand, it is plausible that the noncancer effects may enhance the cancer response of HCHO and other carcinogens by providing an increased opportunity to interact with single-strand DNA during cell replication or to promote an initiated cell. Consequently, prudence would dictate that exposure at levels that cause cell proliferation or lesions be avoided. This includes short-term peaks especially if concentration is more important than cumulative dose. Also, it must be remembered that there is a natural background rate of cell turnovers in the nasal mucosa which can provide the opportunity for mutagenic/carcinogenic events to occur. Although such events may be rare, only one such sequence of events may need to occur in a population of 10,000 persons over 70 years to give a cancer risk of 1×10^{-4}.

Finally when discussing acute responses to a chemical such as irritating effects, it should be remembered that there can be a no-effect level at or below which no response is observed no matter how many days of exposure occur. However, once a minimum

effect concentration is reached, the duration of the exposure may have a major impact on the severity of the effect. Although the occurrence of squamous metaplasia and other responses to acute effects may influence the expression of a carcinogenic response, the absence of these acute responses does not signify a no-effect level for a carcinogenic response.

4.4.3.2. Mucous Layer

Besides HCHO's effect on cell proliferation and respiratory response, it also has a major impact on the mucociliary system of the nasal cavity through its irritation and cell killing properties at elevated concentrations. In addition, it has been postulated that below certain HCHO concentrations (1-2 ppm) the mucous layer can trap and remove inhaled HCHO, thus preventing it from reaching underlying cells. However, once the removal capacity of the mucous layer is exceeded, HCHO can then begin to affect the underlying cells as described in the section above. If the mucous layer removed inhaled HCHO below 1 ppm then it would represent a threshold phenomenon at least for the nasal cavity. However, the evidence for this is lacking and the idea is directly contradicted by experimental data. The discussion below describes the effects caused by HCHO on the mucocilary system and the support for the "barrier" action postulated.

The nasal cavity is primarily composed of ciliated respiratory and olfactory epithelium which is covered by a moving blanket of mucus. Mucus is composed of approximately 95% water and 0.5-1% glycoproteins and other minor constituents. The human

nose has three functions, two of which depend on the presence of a mucous layer. The first function of the nose is to inform us of the presence of noxious gases, if these stimulate the receptors of the olfactory nerves. The second function of the nose is to drain the secretions of the sinuses and of the lacrimal (tear) glands. The third function of the nose is to prepare the inhaled air for the lungs. This includes warming, moistening, and filtering inspired air. Dust and many bacteria found in the inspired air are precipitated in the mucous that bathes the mucous membrane and, by the action of the cilia of the nasal passage, are moved outward (Tuttle et al., 1969).

As research by Morgan et al. (1983a, 1983b, 1984) indicates, HCHO has a number of effects on the workings of the mucociliary apparatus. Using in vitro and in vivo techniques, Morgan et al. (1983a) examined mucous flow patterns in the rat nasal cavity and the effect of HCHO on the mucociliary apparatus. Results of the in vitro analysis indicate that mucus was present as a flowing continuous coat over the respiratory epithelium except on the most anteriorcentral extremity of the nasoturbinates and the anteriomedial extremity of the maxilloturbinates. Mucous flow rates ranged from 0.28 to 9.02 mm/minute. When rats were exposed to 15 ppm HCHO, 6 hrs per day for 1, 2, 4, or 9 days, mucostasis followed by ciliastasis was evident in a number of anatomical regions of the rat nasal cavity. In another study by Morgan et al. (1983b), male rats were exposed for 6 hours per day for 1, 2, 4 or 9 days, to 0.5, 2, 6 or 15 ppm HCHO. There was a clear

dose-dependent affect on mucociliary activity. At 15 ppm there was significant inhibition of mucociliary activity which progressed from anterior to posterior regions of nasal tissue. Only slight effects were noted in animals exposed to 2 or 6 ppm. At 0.5 ppm no effects were observed. Finally, using frog palate, Morgan et al. (1984) found that mucous stasis, and ciliastasis occurred at 4.36 and 9.58 ppm, respectively. At 1.37 ppm an initial increase in ciliary activity was observed but there was no mucous stasis or ciliastasis, while at 0.23 ppm there was no effect.

The above results indicate that a concentration relationship exists where mucociliary flow would be impaired at 15 ppm and less so at 6 and 2 ppm. This range corresponds to the range where the steep dose-response in carcinogenicity of HCHO was seen in the Kern et al. (1983) study. Whether the mucous layer has some finite capacity to absorb HCHO and wash it away to prevent it from reaching the underlying cells, or the response seen is simply the overt signs of gradual cell toxicity, is unknown. However, a number of factors must be considered when discussing the protective ability of the mucous layer. First, humans can detect HCHO at levels below 1 ppm which indicates that, at least in the olfactory region of the nasal cavity, HCHO is not completely removed by the mucous layer. The mucous layer is reported to be immobile or flowing extremely slowly in this region (CIIT, 1984). However, it would seem that if a greatly reduced removal capacity of the mucous layer in the olfactory

region played a role, this region should have been a target for effects in the Kern et al. (1983) study. This was not the case. The significant neoplastic and nonneoplastic effects were generally seen in the anterior regions of the rat nasal cavity.

Second, in a study by Casanova-Schmitz et al., 1984), which measured the difference between metabolic incorporation and covalent binding of labelled HCHO to macromolecules, it was found that covalent binding to protein increased in a linear manner with increases in airborne concentrations (0.3 - 15 ppm). These data do not support the concept that at doses lower than 1-2 ppm the mucous layer can act as a sink for inhaled HCHO which prevents it from reaching underlying cells.

Finally, no data have been presented that show that HCHO is bound and removed by the mucous layer. This is not to say that the mucous layer has no capacity for HCHO removal, but in the face of no pertinent data in this regard and the results of the Casanova-Schmitz et al. (1984) study discussed above, it must be concluded, at this time, that there is little support for a threshold effect due to the mucous layer. Although it is clear that HCHO disrupts the mucociliary system, this is more likely due to a gradual poisoning of mucosal cells once the thresold for deleterious effects is reached, and not because the removal capacity is exceeded.

4.4.3.3. Conclusion

In conclusion, it is consistent with some of the data described above to assume that HCHO's irritant and cytotoxic

properties may have contributed to the nonlinearity of the malignant tumor response seen in the Kern et al. (1983) study. HCHO's demonstrated ability to increase cell turnover could provide greater opportunity for HCHO to interact with nuclear material. As the concentration of HCHO increases, greater cell proliferation and cell death occur which provide even more opportunities for HCHO-DNA interactions. To what degree the mucous layer protects against HCHO's cytotoxic effects is not clear, but the experimental data do not suggest a large role for this. Although it seems probable that some HCHO could react with protein in the mucous layer, data have not been developed to show that the ratio between the airborne concentration and the amount entering target cells is nonlinear, on the contrary, data have been developed to show that it is linear. (Data relevant to the formation of HCHO-DNA adducts is discussed in another section--Short-Term Tests-Mutagenicity.) Regarding the impact of changes in respiratory response to sensory irritants, it is likely that this response is responsible for the different response of rats and mice in the Kern et al. (1983) study. Also, other data presented by Swenberg et al. (1983) indicate that rats only inhaled twice as much HCHO at 15 ppm as they did at 5.6 ppm, which indicates that the dose-response curve may be even steeper when tissue dose is plotted rather than concentration.

Thus, it seems likely that many of the factors outlined above have contributed to the differences seen among species in their response to HCHO as well as the steep dose-response seen in

the Kern et al. (1983) study. However, an examination of the data described in the sections above (1) does not support the concept that the action of the mucous layer presents a "barrier" to HCHO and thus a threshold for its carcinogenic effects, (2) that the appearance of and severity of noncancer lesions can be used to predict the nature of the cancer response, and (3) that the appearance of noncancerous lesions is a necessary prerequisite for cancer induction.

4.5. Metabolism and Pharmacokinetics

4.5.1. Absorption

HCHO can enter the body as a result of inhalation, ingestion, or dermal absorption. Absorption of HCHO through the upper respiratory tract in dogs has been estimated to exceed 95% of the inhaled dose (Egle, 1972). Studies by Heck et al. (1983) indicate that most of the radiolabel from radiolabelled HCHO inhaled by rats was found in tissues from the anterior portion of the nasal cavity (the concentration was 10-100 fold greater than other tissues). Radiolabel was found in other tissues, but it is unlikely given HCHO's rapid metabolism that the radiolabel found was HCHO. In another study by Heck et al. (1982a), the quantity of HCHO was measured in rat tissue before and after inhalation of HCHO or chloromethane. The analytical method used cannot distinguish between free and bound HCHO. Measured HCHO concentrations were as follows; 0.42 umol/g for nasal mucosa, 0.097 umol/g for brain, an 0.20 umol/g for liver. Inhalation of 6 ppm HCHO for 6 hrs/day for 10 days did not significally alter

the nasal mucosa HCHO concentration. Following oral exposure of dogs to HCHO, formate levels in the blood increased rapidly, indicating rapid uptake and metabolism (Malorny et al., 1965). Dermal absorption has been demonstrated in guinea pigs (Usdin and Arnold, 1979), but does not appear to be significant in comparison to inhalation or ingestion. Studies have also demonstrated the dermal absorption of [^{14}C] HCHO in rats and monkeys, and rabbits, respectively (Ulsamer et al. 1984). The chemical form of the radiolabel has not been determined, but it has been reported by Ulsamer et al. (1984) that data from in vitro diffusion studies using rabbit skin indicate that free HCHO cannot be detected enzymatically.

4.5.2. Pharmacokinetics

4.5.2.1. Conversion to formate

HCHO that enters the body appears to be converted rapidly to formate and CO_2 (Malorny et al., 1965; McMartin et al., 1979) or to combine with tissue constituents. The conversion of HCHO to formate occurs following intravenous (i.v.) infusion, subcutaneous injection, gastric intubation, or inhalation. Studies using i.v. infusion of 0.2M HCHO to dogs have shown that only a small amount of HCHO appears in the plasma during exposure (Malorny et al., 1965). This becomes undetectable within 1 hour after cessation of infusion. The peak formate concentration following HCHO infusion was the same as when formate (0.2M) itself was infused. The plasma half-life for formate (between 80 and 90 min.) was also similar. In the same study, HCHO could not

be detected after oral administration of 0.2M HCHO, although formate increased rapidly in the plasma with a half-life of 81.5 minutes.

Similar experiments using Cynomolgus monkeys, in which 0.2M HCHO was infused i.v., showed no accumulation of HCHO in blood (McMartin et al., 1979). The blood half-life was estimated to be 1.5 minutes. Similar half-lives for blood HCHO have been observed in rats, guinea pigs, rabbits, and cats (Rietbrock, 1969). Studies by Heck (1982b) have shown that [^{14}C] formate and [^{14}C] HCHO have similar distribution patterns in rat blood cells and plasma following i.v. injection, and follow the same decay curve. In a somewhat different experiment, McMartin et al. (1979) administered C^{14}-labelled methanol by gastric intubation. Again, HCHO could not be detected in the blood although formate levels increased rapidly. A study in which humans were exposed to HCHO gas (0.78 mg/m^3) for 3 hours also demonstrated a rapid rise in blood and urine formate levels (Einbrodt et al., 1976). In a more recent study by Heck et al. (1985), HCHO concentrations in the blood of rats and humans were investigated. The rats (8 exposed and 8 controls) were exposed to approximately 14.4 ppm HCHO for 2 hrs. Blood was collected immediately after exposure and analyzed by gas chromatography/ mass spectrophotometry. No significant differences were seen between exposed and control rats. Six human volunteers (4M, 2F) were exposed to 1.9 ppm of HCHO for 40 minutes. Venous blood was analyzed for HCHO levels before and after exposure. There was

not a statistically significant effect of exposure on the average HCHO blood concentrations of the volunteers. However, significant differences were seen in some of the subjects' (either decrease or increase) HCHO concentration between blood taken before and after exposure.

The rapid conversion of HCHO to formate occurred in many tissues in the various species examined, including human erythrocytes (Malorney et al., 1965), liver and brain; sheep liver; rat brain, kidney, and muscle, rabbit brain; and bovine brain and adrenals (Uotila and Koivusalo, 1974). The enzymes involved have been studied by Strittmatter and Ball (1975) as well by Uotila and Koivusalo (1974). The oxidative process is initiated by formation of S-formyl glutathione, which is then oxidized by NAD and finally cleaved by thiol esterase, releasing formic acid and glutathione. HCHO also has been reported to be oxidized to formic acid by a nonspecific aldehydehydrogenase and through the tetrahydrofolic acid pathway (Huennekens and Osborn, 1959).

4.5.2.2. Conversion to CO_2 and other metabolites

Additional studies (DuVigneaud et al., 1950) have shown that following subcutaneous administration of ^{14}C-HCHO to rats, approximately 81% of the radioactivity was found in choline. Almost 60% of a subcutaneous dose of ^{14}C-formate appeared as $^{14}CO_2$, with small amounts of radioactivity in choline. Neely (1964) administered radiolabelled HCHO intraperitoneally (i.p.) to rats and found that 82% of the radiolabel was recovered as CO_2

and 13-14% as urinary methionine, serine, and a cysteine adduct. At lower doses, only radiolabelled methionine was formed. The author postulated that CO_2 was derived from serine (formed from glycine and N^5,N^{10} methylene tetrahydrofolate) by deamination to pyruvate and oxidation in the Krebs cycle. In a study by Mashford et al. (1982), it was found that in rats administered 4 mg/kg of radiolabelled HCHO, most was exhaled within 48 hrs as CO_2; 5.5% was found in the urine. At a dose 10 times higher (40 mg/kg), 78% was exhaled as CO_2 after 48 hrs, while 11% was found in the urine. When HCHO was administered to rats by inhalation, 40% of the radiolabel was found in tissues, 40% was exhaled, and 20% appeared in the urine (Heck, 1982b). It was found by Heck (1983), that the greatest amount of radiolabel in the rat nasal mucosa was found in RNA, with a lesser amount in protein and a small amount in DNA.

The formation of methionine from ^{14}C-HCHO and homocysteine had previously been demonstrated by Berg (1951). Formation of methionine would also account for the labelled choline observed by Duvigneaud et al. (1950) via methylation of phosphatidyl ethanolamine. More recent work by Pruett et al. (1980) has demonstrated the incorporation of ^{14}C-HCHO into the nucleic acid and protein fractions of WI 38 human diploid fibroblasts. Most of the radiolabel was found in RNA with lesser amounts in DNA and protein. The purine bases of both DNA and RNA were most heavily labelled. Besides being converted rapidly to CO_2 and formate, and being incorporated into other chemicals, HCHO can alkylate

macromolecules such as amino acids, proteins, nucleotides, and DNA (Ulsamer et al., 1984). Casanova-Schmitz et al. (1984) have determined that DNA-protein cross-links are the only important reaction products of HCHO with DNA, but this assertion has been questioned by Cohn et al. (1985).

In addition to the serine pathway to CO_2 postulated above (Neely, 1964), two other pathways have been identified, and are diagrammed in Figure 4-4.

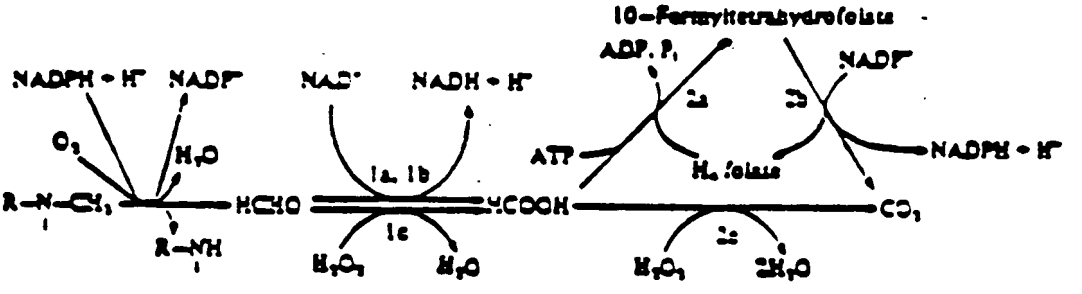
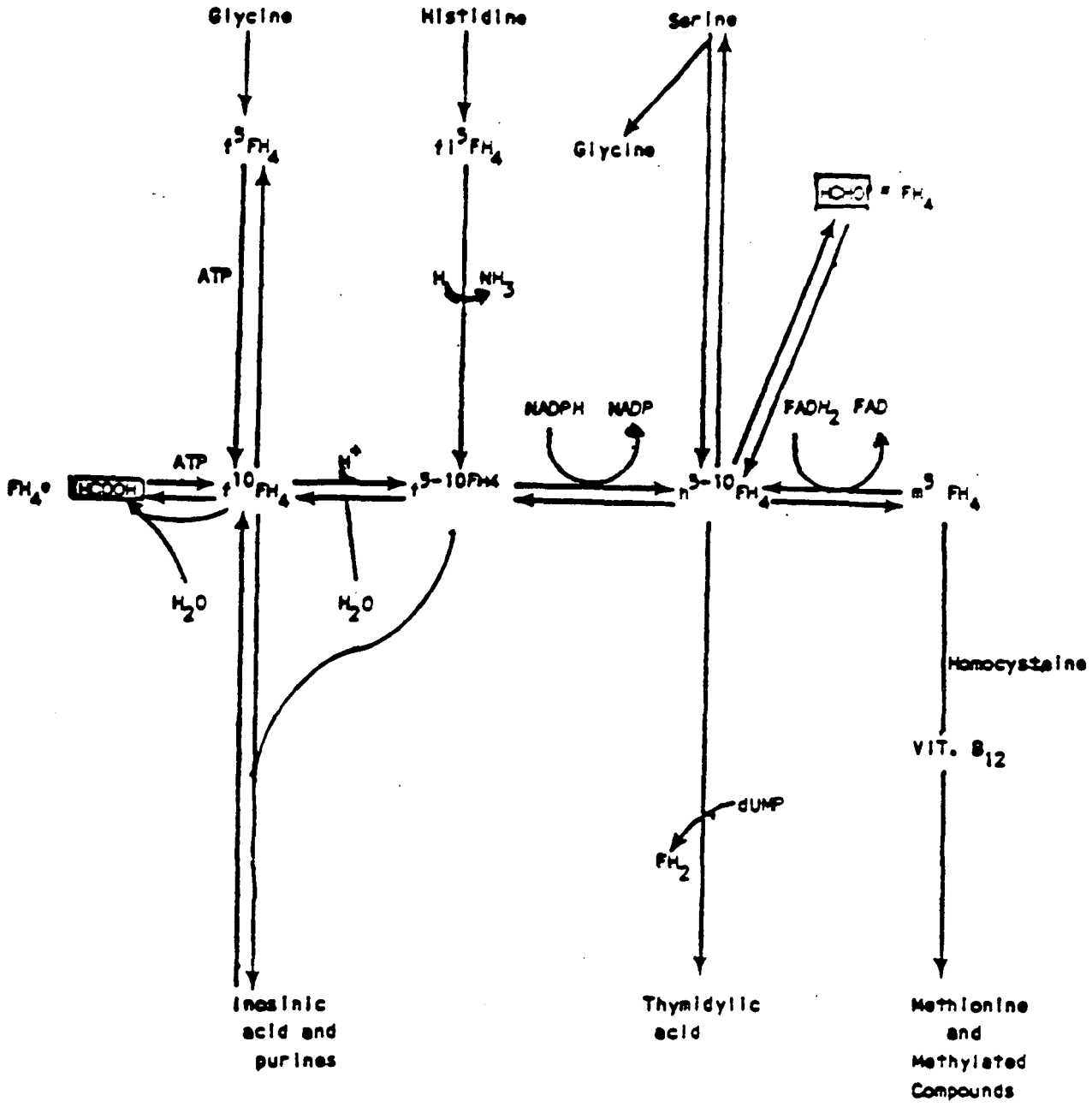


Figure 4-4. Simplified reaction sequence from drug N-demethylation (cytochrome-P-450-dependent monooxygenase) to HCHO, formate, and CO_2 production (from Waydhas et al., 1978). Reactions are: 1a, HCHO dehydrogenase (GSH); 1b, aldehyde dehydrogenase; 1c, catalase (peroxidatic mode); 2a, 10-formyltetrahydrofolate synthetase; 2b, 10-formyltetrahydrofolate dehydrogenase; 2c, catalase (peroxidatic mode).

Waydhas et al. (1978), McMartin et al. (1977), and Palese and Tephyl (1975) have demonstrated that the catalase reaction (Figure 4-4) is not of major importance and that the primary pathway to CO_2 from formate occurs via the tetrahydrofolic acid pathway. This has been demonstrated in rat liver perfusates (Waydhas et al., 1978) monkeys (McMartin et al., 1977), and rats (Palese and Tephly, 1975). Since the tetrahydrofolic acid pathway (Figure 4-5, from Kitchens et al., 1976) can lead to the transfer of the carbon from formate to a number of other compounds (including serine), it is not clear that the 10-formyltetrahydrofolate dehydrogenase reaction (Figure 4-4) is the only reaction of importance for CO_2 production in this pathway.



FH_4 = tetrahydrofolic acid

$f^{10}FH_4$ = N^{10}-formyltetrahydrofolic acid

$f^{5}FH_4$ = N^{5}-formyltetrahydrofolic acid

$f^{5-10}FH_4$ = N^{5},N^{10}-methenyltetrahydrofolic acid

$fi^{5}FH_4$ = N^{5}-formiminotetrahydrofolic acid

$h^{5-10}FH_4$ = N^{5},N^{10}-methylenetetrahydrofolic acid

Figure 4-5. Tetrahydrofolic acid pathway and 1-carbon transfer for HCHO metabolism.

4.5.2.3. Endogenous HCHO

Endogenous HCHO is primarily produced from the degradation of serine with some contribution from the degradation of other amino acids. Oxidative demethylation of N,N-dimethylglycine (from choline degradation) also contributes significantly to endogenous HCHO. Cytochrome P-450-dependent N-demethylation of drugs can contribute additional HCHO. The rate of HCHO oxidation to formate exceeded the rate of HCHO production in perfused rat liver by a factor of 12 when aminopyrine was used as the substrate for the demethylation reaction. Other xenobiotics including dihalomethanes, methanol, dimethylnitrosamine, hexamethylphosphoramide (HMPA), bis(chloromethyl) ether (BCME), dibromoethane, and dimethylsulfoxide lead to the production of HCHO. HCHO is also formed *in vitro* in the presence of an amine acceptor, apparently by nonenzymatic breakdown of N^5,N^{10}-methylene-tetrahydrofolate This reaction produces alkaloids from biogenic amines or drugs *in vitro* and probably *in vivo*.

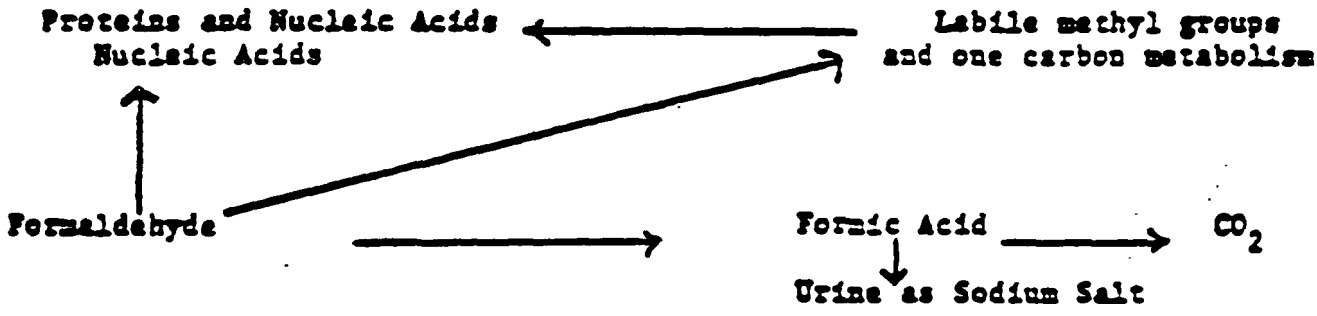
Whereas the conversion of HCHO to CO_2 occurs in a similar manner in the different species studied, the relative importance of each reaction differs among species and tissues. Thus, the rat is able to convert formate to CO_2 at more than twice the rate of monkeys (or humans) and, as a result, has lower blood formate levels (McMartin et al., 1977) and does not excrete formate in the urine (Neely, 1964). Man additionally possesses 50% more hepatic dehydrogenase than do rats (Goodman and Tephly, 1971).

Den Engelse et al. (1975) have shown that mouse (C3Hf/A) and hamster (Syrian golden) lungs do not convert formate to CO_2 as efficiently as liver tissue does.

4.5.3. Summary

In summary, free HCHO is not usually found in plasma or other body tissues in measurable quantities, endogenous HCHO that is produced may be reasonably presumed to be metabolized rapidly to formate or to enter the one-carbon pool. When exogenous exposure does occur, HCHO is likewise rapidly metabolized to formate and excreted, converted to CO_2 and/or incorporated into other molecules. The same pathways seem to occur in all mammalian species examined to date, but reaction rates differ among various species and tissues. Neither the ratio of metabolic deactivation to binding (to tissue or small molecules) nor the effect of route of exposure on this ratio is known at this time. Thus, although Egle's work (1972) suggests that the respiratory tract tissues would receive the greatest dose, other body sites cannot be ruled out.

The overall metabolism of HCHO is summarized in Figure 4-6 (adopted from Kitchens et al., 1976):



Figures 4-6. Overall metabolism of HCHO (from Kitchens et al., 1976).

As can be seen from Figure 4-6, HCHO is more chemically active than any of its direct metabolites and would, therefore, appear to be the chemical substance of most concern for carcinogenicity. The possibility exists, that the actual carcinogenic agent may be an amino acid (or other) adduct (EPA, 1981).

4.6. Structure-Activity Relationships

HCHO is structurally similar to other aldehydes such as acetaldehyde, malondialdehyde and glycidaldehyde. These aldehydes have been shown to have oncogenic activity in laboratory animals. For instance, inhalation of acetaldehyde has produced tumors of the nose and larynx in hamsters and tumors of the nose in rats, when administered by inhalation, and glycidaldehyde has produced skin tumors in mice in skin painting tests. Since acetaldehyde is the closest in structure to HCHO, and its effects on animals have been compared in a previous section, the significant studies related to its oncogenic potential will be described.

Acetaldehyde was not mutagenic in the standard Ames test using Salmonella typhimurium (Commoner, 1976) and Escherichia coli WP2uvrA (Hemminki et al., 1980). It had weak mutagenic activity in the fruit fly Drosophila melanogaster (Rapoport, 1948). The potential of acetaldehyde to damage chromosomes has been indicated by the dose-dependent sister chromatid exchanges in the Chinese hamster ovary cells (Obe and Ristow, 1977) and human lymphocyte cells (Ristow and Obe, 1978).

The carcinogenic effects of the inhalation of acetaldehyde vapor were studied in hamsters by Feron (1979). Male hamsters were exposed to 1500 ppm acetaldehyde vapor (7 hr/day, 5 days/wk) alone or simultaneously with benzo(a)pyrene (BP) as a weekly intratracheal injection for 52 weeks. The weekly concentrations of BP used were 0.0625, 0.125, 0.25, 0.5, and 1.0 mg/animal. The maximum dose of BP administered throughout the entire experiment was 52 mg/animal. Control animals were exposed to air alone or simultaneously with the same concentrations of BP. At the end of the treatment period, 5 randomly selected animals from each group were killed and autopsied. All remaining animals were allowed to recover for 20 weeks and sacrificed by week 72.

Exposure of hamsters to 1500 ppm acetaldehyde vapor produced abnormalities in the respiratory tract which were characterized primarily by reversible hyperplastic, metaplastic, and inflammatory changes. Neoplastic alterations attributable to acetaldehyde exposure alone were not found. Intratracheal instillation of the highest dose of BP (52 mg, 1 mg/wk for 52 weeks) combined with inhalation of acetaldehyde produced twice as many tracheal tumors (squamous cell carcinoma and squamous adenocarcinoma) and a shorter latent period as intratracheal instillation of BP alone. However, such a synergistic effect of acetaldehyde was not noticeable at any of the lower BP levels. No significant differences in the number of tumors in the larynx, bronchi, bronchioles, or alveoli were found among the different treatment groups.

In a separate experiment, male and female hamsters were treated intratracheally with acetaldehyde for a period of 52 weeks. The intratracheal instillations were given either weekly or fortnightly with acetaldehyde (2% and 4%) alone or in the presence of either BP (0.25% and 0.5%) or diethylnitrosamine (DEN, 0.5%), two proven carcinogens. Interim sacrifices of 3 animals/sex/group were performed after 13, 26, and 52 weeks. All remaining animals were sacrificed after 104 weeks.

Intratracheal administration of acetaldehyde at both dose levels caused severe hyperplastic and inflammatory changes in the bronchioalveolar region of the respiratory tract; however, only one case of pulmonary adenoma was found out of 134 animals treated with acetaldehyde alone. This is not considered to be an indication of carcinogenic activity of acetaldehyde. Despite the high degree and frequency of peribronchiolar adenomatoid lesions found following intratracheal instillation of acetaldehyde, the neoplastic response of the bronchioalveolar tissues was clearly lower in animals treated with BP plus acetaldehyde than in those given BP alone. Thus, acetaldehyde did not influence the carcinogenic effect of BP. Similarly, the carcinogenic effect of DEN was also not influenced by the treatment with acetaldehyde.

In another study, Feron et al. (1982), studied respiratory tract tumors in male and female hamsters exposed to high concentrations of acetaldehyde vapor alone or simultaneously with either benzo(a)pyrene (BP) or diethylnitrosamine (DEN) were studied. The animals were exposed 7 hrs/day, 5 days/wk for 52

weeks to an average concentration of acetaldehyde of 2500 ppm during the first 9 weeks; 2250 ppm during weeks 10-20; 2000 ppm during weeks 21-29; 1800 ppm during weeks 30-44; and 1650 ppm during weeks 45-52. Animals exposed to air or air plus BP or DEN served as controls. At the end of the exposure period (week 52), 3 animals per sex were taken from groups 1 and 2 for autopsy. All remaining animals were sacrificed after 81 weeks.

At the end of the exposure period, (i.e., at week 52) distinct histopathological changes, similar to those of the previous studies, were found in the nose, trachea, and larynges of animals exposed to acetaldehyde. No tumors were found in hamsters killed immediately at the end of the exposure period.

Acetaldehyde-exposed animals which were found dead or sacrificed at week 81 exhibited inflammatory, hyperplastic, and metaplastic changes in the nose and larynx, suggesting a persistence of those alterations. Tumors were encountered in the nose (adenoma, adenocarcinoma, anaplastic carcinoma) and the larynx (papilloma, carcinoma in situ, squamous cell carcinoma, adeno-squamous carcinoma); animals exposed to acetaldehyde plus BP or DEN also exhibited tumors of the trachea and the lung. The neoplastic and nonneoplastic lesions in the larynx were mainly located either on the true vocal folds or in the most anterior part of the larynx. None of the animals exposed to air alone demonstrated nasal or laryngeal tumors nor atypical laryngeal hyperplasia and metaplasia. The incidence of nasal and laryngeal tumors in hamsters exposed to acetaldehyde and treated with

either BP or DEN was similar to that found in hamsters exposed to acetaldehyde alone. Carcinomas in situ and squamous cell carcinomas of the larynges were found after combined treatment, but were not observed after treatment with either BP or DEN alone. Based upon these findings, the authors concluded that "acetaldehyde is an irritant as well as a carcinogen to the nose and larynx with a weak initiating and a strong 'promoting' (cocarcinogenic) activity" (sic).

Finally, in a study by Woulersen et al. (1984) male and female Wistar rats were exposed to 0, 750, 1500, and 3000/1000 ppm of acetaldehyde for 6 hrs/day, 5 days/week for up to 27 months. There was significant nonneoplastic lesions of the olfactory epithelium at each exposure level. In contrast, significant nonneoplastic lesions were seen in the respiratory epithelium only at the highest dose. Statistically significant numbers of adenocarcinomas were observed at each dose level in males and females. Squamous cell carcinomas were observed at the two highest dose levels in males and at the highest dose level in females. Most of the tumors originated from the olfactory epithelium. Table 4-12 presents summary tumor response of the nasal cavity for this study.

4.7. Epidemiologic Studies

Since 1981, findings from fourteen new studies have been made public, with another five studies forthcoming. The five as yet ongoing studies, are: a case-control study of nasal cancers by CDC, EPA's case-control study of nasal and pharyngeal cancers,

Table 4-12.
INHALATION CARCINOGENICITY OF ACETALDEHYDE IN RATS -- Summary of Nasal Tumors+

	Incidence of Tumors							
	Males				Females			
	0	750	1500	3000	0	750	1500	3000
Number of Rats	55 (49)	54 (52)	55 (53)	53 (49)	54 (50)	55 (48)	55 (53)	55 (53)
Papilloma	0	0	0	0	0	1	0	0
Early adenocarcinoma	0	2	7*	2	0	0	2	2
Adenocarcinoma	0	14*	23**	18**	0	6	26**	20**
Metastasizing adenocarcinoma	0	0	1	1	0	0	0	1
Carcinoma-in-situ	0	0	0	1	0	0	3	5
Early squamous cell carcinoma	0	0	1	3	0	0	0	3
Squamous cell carcinoma	1	1	9*	11**	0	0	5	14**
Metastasizing squamous cell carcinoma	0	0	0	1	0	0	0	0

+Table taken from Feron, 1984.

Figures in brackets represent the number of animals from which this tissue was examined microscopically.
In this table, a benign tumor is ignored if a malignant tumor of the same histogenetic origin is also present in the same tissues.
The absence of a numeral indicates that the lesion specified was not identified
Significance of differences in a pairwise (Fisher's) test between each treatment and control incidence: *$P<0.05$, **$P<0.01$.

an SMR study of HCHO-exposed workers by NCI and the Formaldehyde Institute, a prospective study by Partanen of industrial workers in Finland, and a cohort study of garment workers by NIOSH.

The new studies released since 1981 have broadened our knowledge regarding the potential carcinogenicity of HCHO. The new epidemiologic studies have contributed stronger evidence and have supported previous studies which suggested HCHO may be a human carcinogen. In particular, the Epidemiology Panel of the Consensus Workshop on Formaldehyde (1984) and the EPA (1984b) examined a group of studies and concluded that a group of professionals (anatomists, pathologists, embalmers, and undertakers) have a significantly increased mortality from leukemias and brain neoplasms. These excesses in mortality can not be attributed to diagnostic bias since these excesses remained when other professional or like socioeconomic groups were used as referents (Consensus Workshop on Formaldehyde, 1984). In addition, epidemiologic information in the form of one study and one abstract report increased nasal cancer risks with HCHO exposure.

Although all the studies are of cohort or case-control design, designs essential for judging causality, many of the studies suffer from limitations that influence their conclusions. Major drawbacks are: (1) the inability to separate the contributions of HCHO from the contributions of other occupational or personal exposures; (2) small sample sizes for the cohort studies; (3) insufficient follow-up; and (4) low statistical power.

One outcome of the design limitations has been low power in each study to detect small relative risks for rare forms of cancer.* The ability of a well-conducted study to detect an increased risk depends upon sample size, years of follow-up, magnitude of the increase, background incidence of the disease, desired statistical significance, and type of analysis.

The following text describes the current pool of epidemiologic data with study designs and findings highlighted. Table 4-13 identifies these studies. Tables 4-14 through 4-16 present selected power calculations for several of the studies shown in Table 4-13.

4.7.1 Review of Studies

Twenty-three studies of populations who may have been exposed to HCHO report findings of excess cancers. These studies are either cohort or case-control designed. Results are expressed as Standardized Mortality Ratios** or as odds ratios***. All findings are nonsignificant unless noted

*The power of a study is the ability to detect true association of the exposure and disease. If a study is likely to claim that the exposure is not associated with a disease, when in fact an association existed, it has a low power for detecting that association.
**Standardized Mortality Ratios (SMR), from cohort studies, are measures of the extent to which mortality in the exposed cohort under study compares to the mortality experience among unexposed persons. An SMR divided by 100 is called a risk ratio.
***The odds ratio, from a case-control study, gives the extent to which exposed individuals are represented among the affected cases more than among the controls to whom they are compared. If the disease under study is rare, the odds ratio is numerically very close to its associated SMR, but the causal inference is not as direct. In addition, an odds ratio obtained from a case-control study nested within a cohort design can be used to support conclusions from the cohort study.

Table 4-13.

Summary of Studies Relevant to Formaldehyde

Type of Study	Author	Study Group	Reference Group
PMR	Levine et al.	Ontario morticians (male)	U.S. white male age and calendar year-specific mortality rates
PMR	Harrington and Shannon	Pathologists	England, Wales or Scotland male age and calendar year-specific mortality rates
PMR	Tabershaw Associates	Chemical workers	U.S. age-sex and calendar year-specific mortality rates
PMR	Acheson et al.	Chemical workers	Male mortality rates of England/Wales
PMR	Harrington and Oakes	Pathologists	England and Wales, Scotland or Northern Ireland age-sex and calendar year-specific mortality rates
PMR	Stroup et al.	Anatomists	a) Psychiatrists; b) U.S. white male age-specific mortality
PMR	Dartenni et al.	Formaldehyde resin workers	National and local male specific mortality rates
PMR	Marsh	Chemical workers (male)	U.S. age-race-sex and calendar year-specific mortality rates
PMR	Walrath and Fraumeni	N.Y. embalmers and funeral directors	U.S. age-race and calendar year-specific proportions of deaths
PMR	Walrath	California embalmers	U.S. age-race and calendar year-specific proportions of deaths
PMR	Stayner et al.	Garment workers	U.S. age-race and calendar year-specific proportions of deaths
PMR	Ewell and Gafferman	Textile workers	U.S. age and calendar year-specific proportions of white female deaths
Case-Control	Fayerweather et al.	Chemical workers	One male employee matched for age, adjusted service date, plant location and pay class
Case-Control	Brinton et al.	Nasal and paranasal sinus cancer cases in N.C. and VA.	Two hospital controls or one hospital control and one deceased control matched for age, sex, race, state economic area of usual residence, and year of hospital admission
Case-Control	Vaio et al.	Nasal and paranasal sinus cancer cases in Finland	One non-respiratory cancer control matched for age and sex.
Case-Control	Hernberg et al.	Nasal and sinonasal cancer cases in Finland, Sweden, and Denmark	One colorectal cancer control matched for age-at-diagnosis, sex, and country.
Case-Control	Olsen et al.	Nasal and sinonasal cancer cases in Denmark	Colon, rectum, prostate or breast controls matched for age-sex-year of diagnosis
Case-Control	Huyen et al.	Nasal and sinonasal cancer cases in Holland	Living and deceased population controls

Table 4-14.

Power Calculations for SMR Studies[a]

Study	Size	Cancer Type	Observed	Expected	SMR	Least Relative Risk to detect with power[b] 80%	90%
Levine et al. morticians (1983)	1477	lung	19	21.3	89	1.6	1.8
		lymphatic/hematopoietic	9	7.2	125	2.2	2.5
		leukemia/aleukemia	5	2.9	175	3.1	3.7
		prostatic	2	3.1	65	2.9	3.4
		brain	3	2.5	118	3.2	3.7
		buccal cavity and pharynx	1	2.4	42	3.3	3.9
		nose	0	0.3	--	15.0	19.5
Harrington and Shannon (1975) pathologists	2079	lung, trachea and bronchus	11	27.9	39	1.5	1.6
		lymphopoietic	8	4.0	*200	2.8	3.3
		leukemia	1	1.6	63	4.2	5.1
Wong (1983) chemical workers	2026	respiratory	12	12.4	97	1.8	2.0
		lymphopoietic	6	4.4	136	2.6	3.0
		leukemia	2	0.6	308	7.2	9.0
		prostatic	4	1.3	305	4.3	5.2
		brain	3	1.6	188	4.3	5.0
Tabershaw Associates (1982) chemical workers	867	respiratory	3	5.5	54	2.5	2.9
		lymphopoietic	3	2.0	152	4.0	4.7
		prostatic	2	0.6	364	7.8	9.8
		brain/CNS	1	0.7	135	5.8	7.3
Acheson (1981) chemical workers	7716	lung	205	196.0	105	1.0[c]	1.0[c]
		lymphatic	20	26.3	76	1.6	1.7
		leukemia	9	11.4	79	1.8	2.0
		brain	5	12.5	40	1.9	2.1
		buccal cavity and pharynx	5	4.3	116	2.6	3.0
		nose	0	1.2	--	4.7	5.6
	RIP plant	lung	166	141.0	118	1.3	1.4
		nose	0	7.0	--	6.1	7.7
Harrington and Oakes (1982) male pathologists	2307	lung	9	22.0	41	1.6	1.8
		lymphopoietic	2	3.0	67	3.0	3.5
		leukemia	1	1.1	91	5.1	6.1
		brain	4	1.2	*331	4.7	5.6
Strom et al. (1984) anatomists	2239	respiratory	13	46.0	28	1.4	1.5
		lymphopoietic	24	17.0	141	1.7	1.9
		leukemia	10	6.7	148	2.2	2.5
		brain	10	3.7	*271	2.7	3.2
		buccal cavity and pharynx	1	6.7	*15	2.2	2.4
Bertazzi et al. (1984) formaldehyde resin mfg. workers	4462	lung	18	7.6	*237	2.1	2.4
		digestive system	14	9.0	156	2.2	2.2
		lymphopoietic	5	2.6	200	3.7	3.7

*p < 0.05

a Matanoski (1980) not included since observed and expected numbers of deaths were not included in paper.

b These numbers were obtained using Molina's tables of Poisson's Exponential Binomial Limit (Molina, 1942).

c Because the expected number was large, these numbers were obtained by the approximation of Beaumont and Breslow (1981) and checked by the approximation to the Poisson.

Table 4-15

Conditional Power Calculations for PMR Studies[a]

Study	Size	Cancer Type	Observed	Expected	PMR	Least detectable PMR with power: 80%	90%
Marsh (1983) chemical workers	2490	respiratory [c]	6	7.5	80	210	240
		lymphopoietic [c]	2	2.3	86	350	400
		pancreas	2	1.2	160	460	550
		genitourinary tract	3	2.5	120	320	370
		bladder	2	0.6	320	720	880
Walrath et al. (1983) N.Y. embalmers and funeral directors	1132	respiratory	74	70.7	105	130	140
		lymphatic and hematopoietic	25	20.6	121	160	170
		leukemia	12	8.5	140	210	240
		prostatic	15	16.4	91	170	190
		brain and CNS	9	5.8	156	240	280
		buccal cavity and pharynx	8	7.1	113	230	250
		skin	8	3.6	*221	280	330
		colon	29	20.3	*143	170	180
Walrath (1983) California embalmers	1050	respiratory	43	46.0	94	140	150
		lymphatic and hematopoietic	19	15.5	123	170	190
		leukemia/aleukemia	12	6.9	* 175	210	250
		prostatic	23	13.1	* 176	180	200
		brain	9	4.7	* 193	270	300
		buccal cavity and pharynx	8	6.1	131	220	260
		skin	2	3.4	59	300	340
Stayner et al. garment workers	256	respiratory	11	12.2	90	180	200
		lymphatic and hematopoietic	10	6.1	163	220	250
		leukemia/aleukemia	4	2.4	168	330	380
		brain	1	2.1	48	380	440
		buccal cavity	3	0.4	* 750	1320	
		skin	2	1.1	179	500	600
		biliary passages and liver	4	1.3	* 313	420	510
Dalzell and Grufferman textile workers	4462	lung	106	117.8	90	1.2	1.3
		lymphopoietic	121	64.2	* 188	1.3	1.4
		leukemia	45	37.5	120	1.4	1.8
		brain	17	18.9	90	1.7	1.8
		buccal cavity and pharynx	18	18.0	100	1.7	1.8

* $p<0.005$

[a] Conditional on the observed number of deaths since distribution of H_0 and H_1 might not have a Poisson distribution (Miettinen and Wang, 1981).

[b] These numbers were obtained using Molina's tables of Poisson's Exponential Binomial Limit (Molina, 1942).

[c] Includes only workers with $\geq$ one month exposure to formaldehyde.

Table 4-16

Power Calculations for Case-Control Studies[a]

Study	Size	Cancer Type	Exposure Ratio = p_o	Odds Ratio	Least Relative Odds to detect with power[b] 80%	90
Fayerweather et al. (1982) cancer deaths in chemical workers	481 cases/ 481 controls (1:1 match)	lung, bronchus, and trachea	formaldehyde: males workers (20%)	0.74	2.0	2.2
		lymphopoietic		0.72	3.5	4.1
		prostate		3.20	4.4	5.5
		brain		0.45	11.6	16.8
Brinton et al. (1983) nasal and paranasal sinus cases in NC and VA	160 cases/ 290 controls (1:2 match)	nasal cavity and sinuses	textile workers: females (17.4%)	1.8	2.5	2.8
Olsen et al. (1984) nasal cancer cases in Denmark	839 cases/ 2465 controls (1:3 match)	nasal cavity and sinuses	formaldehyde: females (0.1%)	2.8	15.0	18.0
			males (4.2%)	2.8	2.1	2.3
			textile dust: females (2.5%)	1.3	2.8	3.2
			males (1.9%)	0.7	2.4	2.7
Hayes et al. (1984) nasal and nasal sinus cases in the Netherlands	144 cases/ 353 controls (1:2 match)	nasal cavity and sinuses	formaldehyde: males not exposed to wood dust (6.2%)	2.8	3.4	3.7
			males exposed to wood dust (50%)	1.0	5.2	6.5

[a] Power calculations for Tola et al. (1980) and Hernberg et al. (1983) could not be calculated due to the unknown exposure ratio (p_o) among the controls.

[b] Obtained from the study by Fayerweather et al. (1982) or was calculated using the method in Rothman and Boice (1982) for the studies by Brinton et al. (1983), Olsen et al. (1984), and Hayes et al. (1984).

otherwise. Ten studies are of chemical or industrial workers and seven studies of medically-related professions. The medically-related professions represent formalin exposures such as those encountered by morticians, embalmers, anatomists, and pathologists. This group has other chemical exposures, but by nature of their professions, formalin is an integral component and represents the exposure of concern. Lastly, six other case-control studies examine an occupational etiology of nasal cavity and sinus cancers. These studies examine the relationship between nasal cavity and sinus cancer and HCHO exposure or between these cancers and particular occupational groups where HCHO has been known to occur.

1. Matanoski (1980) of John Hopkins University examined mortality patterns of male pathologists in two professional societies. She observed a 62% excess risk for multiple myeloma and a 42% excess risk for other lymphomas for members of the American Association of Pathologists and Bacteriologists (1900-1929) when compared to radiologists. When compared to U.S. white males, Matanoski observed a significant increase in deaths when she combined the two cancer categories. Matanoski continued following this cohort until 1974 and reported a 3-fold significant excess of lymphatic and multiple myeloma tumors and a 2-fold excess of brain cancers when compared to age-specific rates for U.S. white males. Matanoski observed the same pattern of

significant increases for lymphomas and multiple myelomas in a second cohort of pathologists belonging to the Association of Experimental Pathologists. Combining the two groups without overlap, about 2200 individuals, Matanoski reported increased mortality from lymphatic (3-fold excess, $p \leq 0.001$) and from brain cancer ($p \leq 0.05$).

2. Harrington and Shannon (1975) of the London School of Hygiene and Tropical Medicine conducted an SMR analysis of 2,079 pathologists who were members of the Royal College of Pathologists or the Pathological Society of Great Britain during 1955 to 1973. In the period, 156 deaths occurred. The authors reported a significant excess in mortality from lymphopoietic system cancers (SMR=200, 8 observed, $p<0.05$), particularly from lymphatic and hematopoietic diseases not due to Hodgkin's disease or leukemia (SMR=353, 6 observed, $p<0.01$). Additionally, a nonsignificant increase in mortality was observed from Hodgkin's disease (SMR=167, 1 observed) for male pathologists in England and Wales.

3. Harrington and Oakes (1982) more recently followed the Royal College of Pathologists' cohort from 1974 to 1980 and performed an SMR analysis of 2,720 members (2,307 males and 413 females), in which 126 total deaths (110 males, 16 females) occurred. Harrington and Oakes observed increased mortality in males from cancers of the brain (SMR=331, 4 observed, $p<0.05$) and bladder

(SMR=107, 2 observed), from accidents (SMR=170, 13 observed, $p<0.05$), and from suicides (SMR=353, 7 observed, $p<0.01$). Increased mortality from lymphatic and hematopoietic neoplasms was not reported for male pathologists (only 2 observed deaths) but was reported for female pathologists (SMR=370, only 1 observed death).

All the malignant brain tumors were of the astrocytoma/glioma cell type. This finding supports a hypothesis of a common etiologic agent within this study.

4. Levine et al. (1984) of CIIT in an SMR analysis found excess mortality among Ontario morticians, relative to U.S. white males, from lymphopoietic cancer (SMR=125, 9 observed), particularly, leukemias/aleukemias (SMR=175, 5 observed), and brain cancers (SMR=118, 3 observed). None of these malignancies was significantly elevated. Only cirrhosis of the liver showed a significant excess (SMR=171, 18 observed). In analyses for latency, Levine observed increasing SMR's with increasing time since first exposed for cancers of the brain, lymphopoietic system, and leukemia/aleukemia.

5. Stroup et al. (1984) has noted excesses, when compared to U.S. white males, in mortality due to brain cancers (SMR=271, 10 observed, $p<0.01$) and leukemias (SMR=148, 10 observed) in anatomists in her yet-to-be-published

SMR study. Stroup et al. noted excesses of the cell types astrocytoma/glioblastoma (all ten brain tumors) and myeloid leukemias. Stroup et al. also used psychiatrists as a comparison group. In this comparison, Stroup et al. observed a significant excess in mortality from both leukemia (SMR=212, $p<0.05$) and brain cancer (SMR=571, $p<0.01$). In an additional comparison using the records of Olmsted County, MN as the referent, the excess mortality from brain cancer remained.

Ascertainment bias is not thought to be present in Stroup's study due to the significant excesses in the comparison with psychiatrists and to the observation of a specific cell type with the brain tumors.

6. Wong (1983) observed among 2,026 workers employed in a HCHO manufacturing plant nonsignificant excesses in mortality for all cancers (SMR=101) when compared to U.S. males. Among the cancers, nonsignificantly increased mortality was observed for skin (SMR=109, 1 observed), bone (SMR=430, 1 observed), prostate (SMR=305, 4 observed), bladder (SMR=122, 1 observed), kidney (SMR=102, 1 observed), brain (SMR=186, 3 observed), and lymphopoietic system (SMR=136, 6 observed), including Hodgkin's disease (SMR=240, 2 observed) and leukemia/aleukemia (SMR=118, 2 observed). Accounting for a latency of 20 years, Wong

observed significantly increased mortality from cancer of the prostate (SMR=431, 4 observed, $p<0.05$) and nonsignificantly increased mortality from lymphopoietic system (SMR=231, 4 observed), including Hodgkin's disease (SMR=582, 1 observed) and leukemia/aleukemia (SMR=306, 2 observed), cancers.

Wong's study is limited by a small cohort size, lack of work histories, and lack of control for such confounding variables as smoking and multiple exposures. Besides HCHO, this cohort had potential exposures to other oxygenated hydrocarbons, benzene, asbestos, and inorganic and organic pigments. Exposure to benzene is particularly important since the literature reports a causal association between leukemia and benzene exposure (Heath, 1982).

7. Tabershaw Associates (1982) studied the same cohort as Wong, with 58 men added who had incorrectly been excluded and with the HCHO-exposed workers identified. An SMR analysis of the exposed and unexposed cohorts and a case-control analysis using randomly-selected controls among the non-cancer cases were conducted. In the SMR analysis of 867 HCHO-exposed workers, nonsignificantly increased mortality from prostatic (SMR=364, 2 observed), brain/CNS (SMR=135, 1 observed), and lymphopoietic (SMR=152, 3 observed) cancers and from all accidents (SMR=103, 11 observed) was reported.

Interestingly, Tabershaw Associates base the brain/CNS conclusion on one observed death, yet the text describes two observed deaths among men who had 6.7 years and 6.9 years of exposure.

In the case-control analysis, nonsignificantly increased odds ratios for cancers of the prostate (OR=2.67) and lymphopoietic system (OR=3.0), and for all neoplasms (OR=1.2) with 5 to 10 years of HCHO exposure were reported. No increasing risks were observed with increasing years of exposure. Tabershaw Associates did not use an unexposed group as a comparison, but compared the exposed employees to those with less than 5 years of exposure.

8. Friedlander et al. (1983) of Eastman Kodak conducted a mortality and incidence study of 464 photo processors in Eastman Kodak's Color Print and Processing laboratories. These workers had been exposed to HCHO, along with other photographic chemicals. In the mortality study, Friedlander et al. compared the death rates in this cohort to age-sex-specific death rates in two other Kodak manufacturing plants. Friedlander et al. observed excess mortality from cancers of the brain and CNS (2 observed, Plant 1 comparison - SMR=286; Plant 2 comparison - SMR=667, $p<0.05$) and digestive organs and peritoneum (5 observed, SMR=128, for each comparison group). Nonsignificant excess mortality from cancer of

the buccal cavity and pharynx was also observed (1 observed, Plant 1 comparison - 0.2 expected, Plant 2 comparison - 0.1 expected). From the incidence analysis, Friedlander et al. also reported the incidence of brain and CNS cancers increased (2 observed, 0.4 expected, $p<0.05$) among this group when compared to the population incidence for upstate New York.

Limitations in the study of Friedlander et al. include small cohort size, no separation of work exposures, insufficient length of follow-up, insufficient follow-up of retired and terminated employees, and no control for smoking.

9. Acheson (1984a) of MRC Environmental Epidemiology Unit, Southampton General Hospital, in an ongoing study of six plants which use or manufacture HCHO, has observed significant increases in overall mortality (SMR=124, 456 observed) and nonsignificant increases from pharyngeal (SMR=121, 5 observed), esophageal (SMR=103, 13 observed), respiratory (SMR=102, 236 observed), and lung (SMR=105, 205 observed) cancers. Additionally, Acheson found a significant excess of bone cancer and a significant dose-response relationship for lung cancer in one plant (BIP), the cohort with the highest exposure. In a comparison with local controls, the dose-response relationship, although nonsignificant, was still observed. Acheson lacks smoking histories for the

entire conort, and the BIP plant is located in the West Midlands area, an industrially polluted area with high referent lung cancer rates. The use of a local comparison may have overestimated the number of expected lung cancer deaths. In a subsequent analysis of the mortality data for lung cancer among individuals employed at this plant, Acheson et al. (1984b) observed that the risks for lung cancer did not increase with duration of exposure, length of follow-up, or cumulative doses.

10. Marsh (1983) of the University of Pittsburgh conducted an SMR analysis and a case-control study nested within the cohort of a Monsanto chemical plant. This plant produced plastics and workers had potential exposures to HCHO, vinyl chloride, styrene, and cellulose acetate. Marsh compared the mortality experience of all workers to the white male populations of the U.S., of Massachusetts, and of Hampden County, the county from which the workforce was drawn. In the SMR study, the cohort consisted of 2,490 male workers with a minimum of one year employment. Among the 2,490 workers, 591 deaths were identified by the company or by death certificate searches. Marsh reported nonsignificantly increased mortality due to all neoplasms (SMR=107, 127 observed). Among all neoplasms, excess mortality was observed from cancer of the buccal cavity and pharynx

(SMR=155, 6 observed), digestive organs and peritoneum (SMR=126, 44 observed), prostate (SMR=178, 14 observed), bladder (SMR=135, 5 observed), genitourinary tract (SMR=169, 26 observed, $p<0.05$), Hodgkin's disease (SMR=118, 2 observed), and all other lymphopoietic tissue (SMR=153, 4 observed). No relationship was observed between genitourinary system neoplasms and length of employment.

In the matched case-control study based on the cancer deaths, Marsh presented odds ratios for digestive system, rectal, genitourinary, and prostatic cancers and 21 occupational exposure categories. Two of the 21 categories had pertinent exposure to HCHO either as a chemical (resin production) or in a product (resins processing). Marsh observed nonsignificantly increased odds ratios for digestive system cancer in the resins processing category (OR=1.83) and for rectal cancer in both categories (resins production, OR=3.75; resins processing, OR=2.00). All cases in the occupational categories had from 1 month to 5 years exposure and increasing risk was not observed with increasing duration of exposure.

11. Fayerweather et al. (1982) of DuPont showed elevated odds ratios, after a 15 year latency, for cancers of the prostate (OR=4.8, 8 cases), lymphopoietic system (OR=1.91, 6 cases), bone (OR=1.25, 3 cases), and bladder

(OR=7.0, 6 cases) among workers eligible for pension who were exposed to HCHO five or more years. Additionally, these elevations were not significant upon adjusting for a variety of concommitant variables. Fayerweather et al. did not follow those employees ineligible for pension or those who had transferred, potentially comprising 15 to 20% of the work group. Thus, these analyses were performed on an incomplete cohort and the results may be biased.

12. Brinton et al. (1984a) of NCI conducted a case-control study for cancer of the nasal cavity and sinuses. They observed nonsignificantly increased odds ratios among males employed in the leather or shoe, chemical manufacturing, and carpentry industries and for exposures to chromium/chromates, nickel, and insecticides/pesticides/herbicides. Among females, increased odds ratios were observed with employment in the textile/clothing/hosiery and paper/pulp mill industries and for exposures to mineral oils and other mineral/chemical gases. None of the increased odds ratios was significant in the presence of control for confounding variables. Brinton et al. additionally assessed reported occupational HCHO exposure and found an odds ratio less than 1.0. This ratio was unstable, based on only one male and one female.

To examine the relationship between employment in the textile and apparel industries with the risk of nasal cancer, Brinton et al. (1984b) further analyzed the data from their previously published case-control study (1984a). The industries included textile and cotton mills, apparel manufacturing, and hosiery. Brinton et al. found an elevated risk of nasal cancers associated with employment in the textile or apparel industries, but the increased relative risk was found only among female workers. When histologic types of nasal cancer were evaluated, both males and females were found to be at increased risk of nasal adenocarcinoma, with further enhancement of risks for those experiencing dusty work conditions. The authors stated that this study provides further evidence of an association between employment in the textile industry and risk of nasal cancer.

13. Tola et al. (1980) of the Institute of Occupational Health, Finland, conducted a case-control study for cancer of the nose and paranasal sinuses. Forty-five cases were collected from the Finnish Cancer Registry between 1970 and 1973 and were age-sex matched to non-respiratory cancer controls.

Analyses examining an occupational etiology showed no single occupation being more common among the cases than among the controls, but leisure time knitting and sewing was significantly more common among female cases than

among female controls (OR=4.8, 19 cases). Other factors significantly associated with the cases were histories of serious nasal trauma, chronic rhinitis, and sinusitis. Smoking was not significantly associated with nasal cavity and sinus cancer.

14. Hernberg et al. (1983) of the Institute of Occupational Health, Finland, conducted, with participation from Denmark and Sweden, a collaborative case-control study of nasal and sinonasal cancer and its possible occupational etiology. One hundred seventy cases diagnosed between 1977 and 1980 and reported to the prospective cancer registries were selected. Each case was sex-country-age at diagnosis matched with colorectal cancer controls.

    Elevated odds ratios were observed among cabinetmakers (OR=9.0) and mechanical engineering shop workers (OR=2.13). Analysis for exposures showed elevated risk with hardwood dust (OR=1.7)*, softwood dust (OR=3.4, $p<0.05$)* hardwood and softwood dust (OR=6.7, $p<0.05$)*, welding-flame cutting-soldering (OR=2.0, 17:6, $p<0.05$)**, chromium (OR=2.7, 16:6, $p<0.05$)**, nickel (OR=2.4, 12:5)**, electroplating (OR=1.5, 9:6)**, and paint-lacquer (OR=3.0, 18 cases). HCHO exposures may occur in this last category. However, wood dust exposure is common and confounds the observed elevation.

*Adjusted for smoking.
**Odds ratio based on discordant pairs, discordant paris noted.

15. Stayner et al. (1984) of NIOSH conducted a PMR study of 256 deaths among garment workers. Stayner et al. identified these deaths from a death benefit fund. In this cohort, which represented three plants in two different states, Stayner et al. observed significantly elevated mortality from buccal cavity (PMR=750, 3 observed), biliary passages and liver (PMR=313, 4 observed), and other lymphatic and hematopoietic site (PMR=400, 4 observed) cancers. In analyses examining only the cancer deaths, buccal cavity (PCMR=682) and other lymphatic and hematopoietic site (PCMR=342) cancers remained significantly elevated. Additionally, those workers with both latency and duration of exposure of 10 years or greater showed significantly elevated mortality from all malignancies (PMR=137, 51 observed), buccal cavity (PMR=925, 2 observed), biliary passages and liver (PMR=467, 3 observed), and all lymphatic/ hematopoietic sites (PMR=283,8 observed), particularly other lymphatic and hematopoietic (PMR=761, 4 observed) cancers.

Nonsignificant elevations in mortality were reported for liver not specified (PMR=426, 2 observed), skin (PMR=179, 2 observed), and all lymphatic and hematopoietic sites (PMR=163, 10 observed), including leukemia (PMR=400, 4 observed).

16. Walrath and Fraumeni (1983) of NCI conducted a PMR study of 1,132 funeral directors or embalmers licensed in New York. In this cohort, Walrath and Fraumeni observed significantly elevated mortality from skin (PMR=221, 8 observed) and colon (PMR=143, 29 observed) neoplasms. Nonsignificant elevations were observed for cancer of the buccal cavity and pharynx (PMR=113, 8 observed), digestive system (PMR=104, 68 observed), particularly liver (PMR=106, 5 observed) and pancreas (SMR=105, 13 observed), respiratory system (PMR=105, 74 observed), brain/CNS (PMR=156, 9 observed), kidney (PMR=150, 8 observed), and lymphatic/hematopoietic system (PMR=121, 25 observed). Among those licensed as embalmers only, Walrath and Fraumeni observed increases in mortality from buccal cavity and pharyngeal (PMR=201, 7 observed), skin (PMR=326, 5 observed, $p<0.05$), kidney (PMR=247, 6 observed, $p<0.05$) and brain/CNS (PMR=234, 6 observed, $p<0.05$) cancers. In the analysis for latency, Walrath and Fraumeni observed, for the entire cohort, increasing PMRs for skin (significantly so) and brain/CNS neoplasms for increasing time since first exposed.

17. Walrath (1983) conducted another PMR analysis of 1050 embalmers in California and reported similar findings as those in the N.Y. cohort. Walrath observed significantly increased mortality from neoplasms of the brain (PMR=193, 9 observed), leukemia (PMR=175, 12

observed), and prostate (PMR=176, 23 observed). Nonsignificant increases were reported for lymphatic/hematopoietic system (PMR=123, 19 observed) and buccal cavity and pharyngeal (PMR=131, 8 observed) cancers.

18. Marsh (1983) of the University of Pittsburgh conducted a PMR analysis of HCHO-exposed workers at the Monsanto plant described previously. Marsh found 136 death among male workers with exposure of one month or greater in a "formaldehyde related plant area". Marsh compared their mortality experience to U.S. male, age-race adjusted, proportional mortality data.

    In the HCHO-exposed white males, Marsh observed increased (not statistically significant) mortality from cancers of the genitourinary system (PMR=121, 3 observed), including the bladder (PMR=330, 2 observed) and of the digestive organs and peritoneum (PMR=127, 8 observed), particularly the pancreas (PMR=160, 2 observed). In the non-white exposed workers, Marsh does not report any increases in neoplastic deaths, but observed increases among the non-neoplastic deaths, particularly diseases of the circulatory system (PMR=102, 7 observed), digestive system (PMR=158, 2 observed), and accidents (PMR=106, 2 observed). In the unexposed group, white males exhibited increased mortality from genitourinary tract cancers (PMR=192, 22

observed) and digestive organs and peritoneal cancers (PMR=130, 33 observed). Non-white unexposed males exhibited increased mortality from all malignant neoplasms (PMR=251, 5 observed), particularly in the categories "all other malignant neoplasms" (PMR=882, 3 observed, $p<0.01$), diseases of the nervous system (PMR=155, 2 observed), and circulatory disease (not including arteriosclerotic heart disease) (PMR=207, 3 observed).

Since Marsh published this study, Peter Infante of OSHA has found one cancer of the nasal sinus and one nasopharyngeal cancer. Both men died three years after Marsh's follow-up period. The worker who later died of cancer of the nasopharynx was a member of Marsh's cohort, but had been counted as living since he had not died at that time.

19. An overlapping study was conducted by Liebling et al. (1984) (as reported by OSHA, 1984). Liebling et al. identified 24 male workers who died between January 1, 1976 and December 31, 1980 through union records, reports of former coworkers, and a systematic review of obituaries in local newspapers. Work histories were obtained from seniority lists.

Proportionate mortality ratios were calculated to examine cause-specific mortality using the age, sex, race and cause-specific mortality proportions of the

U.S. and county in which the plant is located. To adjust for the healthy worker effect, age, sex, and race-standardized PCMRs based on county comparisons were also calculated. Deaths among eighteen white and six black males with known HCHO exposure were identified. Race-age-sex adjusted PMRs were significantly elevated for cancer of the colon based on U.S., county, and county cancer mortality proportions (PMR = 702, 424, 333, $p \leq 0.05$), as were PMRs for the cateogry buccal and pharyngeal cancer (PMR = 870, 952, 833, $p \leq 0.05$). Liebling et al. stated that the occurrence of a significant increase in proportionate mortality from buccal and pharyngeal cancer in this investigation is in accord with the type of cancer found in HCHO-exposed rodents. Furthermore, the authors postulated that besides nasopharyngeal cancer, an association between HCHO exposure and cancer of the buccal cavity and pharynx in humans is biologically feasible since humans breathe through both the nose and mouth, while rats and mice are obligatory nose-breathers. Like many other studies, this study is limited by the inability to completely separate HCHO exposure from exposure to other chemicals.

20. Olsen et al. (1984) of the Danish Cancer Registry conducted a case-cohort study of nasal cancers. This study examined 839 cancer registry cases (560 males, 279

females), diagnosed between the years 1970-1982, who were matched with 2,467 controls with cancer of the colon, rectum, prostate, and breast on age-sex-year of diagnosis. The researchers used a nationwide data linkage system which has linked cancer cases and previous employment. Occupational histories came from the National Supplementary Pension fund, established in 1964, and the Central Population Registry. Use of these national data sets eliminated the potential for recall bias since cases and controls were not interviewed. In this case-control study, Olsen et al. tested for associations between HCHO, wood dust, paint-laquer-glue, and metal exposure and sino-nasal cancers. Significantly increased risks were found for nasal cavity cancer for exposure to HCHO (OR=2.8), wood dust (OR=2.5), and paint-lacquer-glue (OR=2.1). Exposure to both wood dust and HCHO can occur simultaneously, and Olsen et al. performed a stratified analysis which controlled for wood dust exposure. In this analysis, the elevated risk with HCHO exposure was reduced to 1.6 and became nonsignificant. In this stratified analysis, both HCHO and wood dust exposure together resulted in an additive risk (OR=4.1, $p \leq 0.05$).

21. Hayes et al. (1984) of the Erasmus University of Rotterdam presented findings of a case-control study of nose and nasal sinuses tumors at the 3rd International

Conference on Epidemiology and Occupational Health in Dublin, Ireland. The Hayes et al. study identified factors associated with 144 cases of nasal and sino-nasal neoplasms diagnosed between 1978 and 1981. Living and deceased population controls were used as the comparison group, but Hayes et al. did not identify the criteria for control selection. Hayes et al. observed associations between male adenocarcinoma cases and work in furniture making (OR=132) and joinery (OR=21). In addition, Hayes et al. noted significantly increased risks between nonadenocarcinomas and paint (OR=4.1), benzene (OR=2.3), and HCHO (OR-2.4) exposure. In analyses which controlled for simultaneous wood-dust and HCHO exposures, Hayes et al. observed a nonsignificantly elevated risk for exposure to only HCHO (OR=2.8). Hayes et al. did not show, however, an addition of risk for both HCHO and wood-dust exposures like Olsen et al. reported.

22. Bertazzi et al. (1984) of the Institute of Occupational Health, University of Milan presented at the above conference findings of a cohort study of HCHO resin manufacturing workers. The mortality experience of 1,332 male employees who had worked six (6) months or more between 1959 and 1980 was compared to the expected number of deaths using national and local rates. Bertazzi et al. noted that ambient monitoring of many

work areas were above the Threshold Limit Value (value not given), but the researchers do not identify when these samples were obtained or where the monitors were located.

For the entire cohort, Bertazzi et al. observed significantly increased mortality for lung cancer when both national (18 observed, 7.6 expected) and local (9.7 expected) rates were used as the referent. Mortality from digestive neoplasms and lymphopoeitic neoplasms was nonsignificantly elevated.

Bertazzi et al. compared the mortality of HCHO exposed workers to non-exposed workers. In this analysis, the increased mortality from lymphatic and hematopoietic system and from digestive neoplasms was observed only among the HCHO exposed. Elevated mortality was observed in both the HCHO exposed and nonexposed groups.

23. Delzell and Grufferman (1983) of Duke University examined the mortality experience of 4,462 deaths between 1976-1978 of white female textile workes. Deaths and occupation as recorded on the death certificates were identified from state computer files. In this study, textile worker occupational code included workers in industries that manufactured textile mill products, apparel, or other fabricated textile products. Delzell et al. observed significant excesses in mortality from cancer of the larynx (PMR=280, 5

observed), connective tissue (PMR = 260, 10 observed), cervix (PMR=210, 59 observed), other unspecified genital organs (PMR=270, 16 observed), and non-Hodgkin's lymphoma (PMR=170, 51 observed), and all lymphopoietic sites (ICDA 200-207) (PMR=188, 121 observed), mortality from Hodgkin's disease (PMR= 111, 8 observed) and leukemia (PMR=120, 45 observed). The elevated mortality from all lymphopoietic sites and from specific lymphopoietic sites are particularly interesting since HCHO, along with other chemicals, may comprise exposures in textile mills. EPA used an exposure level of 0.10 ppm (personal sample) and 0.42 ppm (area sample) in its Quantitative Risk Assessment for Formaldehyde (EPA, 1984). Since this study was unable to identify individual exposures, we do not know if any or all deaths may have had previous HCHO exposure.

4.7.2. Conclusion

The epidemiologic literature report, for the first time, a significant association between nasal cancer and HCHO. This observation was confounded due to wood dust exposures, but when the analyses controlled for wood dust, the risk remained elevated (nonsignificantly). The association between nasal cancer and HCHO may be further supported by the report of Hayes et al. (1984). A critical review of the Hayes et al. study needs to be done and EPA epidemiologists have requested, but have not received, a copy of the paper. In addition, the significant

excesses in leukemia and brain cancer mortality among anatomists, pathologists, and embalmers are also important. These observed excesses can not be explained by diagnostic bias or socioeconomic factors.

Low power is a characteristic of several studies (Tables 4-14 through 4-16). Selecting lymphatic and hematopoietic cancer as an example, Table 4-14 shows that Levine et al. (1983) could detect, with 80% power, a relative risk of 2.2 or greater and with 90% power, a relative risk of 2.5 or greater. Insufficient follow-up and small sample sizes contribute doubly to low power through insufficient person-years and through cancers not yet having appeared. Thus, absence of significant elevations in either brain cancer, lymphopoietic cancer, or leukemia in individual studies should not override the findings in Matanoski, Stroup et al., Walrath and Fraumeni, Walrath, Harrington and Oakes, Harrington and Shannon, Tabershaw Associates, Stayner et al., Olsen et al., and Hayes et al.

Secondly, the discussed studies lack historical exposure estimates and this cannot resolve the possible contributions of HCHO from other chemicals. Leukemias and brain cancers have been associated with other occupational groups. These include chemists, rubber workers, and oil refinery/petrochemical workers (Heath, 1982 and Schoenberg, 1982). These occupational groups are exposed to solvents, benzene, and other organic chemicals. These exposures may be like those of the medically-related professions and the chemical manufacturing workers.

Additionally, nasal cancer and lymphopoietic cancers have been associated with textile workers but we do not know if HCHO off-gasses, dusty/poor sanitary conditions, or yet a third factor could be the etiologic agent.

In summary, the epidemiologic data made public since the 4(f) decision add more weight to the evidence that HCHO may be a human carcinogen. Excess mortality from leukemias and brain cancers have been noted in a group of professionals who use formalin. Additionally, through case-control methods, an association between nasal cancer and HCHO has been observed in one study and a suspect association has been reported in an abstract of another study. At this time, there is limited evidence that HCHO may be a human carcinogen.

4.8. Weight-of-Evidence

4.8.1. Assessment of Human Evidence

EPA has determined, based upon its proposed cancer risk assessment guidelines, that there is limited evidence that HCHO may be a human carcinogen.

As discussed in the Epidemiology section, the literature reports (Hayes et al., 1984; and Olsen et al., 1984), a significant association between nasal cancer and HCHO. However, these observations were confounded due to wood dust exposures. When the analyses controlled for wood dust, the risk remained numerically elevated but lost its statistical significant (p0. 05). The significant excesses in leukemia and brain cancer mortality among anatomists, pathologists, and embalmers are also

important. These observed excesses cannot be explained by diagnostic bias or socioeconomic factors. The determination that there is limited human evidence is based on an examination of the technical merits (power, follow-up, confounding, etc.) of the available studies and the association of HCHO wood dust and nasal cancer and the excess mortality seen in professional groups from leukemias and brain cancers.

4.8.2. Assessment of Animal Studies

The principal evidence indicating that HCHO is able to elicit a carcinogenic response in animals are the studies by CIIT (1981), Albert et al. (1982) and Tobe et al. (1985). In the CIIT (1981) study, statistically significant numbers of squamous cell carcinomas of the nasal cavity of Fischer 344 male and female rats were seen. The CIIT (1981) study was a well conducted, multidose inhalation study. In addition, while not statistically significant, a small number of squamous cell carcinomas were seen in male mice. Because this type of nasal lesion is rare in mice, these data must be considered biologically significant. Supporting the findings above, are the results of the Albert et al. (1982) studies in which statistically significant numbers of squamous cell carcinomas were found in Sprague-Dawley male rats and the results of Tobe et al. (1985) study in which significant numbers of squamous cell carcinomas were also found but in Fischer 344 male rats.

Additional support is provided by studies by Dalbey et al. (1982) in which HCHO increased the production of tumors caused by

a known animal carcinogen; Meuller et al. (1978) in which a solution of formalin produced lesions in the oral mucosa of rabbits which showed histological features of carcinoma *in situ*; and studies by Watanabe et al. (1954, 1955) in which injections of formalin and hexamethyenetetramine produced injection site sarcomas and one adenoma.

HCHO is mutagenic in numerous test systems, and it is able to transform a number of cell lines. In addition, HCHO has been shown to be able to form adducts with DNA in both *in vivo* and *in vitro* tests (Consensus Workshop on Formaldehyde, 1984). Its ability to interfere with DNA repair mechanisms has also been demonstrated. However, evidence demonstrating HCHO's mutagenic potential in *in vivo* tests is lacking (IRMC Report on Systemic Effects, 1984b). The literature reports conflicting data concerning chromosomal effects in humans. However, the weight of this data indicates little if any potential for these effects in the workplace, but this judgement must be tempered by the limitations of the studies.

Although HCHO's acute effects do not demonstrate its carcinogenicity, they do help explain differences in species response, and the severity of the carcinogenic response in the animal studies. HCHO's acute effects may be factor in the promotion of its carcinogenic potential at concentrations greater than 1 ppm in rats and possibly in humans.

HCHO is not the only aldehyde that is carcinogenic in animals. Acetaldehyde, the closest aldehyde to HCHO in structure, is carcinogenic in hamsters and rats, causing cancers in the nose and trachea of the former, and nasal cancers in the latter. In addition, other aldehydes such as glycidaldehyde and malondialdehyde have been shown to be carcinogenic.

Finally, factors such as HCHO's rapid metabolism, the protective action of the mucous layer, respiratory response to sensory irritants, and species differences have been discussed in the HCHO literature as defense mechanisms that may indicate a threshold (at exposures of about 1 ppm) or may substantially reduce cancer risks from HCHO exposure.

In EPA's judgment, the body of metabolism data do not demonstrate a threshold for HCHO's carcinogenicity. Although the data indicate that HCHO is rapidly metabolized in in vivo and in vitro studies, and that transport to sites distant from the point of contact is unlikely, the fact remains that HCHO-DNA interaction is indicated for exposures below 2 ppm. In addition, the finding of benign tumors in the Kern et al (1983) study at 2 ppm is consistent with a conclusion that HCHO is not metabolized (removed) before it can interact with nuclear material. (The assumption is that there is a dose-response below 2 ppm for benign tumors and not a threshold just below 2 ppm.) Whether this pattern of interaction with DNA is linear or non-linear has not been unequivocally determined. However, as discussed in another section, a reasonable interpretation of the data on DNA

adducts by EPA indicates linearity in the exposure range tested. In addition, it is impossible to say at this time, if ever, what level of rapidity of HCHO metabolism versus increases in exposure is an indicator of a threshold.

The defensive role of the mucous layer in preventing exposure of target cells to HCHO has been extensively discussed. However, the data indicate that the mucous layer has not been shown to be able to trap and remove significant amounts of HCHO at the levels tested in Casanova-Schmitz et al. (1984). In fact, the data indicate that a constant proportion of HCHO reaches the underlying cells. While this does not imply that the mucous layer offers no protection, it does not support a threshold hypothesis.

The effect of sensory irritants on the respiratory rates of some laboratory animals is well known. Such a response apparently contributes to the minimal neoplastic response seen in mice. This is an important factor when interpreting inhalation studies and in determining the dose actually received. While a reduction in respiratory rate protects the animal by reducing the amount of the irritant inhaled, it plays no defensive role below exposures which fail to elicit the response. However, it is a factor in the generation of risk estimates since the nominal dose levels used for statistical purposes may need to be changed to reflect this effect.

Another factor that bears on the possible carcinogenicity of HCHO, is the different responses seen in laboratory animals to

HCHO. HCHO have been studied in rats, mice, hamsters, and monkeys by inhalation. In rats a highly statistically significant response was obtained in two strains. In mice only males of one strain showed a marginal response, while hamsters and monkeys showed no neoplastic response. While mice did not show a statistically significant response, the response was biologically significant given the rarity of nasal tumors in mice. However, the studies of respiratory response to sensory irritants indicate that when dose received is adjusted for reductions in respiratory rate, rats and mice appear to respond similarly. The cancer test data on hamsters are negative. However, the possibility exists that they may be responding to a sensory irritant in the same manner as mice. The study using monkeys indicates that, at least for nonneoplastic lesions (squamous metaplasia), rats and monkeys respond similarly.

In addition, as a matter of policy EPA chooses to use the most sensitive species to predict human risk. Even though studies on the hamster show no observed tumors, the studies do not negate the rat data and there are no data to show that the hamster's response to HCHO exposure is more representative of the human response than is the rat's. EPA's position is supported by the Risk Assessment Panel of the Workshop (1984), which stated that there are "no indications that the response by humans would be different than that exhibited by rats, mainly due to the lack of experimental data pertaining to this issue. Qualitatively, the metabolic pathways of HCHO in rats and humans are similar.

The sites of greatest exposure may differ, since rats are obliged to breathe solely through the nose and humans may also breathe orally. Again, no information exists demonstrating that the response would be quantitatively different as a result of differences in distribution of the inhaled dose."

In conclusion, based on EPA's proposed Cancer Risk Assessment Guidelines there is sufficient evidence that HCHO is an animal carcinogen.

4.8.3. Categorization of Overall Evidence

In conducting risk assessments of suspect carcinogens, EPA generally evaluates the overall weight-of-evidence including both primary and secondary evidence of carcinogenicity. As specified in the draft EPA Guidelines for Health Assessment of Suspect Carcinogens (EPA, 1984a), primary evidence derives from long-term animal studies, and epidemiological data insofar as this is available. Secondary, or supplemental, evidence includes structure-activity relationships, the results of short-term tests, pharmacokinetic studies, comparative metabolism studies, and other toxicological responses which may be relevant (EPA, 1984).

In the process of categorizing HCHO, two lines of evidence were assessed, one of which is an assessment of studies of humans and the other is the assessment of evidence from studies in animals. The results from each assessment are then combined to characterize the overall evidence of carcinogenicity. The draft EPA Guidelines also suggest that quantitative risk numbers be

coupled with EPA classifiations of qualitative weight of evidence.

Consequently, based on the determination that there is sufficient evidence that HCHO is an animal carcinogen and the determination that there is limited human evidence, HCHO can be classified under the draft guidelines as a Group B1-Probable Human Carcinogen.

5. HAZARD OF NONCARCINOGENIC EFFECTS

5.1. HCHO-Related Effects of the Eyes and Respiratory System*

Irritation of the eyes and mucous membranes is the principal effect of low concentrations of HCHO observed in humans. Human responses to airborne HCHO at various concentrations are summarized in Table 5-1. Table 5-1 shows a wide range in HCHO concentrations reported to cause specific health and sensory effects. At concentrations below 0.05 ppm none of the effects listed have been reported.

Table 5-1.
REPORTED HEALTH EFFECTS OF FORMALDEHYDE AT VARIOUS CONCENTRATIONS

Health Effects Reported	Approximate HCHO Concentration, ppm*
None reported	0-0.5
Odor threshold	0.05-1.0
Eye irritation	0.01-2.0**
Upper airway irritation	0.10-25
Lower airway and pulmonary effects	5-30
Pulmonary edema, inflammation, pneumonia	50-100
Death	100+

*Range of thresholds for effect listed.
**The low concentration (0.01) was observed in the presence of other pollutants that may have been acting synergistically.

*Unless otherwise cited, from NRC (1981).

Most persons can perceive the odor of HCHO at about 1 ppm, but some persons can detect it as low as 0.05 ppm. Eye irritation has been reported at concentrations as low as 0.05 ppm. At concentrations at or above 1 ppm, nose, throat, and bronchial irritation have been noted. Such irritation was nearly uniformly reported by persons when the concentration reached 5 ppm. HCHO concentrations exceeding 50 ppm cause severe pulmonary reactions, including pneumonia, bronchial inflammation, pulmonary edema, and sometimes result in death.

Table 5-1 shows the variability and overlap of thresholds for responses among subjects. Although the severity of an effect in a person increases with increasing concentration and duration of exposure, a dose-response for an individual, the thresholds for the effects vary in the population as Table 5-1 illustrates. The problem is to determine population dose-response relationships. Tolerance to olfactory, ocular, or upper respiratory tract irritation occurs in some persons. Factors such as smoking habits, socioeconomic status, preexisting disease, and interactions with other pollutants and aerosols are expected to modify these responses.

5.1.1. Eye

A common complaint of persons exposed to HCHO vapor is eye irritation. Some persons can detect HCHO at 0.01 ppm, but it produces a more definable sensation of eye irritation at 0.05-0.5 ppm. Marked irritation with watering of the eyes occurs at a concentration of 20 ppm in air. Permanent eye damage from HCHO

vapor at low concentration is thought not to occur because people close their eyes to avoid discomfort. Increased blink rates are noted at concentrations of 0.3-0.5 ppm in persons studied in chambers. Blink rate, although used as an objective measure of eye irritation, appears variable for any given subject. The irritant effects of HCHO seem to be accentuated when it is mixed with other gases. In smog-chamber tests human subjects tested could readily detect and react to HCHO at as low as 0.01 ppm.

Accidental splash exposures of human eyes to aqueous solutions of HCHO have resulted in a wide variety of injuries, depending on concentration and treatment. These range from discomfort and minor, transient injury to delayed, but permanent, corneal opacity and loss of vision.

In summary, human eyes are very sensitive to HCHO, detecting atmospheric concentrations of 0.01 ppm in some cases (when mixed with other pollutants) and producing a sensation of irritation at 0.05-0.5 ppm. Tolerance to eye irritation is reported to occur. Lacrimation is produced at 20 ppm, but damage is prevented by closing the eyes in response to discomfort. Aqueous solutions of HCHO accidentally splashed into the eyes must be immediately flushed with water to prevent serious injury, such as lid and conjunctival edema, corneal opacity, and loss of vision.

5.1.2. Olfactory System

The odor threshold of HCHO is usually around 1 ppm, but may be as low as 0.05 ppm for a small percent of the population. General olfactory fatigue with associated increases in olfactory

thresholds for rosemary, thymol, camphor, and tar has been reported among plywood and particleboard workers and is thought to be associated with HCHO exposure.

5.1.3. Upper Airway Irritation (Nose and Throat)

Symptoms of upper airway irritation include the feeling of a dry or sore throat, tingling sensation of the nose, and are usually associated with secretion of tears and pain in the eyes. Irritation occurs over a wide range of concentrations, usually beginning at approximately 0.1 ppm, but is reported more frequently at 1-11 ppm (see Table 5-1). Tolerance to eye and upper airway irritation may occur after 1-2 hours of exposure. However, even if tolerance develops, the irritation symptoms can return after a 1- to 2-hour interruption of exposure.

Finally, examinations of the nose and throat reveal chronic changes that are more severe in persons exposed to the higher concentrations HCHO. Exposure to HCHO can cause alterations in the nasal defense mechanisms that include a decrease in mucociliary clearance and a loss of olfactory sensitivity.

5.1.4. Lower Airway and Pulmonary Effects

Lower airway irritation which is characterized by cough, chest tightness, and wheezing is reported often in people exposed to HCHO at 5-30 ppm.

Plumonary edema and pneumonitis could result from very high HCHO concentrations, 50-100 ppm. It is not known what concentrations/durations are lethal to humans, but concentrations exceeding 100 ppm would probably be extremely hazardous to most

exceeding 100 ppm would probably be extremely hazardous to most and might be fatal in sensitive persons.

5.1.5. Asthma

HCHO has been shown to cause bronchial asthmalike symptoms in humans. Although asthmatic attacks may in some cases be due specifically to HCHO sensitization or allergy, HCHO seems to act more commonly as a direct airway irritant in persons who have bronchial asthmatic attacks from other causes. Persons with bronchial asthma respond to numerous agents, such as exogenous irritants and allergens, respiratory infections, cold air, smoke, dust, and stress. The asthmatic person seems to represent an extreme on the scale of respiratory sensitivity to inhaled irritants.

Diagnosis of immune sensitization has been based upon knowledge that individuals were exposed to HCHO before onset of symptoms, and on disease symptoms and the spirometric pattern of changes in respiratory function upon bronchial provocation by inhalation challenge with HCHO. Although the production of specific Immunoglobulin Type E (IgE) antibody has been demonstrated to other chemicals (e.g., trimellitic anhydride, and phthalic anhydride), IgE antibody has not been shown to HCHO. Furthermore, respiratory sensitization with HCHO has not been demonstrated with animals (this may not be critical because there is not a well recognized model for "asthma") nor in some human studies in which patients who complained of respiratory illness did not respond positively to bronchial challenge testing with HCHO gas.

Definite conclusions on whether immune sensitization from HCHO plays a role in asthma and other respiratory disease must await the demonstration of the production of specific IgE or other specific immunological reactions (e.g. specific immune complexes, activation of the complement cascade, cell-mediated reactions in hypersensitivity pneumonitis). Studies are underway to answer some of these points.

5.1.6. Summary

A number of lower airway and pulmonary effects may occur from HCHO exposure. Thresholds have not been established for the irritant effects of inhaled HCHO. However, within the range of 0.1 to 3 ppm, most people experience irritation of the eyes, nose, and throat. In most healthy persons exposed to HCHO, concentrations greater than 5 ppm will cause cough and possibly a feeling of chest tightness. In some susceptible persons, concentrations below 5 ppm can cause these symptoms, including wheezing. In persons with bronchial asthma, the irritation caused by HCHO may precipitate an acute asthmatic attack, possibly at concentrations below 5 ppm. Sufficiently well-controlled studies are not available to definitively establish the development of respiratory tract allergy to HCHO as a gas. In concentrations greater than 50 ppm, severe lower respiratory tract effects can occur, with involvement not only of the airways but also of alveolar tissue. Acute injury of this type includes pneumonia and pulmonary edema.

5.2. Irritation/Sensitization--Dermal and Systemic

In reviewing any analysis of respiratory effects, it is important to remember that irritation and sensitization are two distinct physiologic responses. Irritation is a purely local, immediate response resulting from a chemical reaction between HCHO and the epithelial lining of the airways. The irritant response will resolve with cessation of exposure. It is scientifically accepted that there is a threshold for the irritant response.

A chemical sensitization response is a far more complicated physiologic effect. Some chemical sensitization responses are mediated by the immunologic system, for others antibodies have not yet been identified and the mechanism is as yet unknown. The sensitization response may have one or more components, immediate and/or delayed (8 hrs. after exposure). The response is similar to an asthmatic reaction. It will not immediately resolve itself upon cessation of exposure and may require medical treatment. The key distinction between sensitization and irritation, is the absence of a clear threshold in the former. Once an individual is sensitized, he/she will respond to low effect-triggering exposures. There is debate in the scientific community as to whether or not a threshold exists for the initial chemical sensitizing event(s), but the data is not available to resolve the issue.

It is established that HCHO is a primary skin sensitizing agent producing allergic contact dermatitis. It is also probably a cause of immunologic contact urticaria (Consensus Workshop, 1984).

HCHO induces allergic contact dermatitis by a delayed type (Type IV) hypersensitivity mechanism. Besides contact with HCHO itself, allergic contact dermatitis can be caused by contact with disinfectants and tissue preservatives containing HCHO, HCHO releasers (resins in clothing, and paper products), and with preservatives used for cosmetics, detergents, polishes, etc.

Table 5-2 illustrates some induction concentrations which induce sensitivity and the range of challenge concentrations which elicit the allergic reaction. The threshold for induction has not been clearly defined, but it has been estimated as less than 5 percent formalin in water. The appropriate threshold for elicitation of allergic contact dermatitis in sensitized subjects ranges from 30 ppm for patch testing to 60 ppm for actual product concentrations of HCHO (formalin). However, because of the limited data base these estimates should be used with caution (Consensus Workshop, 1984). Data (induction and challenge concentrations) regarding the ability of HCHO-resin treated textiles to cause contact dermatitis in garment workers for instance are lacking.

Table 5-2.
DELAYED TYPE HYPERSENSITIVITY (HUMAN) DUE TO LOW LEVELS OF FORMALDEHYDE*

Induction Concentration	Challenge Concentration	Results (No. Reacting Humans)
370 ppm	3,700 ppm	0/45
3,700 ppm	3,700 ppm	4/48 (4.5%)
11,000 ppm	3,700 ppm	5/58 (5.7%)
18,500 ppm	3,700 ppm	4/52 (7.7%)
Unknown	30 ppm	4/8 (50%)
(clinical)	60 ppm	5/8 (63%)
	100 ppm	6/8 (75%)
	10,000 ppm	8/8 (100%)
Unknown	32 ppm	0/14
	55 ppm	2/14 (14%)
	144 ppm	7/14 (50%)

*IRMC 1984a

The CIR Expert Panel (1984) stated that "the formulation and manufacture of a cosmetic product should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2 percent measured as free formaldehyde."

HCHO skin irritation is non-immunologic; how its mechanism may differ from other forms of dermal irritation is not known.

Induction of contact urticaria by HCHO has been reported and is presumably a Type 1 allergy (Consensus Workshop, 1984). However, proof that the immunological reactions are due to an allergic response must await the demonstration of specific immune reactions such as the production of IgE or IgG antibody specific for HCHO (IRMC Subgroup on Sensitization, 1984a). Nonimmunologic contact urticaria which requires multiple applications at the same site has been reported (Consensus Workshop, 1984).

Sensitivity caused by the release of HCHO into the blood from blood dialysis treatment has been reported. Frequent eosinophilia (increase in eosinophil leukocytes) and some severe hypersensitivity and asthma-like reactions have been associated with this occurrence. Antibodies reacting with HCHO conjugated red blood cells is evidence of Type II auto allergy. The asthma-like reactions are suggestion of Type I allergy (Consensus Workshop, 1984). However, commenting on this the IRMC Subgroup stated that:

> The hemodialysis patient population should not be considered a source of IgE antibody since: (1) formaldehyde levels present during dialysis have been markedly reduced; (2) these reactions were due to systemic exposure and primarily induced an antigenic change in red blood cell surface markers; (3) only one possible case has been reported of (anaphylactic) sensitization by this route; this may resemble some reactions caused by endotoxins present in dialysis equipment. In this case patients were exposed to allergens other than formaldehyde (personal communication from Ronald M. Easterling, M.D.).

Consequently, results from hemodialysis patients should not be generalized to indicate immunologic properties under other (inhalant) conditions.

5.3. Cellular Changes

Inhalation exposure to HCHO causes a number of cellular effects depending on the concentration and duration of exposure.

In the Kern et al. (1983) study, rats exposed to 2.0 ppm HCHO experienced rhinitis, epithelial dysplasia, and squamous metaplasia after 12 months of exposure. The frequency of squamous metaplasia increased to nearly 100 percent at the end of the exposure period at 24 months. Considerable regression was

noted at 27 months (see Figure 4-1). In a more recent study by Tobe et al. (1985), slight increases in rhinitis and squamous metaplasia were observed in rats exposed to 0.3 ppm for 28 months and those found dead. However, the frequency of squamous metaplasia falls within the 15 percent background rate for this type of lesion as seen in the Kern et al. (1983) study.

A study by Rusch et al. (1983), which measured similar endpoints in monkeys, rats, and hamsters, reported a NOEL for squamous metaplasia of 1.0 ppm. Table 5-3 clearly shows that a threshold for this response exists at about 1 ppm (rats in the Kern study experienced squamous metaplasia at 2.0 ppm). A similar threshold level is suggested for monkeys as Table 5-4 indicates. Although, the authors did not attribute the one case of squamous metaplasia to HCHO exposure, it is possible that HCHO is causing effects at or below 1.0 ppm due to the increased incidence of nasal discharge in monkeys at 0.2 and 1.0 ppm as illustrated in Table 5-5. Such a response may be due to damaged cilia of the respiratory epithelium. Recently submitted data by Woutersen et al. (1984b) on a subchronic (13-week) inhalation toxicity study with HCHO in rats (10 rats per sex at each dose) showed no squamous metaplasia in the controls, 3 of 20 at 1 ppm, 20 of 20 at 10 ppm, and 20 of 20 at 20 ppm.

Table 5-3.
Significant Findings in Nasal Turbinates
in Rats*

Group	Level (ppm)	Squamous Meta/Hyperplasia	Basal Cell Hyperplasia
I (combined (controls)	0	5/77	4/77
II	0.20	1/38	0/38
III	1.00**	3/36	0/36
IV	3.00	23/37	25/37

*Adapted from Rusch et al. (1983)
**NOEL

Table. 5-4.
Significant Findings in Nasal Turbinates
in Monkeys*

Group	Level [ppm]	Squamous Meta/Hyperplasia
I	0	0/6
II	0.02	0/6
III	1.00**	1/6
IV	0	0/6
V	3.00	6/6

*Adapted from Rusch et al. (1983)
**NOEL

Table 5-5.
Total Incidence By Groups of Monkeys*

Group (ppm)	I (0)	II (0.2)	III (1.0)	IV (0)	V (3.0)
Hoarse	0	0	0	0	32
Congestion	0	0	0	0	36
Nasal discharge	9	30	45	5	62

*Adapted from Rusch et al. (1983)

A recent report by Carson et al. (1985) in which ciliary ultrastructure in humans (85 normal children) was studied before, during, and after episodes of upper respiratory infection by electron microscopy postulated that "the frequency and nonability with which abnormal cilia appear may be related to the severity and duration of clinical symptoms such as cough and rhinorrhea (nasal discharge)." Since ciliary structure is integrally related to function, the low incidence of nasal discharge in monkeys at 0.2 and 1.0 ppm may indicate ultrastructural damage by HCHO to the mucociliary clearance system. Thus, monkeys (and humans) may be more sensitive to the effects of HCHO than rats (nasal discharge was not observed in rats).

The effect of HCHO on nasal mucociliary function in the rat has been studied by Morgan et al. (1983b) (see Section 4.4.3.2.). Male Fischer 344 rats were exposed for 6 hours per day for 1, 2, 4 or 9 days, to 0.5, 2, 6 or 15 ppm HCHO. There was a clear dose-dependent affect on mucociliary activity. At 15 ppm there was significant inhibition of mucociliary activity which progressed from anterior to posterior regions of nasal tissue. Only slight effects were noted in animals exposed to 2 or 6 ppm. At 0.5 ppm no effects were observed. Whether ultrastructural changes to cilia occurred below 2.0 ppm is unknown because the endpoints being measured were mucostasis or ciliastasis which was recorded by videocamera.

In summary, it is clear that observable cellular changes begin to occur above 1 ppm HCHO, with the extent and severity

dependent on concentration and duration of exposure. Based on data developed in rats and monkeys the NOEL for squamous metaplasia and rhinitis can be placed at 1.0 ppm. Ultrastructural changes in the mucocillary clearance system may be occurring as low as 0.2 ppm, although this is far from certain.

The practical consequence of the cellular changes noted is a disturbance of the mucociliary clearance mechanism. Since this system is an important defense mechanism in the removal of particulate matter, including microbes, impairment of this defense mechanism may increase the susceptability of persons to infections and other respiratory diseases (Proctor, 1982; Comroe, Jr., 1974; Widdicombe, 1977).

5.4. Central Nervous System Effects

Reports in the literature link HCHO with a number of behavioral and physiologic effects such as thirst, dizziness and apathy, inability to concentrate, sleep disturbances, etc. Central nervous system responses to HCHO have been tested in a variety of ways, including by determination of optical chronaxy, electroencephalographically, and by measuring the sensitivity of the dark-adapted eye to light. Responses are reported to begin in some persons at 0.05 ppm and are maximal in individuals at about 1.5 ppm. HCHO at less than 0.05 ppm probably has little or no objective adverse effect (NRC, 1981).

5.4.1. Neurochemical Changes

Studies using radio labeled HCHO have shown radioactivity in the brains of rats after inhalation exposures. However, the chemical identity of the radioactive material has not been determined.

HCHO has been shown to affect the firing rate of nasopalatine and ethmoidal nerves of the trigeminal nasal sensory system. Besides being able to effect changes in the respiratory rate of animals, HCHO also appears to be able to depress trigeminal nerve response to other irritants, although the data in this regard are not conclusive.

Whether HCHO is capable of causing morphological changes in the CNS is unclear. In two studies reviewed by the Consensus Workshop (1984), conflicting results were seen. In one study, structural and cytochemical changes were seen in the cerebral amygdaloid complex of rats exposed to 1 to 3 mg/m^3 of HCHO for 3 months. In contrast, monkeys injected intravenously over several hours with HCHO for a total dose of 0.9 g/kg showed no histologically detectable effects in the CNS.

5.4.2. Human Studies

A number of reports are available which link chronic HCHO exposure to a number of psychological/behavioral problems including depression, irritability, memory loss and decreased attention capacity, and sleep disturbances. Unfortunately, these studies for the most part have involved field surveys using subjective self-report symptom inventories. Control data are

often inadequate or completely absent. This is a significant problem when dealing with HCHO, which in addition to any direct toxic effects possibly associated with it, produces distinct olfactory cues which may stimulate a spectrum of secondary psychological reactions (e.g., expectancies, irritations, anxieties, fears, etc.). These reactions may in turn exacerbate, mask, or interfere with the more direct neurologic, biochemical, and physiological responses to HCHO (Consensus Workshop, 1984).

Nine studies of human populations were reviewed by the Consensus Workshop (1984), but most had serious methodologic problems. For instance in studies by Dally et al., Sardinas et al., Garry et al., and Woodbury and Zenz, health complaints such as headaches and difficulty in sleeping were linked to HCHO exposure. However, these studies do not include control populations and suffered from selection bias.

Thun and Altman have pointed out some of the difficulties in prevalence surveys of symptoms in residents from UFFI homes, including olfactory cues, respondent and recall biases, and the objective outcomes measured. No significant difference was found in the occurrence of headaches or insomnia in residents of homes with UFFI, compared to neighborhood controls.

In contrast, a study by Olson and Dossing found a significantly greater prevalence of nose and throat irritation, unnatural tiredness, and headaches in exposed subjects than in controls. While this study overcomes many of the design problems previously discussed, responses still may have been based by an awareness of the subjects of the study goals and hypotheses.

Attempts have been made to evaluate reported symptoms using formal tests of neuropsychological function. A study by Schenker et al. found that persons living in UFFI homes who had complained of memory impairment had negative results on formal tests of memory function, although positive findings were seen for many regarding attention span. In addition, a study by Anderson found no effect on performance tests of 16 healthy volunteers exposed to HCHO under controlled laboratory conditions (Consensus Workshop). A more recent study by Kilburn et al. of histology technicians showed a higher prevalence of acute and neurological effects such as headache, loss of balance, insomnia, memory loss, etc., than in controls. When 25 technicians were evaluated using neurobehavioral tests (block design, digit symbol, and embedded figure), a few deficits were seen compared to expected results (IRMC Subgroup on Systemic Effects, 1984b).

Commenting on the human data the Workshop Panel stated that the information "suggests that formaldehyde may affect the psychological functioning of the individual in three ways: (1) directly, as a result of the immediate toxic properties of the substance on the peripheral and central nervous systems; (2) indirectly, as a result of the individual's monitoring and awareness of the aforementioned changes and his/her interpretation and reaction to such changes, which, in turn, feeds back into the central nervous system; and (3) as a result of the individual's psychological reaction and concomitant CNS response to the olfactory properties of the substance. In

practice, these processes are interdependent, yet this simple analysis of a complex series of responses underlines the need to control for 'expectancy' effects in formaldehyde research to permit a differentiation of the direct effects of formaldehyde on psychological functions from it ssecondary effects."

5.4.3. Conclusion

Based on the body of data available on the effects of HCHO on the nervous system, the Workshop Panel concluded that:

> The effects of formaldehyde and/or its metabolites on the biochemistry of the nervous system have not been clearly defined. Various possibilities exist whereby such effects might be mediated.
>
> Some evidence exists that exposure to formic acid (the principal metabolite of formaldehyde) in vapor form at high concentrations exercises nervous system toxicity in intact rats.
>
> The irritant effects of formaldehyde may be reflected in altered function of sensory nerves such as the trigeminal nasal sensory system. The presence of morphological changes in the CNS has been observed in one study and not in another.
>
> The difficulties inherent in any study of psychological/behavioral effects of formaldehyde have not yet been overcome in the course of conducting field surveys.
>
> Epidemiologic studies evaluating neuro-psychological symptoms potentially due to occupational or environmental exposure to formaldehyde have failed to overcome the problems commonly associated with such studies. However, some studies merit further investigation.

5.5. Developmental and Reproductive Effects

5.5.1. Animal Studies

A number of studies have been reported which measured the potential of teratogenic or reproductive effects of HCHO.

Ulsamer et al. (1984) reviewed four inhalation studies. No teratogenic effects were reported. However, other effects in dams and fetuses were reported.

A dermal study by Overman, as reviewed by Ulsamer et al. (1984), reported that applications of formalin to the backs of pregnant hamsters for 2 hours per day on days 7-11 of gestation increased resorptions and birth defects. A repeat of the study did not bear this out.

A study by Marks et al. was reviewed by the Consensus Workshop (1984) which concluded that it was the only adequate study of possible teratogenic effects of HCHO in mammals.

The Workshop review is as follows:

> Marks and colleagues intubated pregnant mice on days 6 through 15 of gestation with 0, 74, 148 or 185 mg/kg/day. At the highest dose, 22 of the 34 pregnant mice died. At that dose, there was an increased incidence of resorptions, but that increase was not statistically significant. At no dose did the incidence of resorptions differ between the treated and control groups. There were also no treatment-related differences in the mean number of implantations, stunted fetuses, live fetuses per litter, or average fetal body weight per litter. At a dose which killed more than 50 percent of the dams, no adverse reproductive outcomes were observed except for the increase in the incidence of resorptions that was not statistically significant.

To measure the teratogenic potential of HCHO generated <u>in vivo</u>, a number of investigators exposed animals to hexamethylenetetramine by feeding or by drinking water. Studies by Della Porta et al., Hurni and Ohder, and Natvig et al. were variously reviewed by the CIR Expert Panel (1984), Ulsamer et al. (1984), NRC (1981), and the Consensus Workshop (1984). No malformations were noted in any of the studies.

The Consensus Workshop (1984) reviewed studies of reproductive effects. In one study, prolonged diestrus, but no impairment of reproductive function was reported. Ovarian involution and endomentrial atrophy were observed in another study, but only in female mice exposed to 40 ppm HCHO (a concentration which killed 80 percent of the animals). Other studies were reviewed but were found to be of little value because of methodologic problems.

5.5.2. Human Data

No data have been found linking HCHO to teratogenic effects in humans. However, the Consensus Conference Panel stated that:

> There is indirect evidence that would argue against formaldehyde being a major human teratogen. Over the last 30 years, the annual production and domestic use of formaldehyde in the United States has gone up fivefold from one billion pounds. Birth defects have been reasonably stable over the last 30 years, although in the last decade, there have been some exceptions to this rule. The reported incidence of ventricular septal defects and patent ductus arterious has increased and that of anencephaly and spina bifida has declined.

Review of reports of reproductive effects by the Consensus Workshop (1984) and the IRMC Systemic Effects Subgroup (1984b) did not lead to firm conclusions regarding HCHO's potential to cause reproductive effects for a number of reasons. In a study by Shumilina, workers exposed to urea-HCHO resins were reported to have a threefold increase in menstrual disorders and produced more babies weighing between 2500 and 3000 g than the controls. The IRMC Systemic Effects Subgroup concluded that because of a lack of information on the worker environment and the

socioeconomic conditions of the study and control groups, plus the fact that other conditions such as stress and personal and nutritional habits are associated with the effects reported, the role of HCHO in the development of the reported disorders is uncertain. In a better designed study, reviewed by the IRMC Subgroup and the Workshop, Olson and Dossing studied a group of female workers in a mobile home day care center who were exposed to 0.43 mg/m^3 of HCHO, they reported increased incidence of eye irritation, headache, and use of analgesics in the group. In addition, 30 percent of the exposed group had a history of menstrual irregularity. The Consensus Workshop (1984) felt that these two studies point to the need for further research, but do not show a cause-and-effect relationship between exposure to HCHO and menstrual disorders.

In two other reports reviewed by the IRMC (1984b), an increased incidence of miscarriages, changes in menstrual cycles, and an increase in ovarian cysts were reported in one study of female histotechnicians while a high incidence of sexual dysfunction among male workers making fiber-reinforced plastic was reported in another. In both instances, the workers were exposed to chemicals other than HCHO, especially the male workers, and the results may be due to the complex effects of numerous chemicals, rather than HCHO alone.

The Consensus Workshop (1984) reviewed three studies related to the potential of HCHO to cause germ-cell mutations. A study by Ponlignie-Houbrechts reported increased pre- and post-

implantation losses in the first week of mating, following exposure of male mice to 50 mg/kg of HCHO by injection, and an increase in preimplantation loss in the third week. No evidence of increased dominant lethal effects were seen in a study by Epsteion et al. where mice were exposed at doses of up to 40 mg/kg, IP. Finally, Cassidy reported increased sperm abnormalities in rats exposed to a 200 mg/kg, but not in rats given 100 mg/kg orally. "Thus the data are not consistent and do not adequately test the possibility that formaldehyde causes germ-cell mutations" (Consensus Workshop, 1984). However, these data may not be inconsistent given different routes of exposure. More work in this area may be needed.

Commenting on the possibility of one type of germ-cell mutation the Workshop stated that "Human germ-cell mutations causing nondisjunction could result in an increase in Down's Syndrome. The constancy of maternal age-specific rates of Down's Syndrome over the last 30 years, in face of increased exposure, suggests that exposure to formaldehyde is not causing nondisjunction in humans."

5.5.3. Conclusion

Ulsamer et al. (1984), the Workshop, and the IRMC Subgroup concluded the following regarding the potential of HCHO to cause teratogenic or reproductive effects.

Ulsamer et al.:

> The currently available data do not show that the embryo is unusually sensitive to formaldehyde nor is there any information to show that formaldehyde is teratogenic in rodents when administered orally or

applied dermally in nontoxic amounts to the dams. Also, the *in vitro* data do not provide any evidence to support the conclusion that formaldehyde causes terata at exposure concentrations that are not toxic to the adult.

Inhalation of formaldehyde has caused fetotoxic effects but not teratogenic effects. Further studies of formaldehyde exposure by inhalation are needed to elucidate the meaning of these changes. Limited evidence suggests that formaldehyde may affect the menstrual cycle and perhaps reproduction in women repeatedly exposed. Additional work is needed to validate these findings.

IRMC Subgroup:

Reproductive function depends upon a sensitive and integrated feedback system between the nervous system and the reproductive organs. Thus, many chemicals that affect the nervous system have the potential to affect reproduction. It is possible that formaldehyde, by affecting the nervous system induces indirect changes in reproductive behavior and reproduction. Although mechanisms for such have not been delineated, several recent reports that show an increase in the incidences of brain tumors in humans exposed to formaldehyde provide indirect evidence of the potential of formaldehyde to significantly affect the CNS.

Consensus Panel:

In summary, the panel could find no evidence clearly demonstrating that formaldehyde caused adverse reproductive outcomes. What it found was a paucity of information from which to make inferences and data that suggested hypotheses to be tested in future studies. This panel feels that formaldehyde poses little, if any, risk as a potential human teratogen. This judgment is based on the irritation potential of formaldehyde at extremely low ambient concentrations (0.05 ppm), existing data from *in vivo* mammalian studies, and toxicokinetic and metabolism data indicating an extremely short half-life (not detected to 1.5 min) of the parent compound, and relatively short half-life (80 to 90 min) of the only known metabolite (formate) in the blood, regardless of the route of exposure.

5.6. Effects on Visceral Organs

The potential effects of HCHO on visceral organs has received relatively little attention. One recent review article by Beall et al. (1984) summarizes the association between exposure to HCHO and the liver. Based on the literature reviewed, it appears that HCHO causes hyperemia or inflammation in liver and kidney in rats. Microscopically, HCHO also causes cloudy swelling, cytoplasmic vacuolization, and necrosis in the liver, and hyperemia, edema, and necrosis in the kidney. Macroscopic changes in the liver have also been produced by HCHO. When exposure is repeated over a period of weeks, changes include a mottled appearance and a decrease in liver weight. Following a single high exposure, liver size may increase. Effects on viscera could result from indirect mechanisms or be secondary to other effects near the site of first contact. Under some circumstances, GSH detoxification mechanisms may be involved (IRMC, 1984b).

Transient effects on the hematopoietic system occurred in rats and mice after 6 months of exposure to HCHO by inhalation. These effects were reflected by statistically significant decreases in (1) reticulocytes in female mice exposed to 2.1, 5.6 or 14.3 ppm; (2) mean corpuscular hemoglobin in male and female rats exposed to 14.3 of HCHO; and (3) mean corpuscular hemoglobin concentration in male rats exposed to 2.1, 5.6 or 143. ppm of HCHO. Male and female rats had significant ($p<0.05$) increases in mean corpuscular hemoglobin, mean corpuscular hemoglobin

concentration, and myeloid to erythroid ratios after 13 weeks of exposure by inhalation to 12.7 ppm of HCHO. This could indicate myeloid hyperplasia or erythroid hypoplasia. Thus, it is possible effects on visceral organs could be partially caused through changes in the hematopoietic system as well as through other mechanisms (IRMC, 1984b).

6. EXPOSURE ASSESSMENT

6.1. Introduction

The sources of HCHO can be grouped into two major categories: direct (or commercial) production and indirect production. The chemical is not imported in any appreciable quantities.

Commercially, HCHO is produced from the catalytic oxidation of methanol, using either silver oxide or a mixed-metal oxide as the catalyst. Processes accounting for the indirect production of HCHO include the photochemical oxidation of airborne hydrocarbons released from incomplete combustion processes, the direct production of HCHO during incomplete combustion of hydrocarbons in fossil fuels and refuse, and certain natural processes.

The 1983 commercial production of HCHO amounted to about 6 billion pounds. The major derivatives are urea-HCHO resins, phenol-HCHO resins, acetal resins, and butanediol. The urea- and phenol-HCHO resins account for about 53 percent of HCHO production. Adhesives and plastics are the major end uses.

The "consumption" of HCHO can be broken down into three major categories: nonconsumptive uses, pseudo-consumptive uses, and consumptive uses. In nonconsumptive uses, the chemical identity of the HCHO does not change. In pseudo-consumptive uses, the chemical identity of HCHO does change, but it is not irreversibly altered. Under appropriate conditions, some or all of the original HCHO may be regenerated. Consumptive uses, on

the other hand, are those uses in which HCHO serves as a feedstock for the preparation of other chemicals. The derivatives are irreversibly formed and usually contain only residual levels of unreacted HCHO. Under extreme conditions, such as very high temperatures or highly acidic conditions, some of the derivatives may degrade and release HCHO.

HCHO's major nonconsumptive uses are (1) disinfectant, (2) preservative, (3) deodorant, and (4) textile and paper uses.

The major pseudo-consumptive uses are (1) urea-HCHO resins which are used in fiberboard, particleboard, plywood, laminates, urea-HCHO foams, molding compounds, and paper, textiles, and protective coatings; (2) urea-HCHO concentrates which are used to produce time-release fertilizers, and (3) hexamethylenetetramine which is used as a special anhydrous form of HCHO to cure resins and to treat textiles and rubber.

The major consumptive uses are (1) melamine-HCHO resins which are used for molding compounds, fiberboard, particleboard, plywood, laminates, paper and textiles, (2) phenol-HCHO resins which are used in fiberboard, particleboard, plywood molding compounds, and insulation; (3) pentaerythritol which is used to produce alkyd resins, (4) 1,4-butanediol which is used to produce tetrahydrofuran, (5) acetal resins which are used in the manufacture of engineering plastics, and (6) trimethylolpropane which is used in the production of urethanes.

6.2. Estimates of Current Human Exposure

To obtain estimates of human exposure to HCHO and its products, the Agency commissioned a contractor study (Versar, 1982). This study integrated the existing monitoring data, engineering or modeling estimates, use data, population estimates, and assessment of the likelihood of exposure from HCHO-related activities into an exposure assessment detailing those activities having a high HCHO exposure potential. EPA has updated some portions of this assessment to reflect new data received in response to the FEDERAL REGISTER notice of November 18, 1983 and other data gathered by EPA. The combined data were used as the basis for this risk assessment.

Since specific monitoring data for all types of potentially exposed worker classifications or operational settings within an industry were generally not available, all workers in a given industry were assumed to be exposed to the mean exposure levels reported for that industry; in this case garment workers. All worker exposure, however, is not in fact identical; worker exposure can vary because of the physical characteristics of the work site and the employee's work station for example. However, in the absence of data EPA must make reasonable assumptions regarding exposure levels. Workers in the garment industry were assumed to be exposed 5 days per week for 40 years. General population exposures (conventional home residents) were assumed to be for 70 years. Manufactured home residents were assumed to be exposed 112 hours per week for 10 years.

The reported exposure levels are assumed to be representative of the actual exposure levels for a given population. The limitation that this assumption presents is that the estimated exposure levels for some populations may differ, in some cases widely, from the actual situation. This is especially true for those populations or subpopulations for which little or no monitoring data are available and also for those populations for which the monitoring data were collected as a result of complaint investigations.

6.3. Populations at Risk

As discussed previously the two populations at risk are certain home residents and garment workers.

6.3.1. Home Residents

The current population of relatively new manufactured homes is approximately 4,500,000. This figure includes those people living in homes manufactured since 1976 (Versar, 1982). However, prospective population estimates are also important. Based on a projection of manufactured housing starts by Versar (1985a), it is estimated that 6,642,000 persons will occupy a new manufactured home during the next ten years. This figure assumes 295,203 starts per year and 2.25 persons per home.

Similarly, 1,579,000 new conventional homes will be started each year for the next ten years with an occupancy rate of 2.53 persons for a total of 40,011,000 persons.

6.3.2. Garment Workers

The number of potentially exposed garment workers is estimated to be 777,000 (Versar, 1982) out of 1,100,000 workers employed in the U.S. apparel industry (Ward, 1984). This figure may drop in the future due to increased foreign competition and the introduction of labor saving equipment.

6.3.3. Summary

Table 6-1 presents population estimates for the two housing segments and garment manufacture. Assuming that the number of potentially exposed garment workers remains steady at 770,000, then a total of 47,430,000 persons over the next ten years may have the potential to be affected by HCHO's noncancer effects.

Table 6-1.
POPULATIONS AT RISK

Category	Present* Population	Future** Estimates	
		per yr	10 yrs
Manufactured homes	4,500,000	664,200	6,642,000
Conventional homes	100,000,000	4,001,100	40,011,000
Garment workers	777,000	N/A	N/A

* Versar, 1982
** Versar, 1985a

6.4. Sources of HCHO in Categories of Concern

The principal sources of HCHO in the two categories of concern are HCHO-based resins, principally urea-HCHO (UF) resins. In homes, these resins are used to bond the wood plys used to make plywood and to bind the wood particle and fibers used to make particleboard and medium density fiberboard. For garments, HCHO-based resins are used to impart permanent press finishes to the garments.

6.4.1. Homes

6.4.1.1. Pressed-wood products

Pressed-wood products are used in flooring, interior walls and doors, cabinetry, and furniture. The three principal types of products containing UF-resin are particleboard, medium-density fiberboard (MDF), and hardwood plywood.

Particleboard is composition board comprised of 6 to 10 percent resin (by weight), and small wood particles. UF resin is used in the majority of particleboard (about 90 percent). The 1983 production of particleboard was over 3 billion square feet, of which 70 percent was used in furniture, fixtures, cabinets, and similar products. The remaining 30 percent is used for construction, including manufactured home manufacture (common uses are as decking or flooring underlayment).

MDF is also a composition board. It is comprised of wood fibers and 7 to 9 percent UF-resin. Approxmately 95 percent of MDF production (over 600 million square feet in 1983) was used to manufacture doors, fixtures, and cabinetry. The extent to which

MDF is used in housing is uncertain and is probably highly variable.

Unlike the two composition boards discussed above, hardwood plywood is a laminated product; the resin is used as a glue to hold thin layers of wood and veneers together. Of the nearly 2 billion square feet produced in 1983, 55 percent was used for indoor paneling, 30 percent for furniture and cabinets, and 15 percent for doors and laminated flooring.

Each of the pressed-wood products described above contain UF resins which release HCHO over time. The release is attributable to incomplete crosslinking of HCHO resin during manufacture and release of HCHO via resin decomposition or hydrolysis.

6.4.1.2. Other Sources of HCHO

Indoor HCHO concentrations may be attributable to sources other than pressed-wood products containing UF resin. The other sources can be characterized as follows:

- Urea-HCHO foam insulation (UFFI) (existing homes only)
- Products with phenol HCHO resins (PF)
  - softwood plywood
  - hardboard
  - waferboard
  - oriented strand board
  - fibrous glass insulation
  - fibrous glass ceiling tiles
- Consumer products that may contain HCHO resins
  - carpeting
  - upholstry fabric
  - drapery fabric
  - other textiles
- Combustion products
  - unvented kerosene and gas appliances
  - smoke from tobacco products
  - combustion of wood or coal in fireplaces

- Outdoor air
  -- ventilation system air exchange

Compared to pressed-wood products, with the exception of UFFI, the other sources are usually minor contributors to HCHO concentrations in conventional and manufactured homes.

6.4.2. Garment Manufacture

The principal source of HCHO in the garment manufacturing workplace, is the release of HCHO from fabric treated with resins that impart durable or permanent press properties. The textiles normally treated are blends of cotton, acetate, and rayon. These fabrics account for 60-80 percent of the textile produced annually.

The resin of choice is dimethyldihydroxyethylene urea (DMDHEU) and its alkylated derivatives. It is estimated that approximately 90 percent of the durable press resin market is accounted for by DMDHEU. Other resins used are urea-HCHO, melamine HCHO, and carbmate resins, plus a HCHO/sulfur dioxide vapor phase process.

HCHO is released from treated fabric in three phases. In Phase I, any HCHO loosely held by Van der Waal forces is released as the fabric is dried. Release of HCHO by this mechanism is usually complete by the time garment workers receive the fabric. Surface desorption occurs during Phase II. This represents the release of HCHO which is not covalently bound to the fabric, and can last up to 240 hours. The material is normally stored during this phase, and increased ventilation can

increase the rate at which HCHO is desorbed. Phase III, in which hemiacetal hydrolysis is the mechanism of release, is thought to be the phase of HCHO release which results in worker exposure at the manufacturing site. Release of HCHO by the hydrolysis mechanism is independent of air changes, but dependent on humidity and temperature (Ward, 1984)

6.5. HCHO Levels in Homes and Garment Manufacturing Sites

6.5.1. Manufactured Homes

HUD has recently promulgated changes in its Manufactured Home Construction and Safety Standards (24 CFR 3280). That set product emission standards for particleboard (0.3 ppm) and plywood (0.2 ppm) as published in the FEDERAL REGISTER of August 9, 1984 (47 FR 31996). HUD believes that if the product standards are met and no other major emitters of formaldehyde are present (e.g., medium density fiberboard), ambient levels will not exceed 0.4 ppm (0.15 ppm 10 year average) under certain temperature, humidity, and ventilation rate conditions. The HUD regulations, however, were designed to reduce acute reactions to HCHO and are not based on HCHO's potential carcinogenicity in humans.

EPA estimates an average ambient HCHO level of 0.19 ppm for manufactured homes (Versar, 1985b). EPA has used this estimate and the estimated 10-year average for homes built under the HUD standard (0.15 ppm) in the quantitative cancer risk assessment. Another study has reported average levels of 0.54 ppm for manufactured homes less than three years old and 0.19 ppm for

homes older than three years (State of Wisconsin, 1983). The Exposure Panel of the Workshop (1984) reported studies that showed average ambient levels of 0.38 ppm for manufactured homes not subject to complaints about HCHO odor by residents, and averages of 0.38 ppm to 0.90 ppm for complaint homes. Thus, an unrealistic worst case exposure estimate was not used to estimate human risk. Also, only 10 years of exposure were assumed for manufactured homes. Specific exposure data follow.

Figure 6-1 details mean HCHO levels in manufactured homes by year of manufacture. However, as Table 6-2 illustrates, reported means for any given home age naturally mask variations in the HCHO levels persons are exposed to. In relatively new homes, levels above 1.0 ppm have been recorded. Consequently, due to construction differences and differences in temperature and humidity, new manufactured homes may experience episodic levels exceeding 1.0 ppm. It is generally accepted that HCHO levels decline with home age as Figure 6-2 illustrates. However, Figure 6-1 makes an additional point. The Conyers (1984) study, initiated in 1980, showed mean HCHO levels for new mobile homes of around 0.875 ppm. Studies begun in more recent years (Hodges, 1984; University of Texas, 1984; MHI, 1984) indicate that initial HCHO levels in new homes have declined to below 0.4 ppm. This is true not only of the MHI (1984) study that sought to test the performance of a new home against the HUD standard, but also of other studies in 1981 and 1983 of homes less than one year old which showed levels around 0.2 ppm HCHO. This interpretation is, however, based on a relatively small data set.

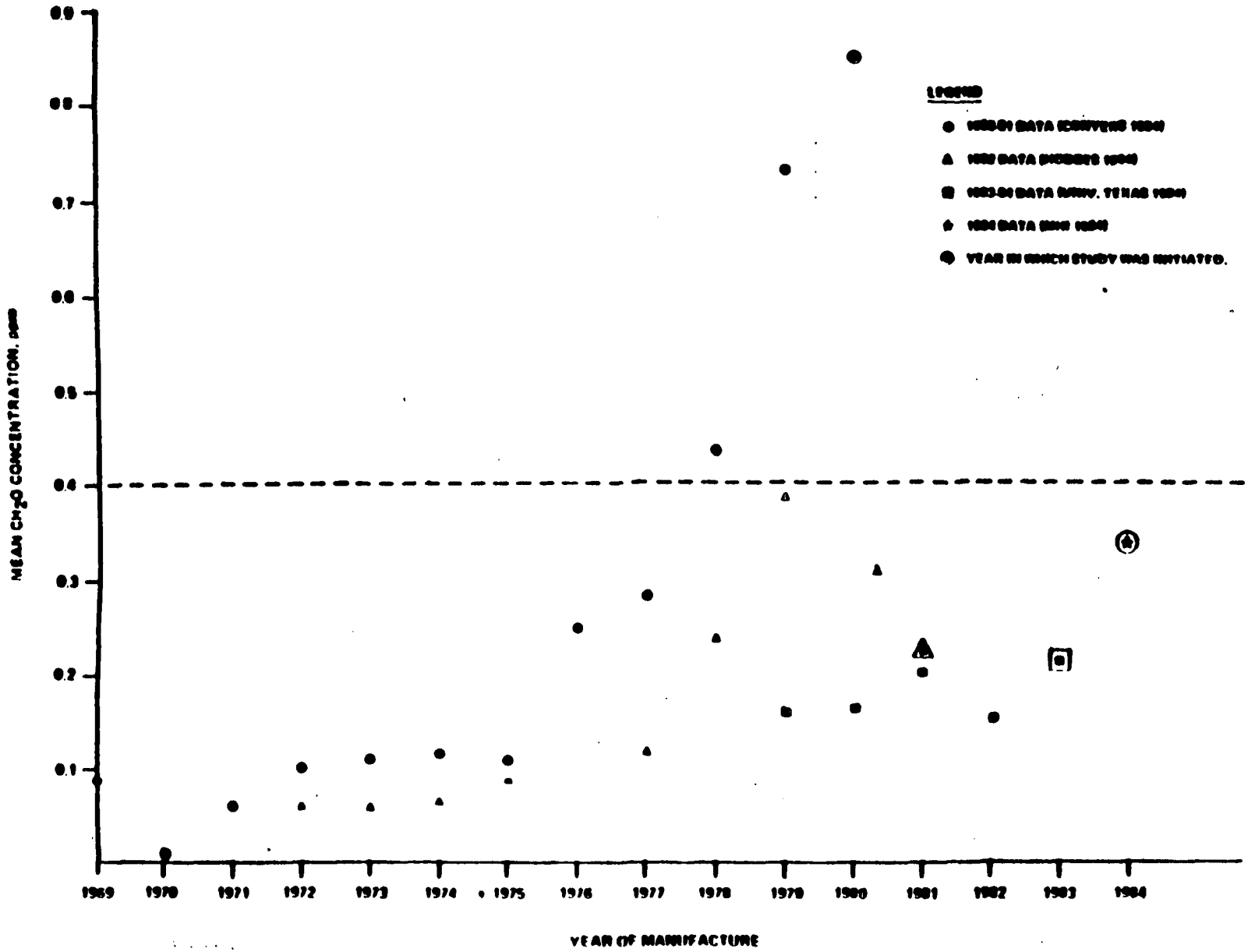
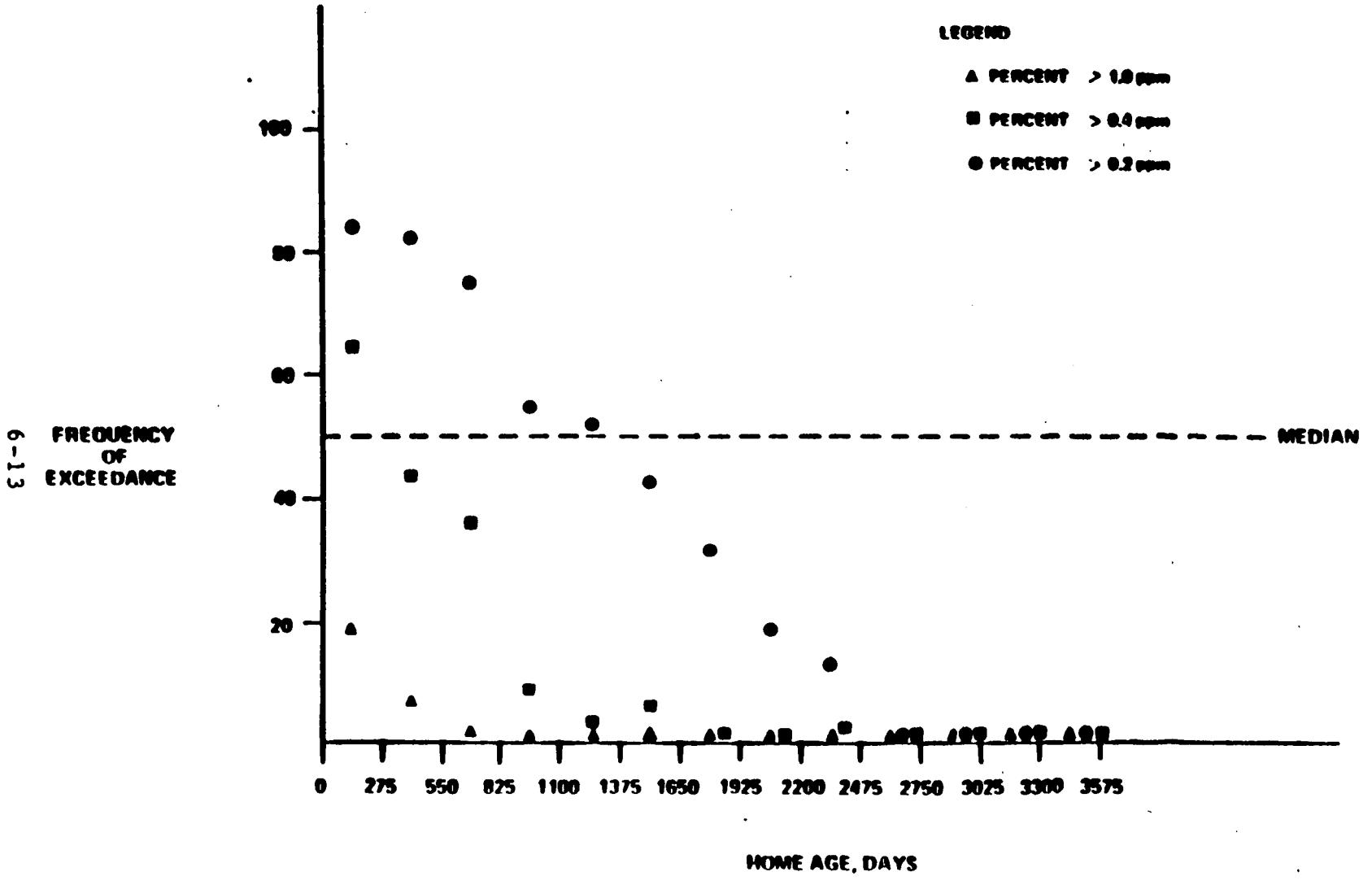


Figure 6-1. LEVELS IN MOBILE HOMES CORRESPONDING TO YEAR OF MANUFACTURE

Table 6-2. Summary of Formaldehyde Concentrations Measured in Complaint Mobile Homes in Kentucky from September 1979 through December 1980

Year of manufacture	Home age (years)	Number of homes sampled	Mean conc. (ppm)	Min. conc. (ppm)	Max conc. (ppm)
1980	<1	8	0.85	0.63	1.53
1979	1-2	31	0.78	0.14	1.99
1978	2-3	17	0.44	0.01	0.87
1977	3-4	7	0.28	0.10	0.72
1976	4-5	10	0.25	0.08	0.53
1975	5-6	5	0.11	0.04	0.23
1974	6-7	8	0.12	0.04	0.31
1973	7-8	7	0.11	0.04	0.28
1972	8-9	3	0.10	0.01	0.22
1971	9-10	2	0.06	<0.04	0.08
1970	10-11	1	0.01	0.01	0.01
1969	11-12	4	0.08	<0.04	0.19

Source: Conyers (1984).


LEGEND
▲ PERCENT > 1.0 ppm
■ PERCENT > 0.4 ppm
● PERCENT > 0.2 ppm
100
80
60
40
20
MEDIAN
FREQUENCY OF EXCEEDANCE
0
275
550
825
1100
1375
1650
1925
2200
2475
2750
3025
3300
3575
HOME AGE, DAYS

Levels measured at any one temperature and humidity can, however, be misleading. Table 6-3 which illustrates the effect of temperature and humidity changes on a 0.4 ppm reading at 25°C/50 percent relative humidity (the HUD standard) shows that under more extreme conditions (30°C/70 percent RH), the predicted level would rise to 0.92 ppm. Changes in temperature and humidity could be expected with diurnal and seasonal weather fluctuations; homes without constant climate control would therefore be affected.

These data illustrate clearly that HCHO levels in homes are the functions of multiple variables; neither age nor temperature and humidity, nor any other variables can account for all variations in residential levels (Versar, 1985b).

As the foregoing illustrates, HCHO levels in new manufactured homes were tending toward 0.4 ppm and in some cases above, until about 1979. After that date, mean HCHO levels in new manufactured homes began to fall or at best leveled off slightly below 0.4 ppm. Even so, peak levels above 0.4 ppm can be expected at times due to adverse temperature and humidity conditions. The frequency for such peaks is not known with confidence, but based on the data available (see Tables 6-4 and 6-5, and Figure 6-1) they could be expected to occur in a substantial fraction of new manufactured homes.

Table 6-3. Potential Effects of Temperature and Relative Humidity Changes on Formaldehyde Air Concentrations (ppm)*

Temperature	Relative Humidity				
	30%	40%	50%	60%	70%
59°F (15°C)	0.08	0.11	0.14	0.17	0.19
68°F (20°C)	0.15	0.19	0.24	0.29	0.33
77°F (25°C)	0.24	0.32	0.40	0.48	0.56
86°F (30°C)	0.40	0.53	0.66	0.79	0.92

*Calculated using equations in Myers, 1984 which were developed primarily from data on relatively new pressed wood products and new homes. Assumes a temperature coefficient of 8,930 and a humidity coefficient of 0.0195. Assumes a base formaldehyde measurement of 0.40 ppm at 25°C and 50 percent relative humidity.

Table 6-4.
FREQUENCY OF OBSERVATIONS FOUND IN CONCENTRATION INTERVALS BY CLAYTON ENVIRONMENTAL CONSULTANTS

Concentration Interval (ppm)	Percent of Sampled Homes[a]		
	≤0.5 yrs	>0.5-1 yr	All Homes
0.0 - .10	3.6	8.0	8.1
.11 - .20	7.9	4.0	19.7
.21 - .30	6.5	36.0	14.3
.31 - .40	7.2	16.0	9.3
.41 - .50	5.8	0.0	5.0
.51 - .60	6.5	12.0	4.6
.61 - .70	5.8	16.0	4.6
.71 - .80	5.8	4.0	3.9
.81 - .90	6.5	0.0	3.9
.91 - 1.00	12.2	4.0	7.7
1.1 - 2.00	24.5	0.0	14.7
2.1 - 3.00	7.9	0.0	4.2
Number of homes	139	25	259

[a] 259 "noncomplaint" mobile homes up to eight years old were sampled in 1980-1981.

Source: Versar statistical analysis of data supplied by Singh et al. (1982).

Table 6-5.
FREQUENCY OF OBSERVATIONS FOUND IN CONCENTRATION INTERVALS BY WISCONSIN DIVISION OF HEALTH

Concentration Interval (ppm)	Percent of Observations[a] ≤0.5 yrs	>0.5-1 yr	All Homes
0.0 - .10	2.63	3.8	14.1
.11 - .20	29.0	13.6	20.4
.21 - .30	0.0	21.1	18.4
.31 - .40	10.5	14.6	14.0
.41 - .50	10.5	11.3	9.2
.51 - .60	13.2	12.2	8.0
.61 - .70	10.5	8.9	5.2
.71 - .80	7.9	5.6	3.6
.81 - .90	2.6	3.3	2.2
.91 - 1.00	2.6	0.0	0.7
1.1 - 2.00	10.5	5.2	3.8
2.1 - 3.00	0.0	0.5	0.3
Number of observations	38	213	976

[a] 137 "noncomplaint" mobile homes up to nine years old were sampled in 1980-1981. Each home was sampled at least six times at monthly intervals. The data in the table reflect the results of 976 measurements.

Source: Versar statistical analysis of data supplied by Wisconsin Division of Health (1984).

6.5.2. Conventional Homes

The average HCHO levels reported in several monitoring studies of conventional homes range from less than 0.03 to 0.09 ppm. Newer homes and energy efficient homes tend to have higher formaldehyde levels (often exceeding 0.1 ppm) than older homes (Versar, 1985b). Much of this information was gathered in homes that were used as controls in studies of UFFI homes. Based on these data, EPA estimates an average HCHO level of around 0.030 to 0.050 ppm in conventional homes as a long-term average. Specific exposure data follow.

The Lawrence Berkeley Laboratory (LBL) has summarized HCHO concentrations in 40 residenital indoor environments since 1979 (Girman et al., 1983). They have found that HCHO concentrations in homes designed to be energy-efficient are somewhat higher than concentrations in conventional homes. The maximum reported value is 0.214 ppm in an energy-efficient home in Mission Viejo, California. Data are not sufficient to allow calculation of mean levels.

As part of the development of an indoor air pollution model based on outdoor pollution and air exchange rates, Moschandreas et al. (1978) studied the patterns of indoor aldehyde levels monitored in 17 houses in the U.S. These data can be useful if we assume HCHO constitutes 60 percent of total aldehydes, based on LBL data (Girman et al., 1983).

The results in Moschandreas et al. (1978) concluded that the 17 houses had an average aldehyde concentration of 0.09 ppm.

Applying the 60 percent factor, the average HCHO concentration for the houses would be 0.05 ppm. The highest mean for any one home was 0.26 ppm; the range for that home was 0.2 to 0.45 ppm. Another home with a mean of 0.20 ppm reported a range of 0.07 to 0.5 ppm. For no other conventional home did levels exceed 0.4 ppm.

A University of Iowa Study (Schutte et al., 1981), performed for the Formaldehyde Institute, monitored 31 conventional, detached homes not containing urea-HCHO foam insulation (UFFI) for HCHO concentrations in the indoor air. Samples were evaluated in relation to outdoor HCHO concentrations, age of the home, and other environmental factors monitored at each of the sampled homes.

The average indoor concentration found in the homes was 0.063 ppm (standard deviation = 0.064) with a range of 0.013 to 0.34 ppm. In only 5 of the 31 homes were average concentrations higher than or equal to 0.1 ppm. The average outside HCHO concentration was 0.002 ppm (standard deviation = 0.0013). In addition, the correlation (from a linear regression) of the natural log [CH_2O] versus age of the home resulted in a correlation significance at the 95 percent confidence level (R = -0.42).

The 1981 Canadian study (UFFI/ICC, 1981) also studied non-UFFI homes. Table 6-6 summarizes these data, showing that levels in none of the 378 homes exceeded 0.2 ppm.

Table 6-6. Comparison of Non-UFFI Canadian Homes by Average HCHO Concentration

Average formaldehyde concentration (ppm)	Number of homes	Percentage	Cumulative percentage
<.01	48	12.7	12.7
.01-.025	111	29.4	42.1
.025-.040	97	25.7	67.8
.040-.055	67	17.7	85.5
.055-.070	30	7.9	93.4
.070-.085	15	4.0	97.4
.085-.10	—	—	—
.1-.15	9	2.4	99.8
.15-.20	1	0.3	100.1
>.2	—	—	—
Totals	378	100.1	

Source: UFFI/ICC (1981).

A report by Virgil J. Konopinski (1983) of the Indiana State Board of Health summarizes the results of a series of investigations conducted from 1979 through 1983 to determine HCHO levels in conventional homes in Indiana. The purpose of the 1983 report was to compare the levels found in those homes using other types of insulation. The mean HCHO level in the 120 homes without UFFI was 0.09 ppm (0.05 for homes with UFFI). That mean could be skewed by the maximum concentration of 1.35 ppm reported in one home.

From April to mid-December 1982, Oak Ridge National Laboratory (ORNL) with the U.S. Consumer Product Safety Commission (CPSC) studied indoor air quality in 40 east Tenessee homes. The objective of the study was to increase the data base of HCHO monitoring in a variety of American homes and further examine the effect of housing types, inhabitant lifestyles, and environmental factors on indoor pollutant levels.

Homes to be sampled were selected based on a stratification to ensure representative home age, insulation types, and heating sources. All were voluntarily enrolled. Twice a month, four samplers at each location monitored HCHO levels in three rooms and outside the house. Samplers were exposed to the air for 24-hour periods. No modifications to the residents' life styles were requested during these measurements.

Table 6-7 summarizes these data by home age and season (indicative of temperature and humidity). HCHO measurements in the 40-home east Tennessee study led to the following major conclusions:

Table 6-7. ORNL/CPSC Mean Formaldehyde Concentrations (ppm) as a Function of Age and Season (Outdoor Means Are Less Than 25 ppb Detection Limit)

Age of house	Season	$\bar{x}^a$	s^a	m	n
all	all	0.062	0.077	5903	40
0-5 years	all	0.084	0.091	3210	18
5-15 years	all	0.042	0.042	1211	11
older	all	0.032	0.042	1482	11
0-5 years	spring	0.087	0.093	1210	
	summer	0.111	0.102	1069	
	fall	0.047	0.055	931	
5-15 years	spring	0.043	0.040	626	
	summer	0.049	0.048	326	
	fall	0.034	0.035	259	
older	spring	0.036	0.051	757	
	summer	0.029	0.037	341	
	fall	0.026	0.023	384	
all	spring	0.062	0.076	2593	
	summer	0.083	0.091	1736	
	fall	0.040	0.047	1574	

Note: $\bar{x}$ = mean concentrations.
s = standard deviation.
m = number of measurements.
n = number of homes.
[a] Includes homes with and without UFFI.

Source: Hawthorne et al. (1984).

(1) The average HCHO levels exceeded 100 ppb (0.1 ppm) in 25 percent of the homes.

(2) HCHO levels were found to be positively related to temperature in homes. Houses with UFFI were frequently found to exhibit a temperature-dependent relationship with measured HCHO levels.

(3) HCHO levels generally decreased with increasing age of the house. This is consistent with decreased emission from materials due to aging.

(4) Elevated levels were found in new houses that did not contain UFFI.

(5) HCHO levels were found to fluctuate significantly both diurnally and seasonally.

Studies by Breysse (1984) evaluated conventional, non-UFFI homes. The University of Washington studied 59 such homes; private laboratories in the state studied an additional 25. The frequency distribution for measured levels are presented in Table 6-8. A total of 6 of the 189 samples (3.1 percent) were over 0.5 ppm.

Traynor and Nitschke (1984) monitored indoor air pollutants in 30 homes with and without suspected combustion (and other) sources. The average HCHO level observed in all the test homes was 40 ppb; a high value of 151 ppb was found in one of the tested residences categorized as containing new furnishings and new paneling as a suspected pollution source.

The results can be summarized as follows:

- The 4 homes with no identified source had a range of means of 0.007 to 0.034 ppm.
- The 3 homes with new furnishings had a range of means of 0.015 to 0.061 ppm.
- The 4 homes with cigarette smokers had a range of means of 0.032 to 0.060 ppm.

Table 6-8. Frequency Distribution of Formaldehyde Levels in Washington Conventional Non-UFFI Homes

Formaldehyde concentration (ppm)	Number of Samples: 59 U. Wash homes	25 Private lab homes	Frequency (percent)
≥ 1.0	2	0	1.0
≥ 0.5 - 0.99	2	2	2.1
≥ 0.1 - 0.49	41	9	26.5
< 0.1	68	65	70.4
TOTAL OBSERVATIONS	113	76	
		Σ = 189	

Source: Breysse (1984)

- The 18 homes with gas, coal, and wood fueled appliances/heaters had a range of means of 0.012 to 0.056 ppm.

- The 12 homes with a combination of sources reported a range of means from 0.013 to 0.064.

Variations in home levels could not be attributed to combustion sources.

A downward tend in HCHO levels in conventional homes is seen in Figure 6-3. The relative proportion of low HCHO levels in homes has increased over the past six years, and the proportion of high levels had decreased. The line of demarcation appears to be between 0.05 and 0.1 ppm (the concentration range in which earlier studies predominate over more recent analyses). Again, these data are limited and caution in interpretation is recommended (Versar, 1985b).

6.5.3. Garment Worker Exposure

HCHO levels in apparel manufacturing facilities were generally below 3 ppm prior to 1980 (see Table 6-9). OSHA had established a 3 ppm TWA (time-weighed average) in 1967. However, OSHA is presently considering establishing a new level. The ACGIH (American Conference of Government Industrial Hygienists) level is 1 ppm TWA. In recent years, however, HCHO levels observed were generally below 1 ppm (see Table 6-10). The data in Tables 6-9 and 6-10 must be viewed with caution because in 1983, NIOSH discovered that the commercially prepared inpregnated charcoal tubes which had been used in previous personal monitoring studies were unstable. Thus, the monitoring data above may be useless since the loss of HCHO from the tubes was

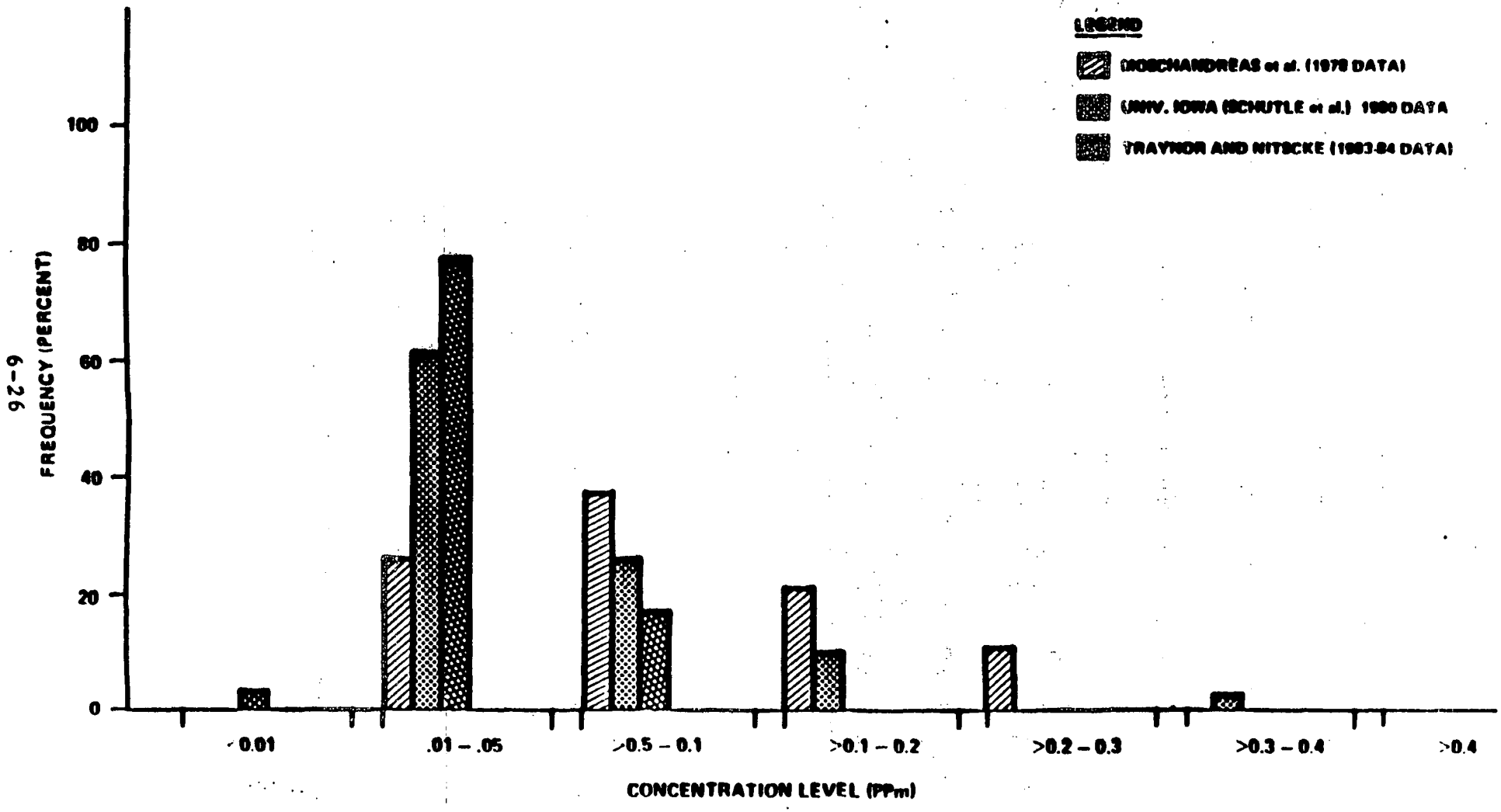


Figure 6-3. FREQUENCY DISTRIBUTION OF LEVELS IN CONVENTIONAL HOMES

Table 6-9. PRE-1980 MONITORING DATA FOR GARMENT MANUFACTURING AND CLOSELY RELATED INDUSTRIES

Industry/facility type	Fabric type/treatment	Measured formaldehyde concentrations, ppm	Number of measurements	Sampling method[a]
Textile plants[b]	NS[c]	0.1 - 1.4 (1979)[d]	43	NS
	Nylon; urea-formaldehyde resins.	3 - 33 (1955)[d]	NS	NS
Garment manufacture	NS; formaldehyde-containing resins.	0.3 - 2.7 (TWA-area, 1966)	32	1
	Permanent press	<0.1 - 1.6 (TWA, 1979)[e]	30	1
	Permanent press	0.15 - 0.30 (TWA, 1966)[e]	9	1
	Permanent press	0.9 - 2.7 (TWA-area, 1966)	NS	2
	Permanent press	0.000-0.960 (TWA-personal, 1975)	40	1,2
	NS	2.000 - 3.040 (TWA-personal, 1979)	4	NS
	NS	ND[f] (Grab, 1979)	NS	6
	NS	2.280 (Ceiling-personal, 1979)	1	NS
	NS	0.030 (TWA-personal, 1979)	1	NS
Garment distribution centers (i.e. - dress shops, clothing warehouse stores, etc.)	NS	0.9 - 3.3 (Ceiling-area, 1966)	NS	3
	NS	0.13 - 0.45 (1959)[d]	NS	NS
	NS	0.04 - 0.73 (TWA, 1979)[e]	22	1,4

[a] Sampling methods:
1. P & CAM 125.
2. Modified P & CAM 125.
3. Fritted midget absorbers containing 3-methyl-2-benzothiazolone hydrazone hydrochloride (MBTH) used for 15 minute sampling times.
4. P & CAM 318.
5. CEA Model 555 ambient air monitor, direct-reading instrument.
6. Dräger brand indicator tubes.
7. P & CAM 354.

[b] No further description available.
[c] Not specified in the reference.
[d] Sample type not specified.
[e] Personal or area not specified.
[f] Not detected.

Table 6-10. RECENT MONITORING DATA FOR FORMALDEHYDE IN THE GARMENT MANUFACTURING INDUSTRY

SIC code[a]	Company	Fabric type/treatment	Measured formaldehyde concentrations, ppm	Number of measurements	Sampling method[b]
2253	Manchester Knitted Fashions, Inc., Concord, NH	NS[c]	0.070-0.100 (TWA-personal, 1980)	2	NS
2311	Coastal Industries, Birmingham, AL	NS	2.0 (Screen, 1982)	1	NS
	Arrow Shirt Co. Lewistown, PA	Polyesters, polyester-cotton blends, nylon blends; [illegible]	0.13-0.37 (TWA-area, 1980)	9	1
			0.14 (TWA-personal, 1980)	1	1
2321	Kaufman Textile Mills, Inc. Harrisburg, PA	NS	2.0 (Screen, 1982)	1	1
	Executive Shirt Mfg. Co., Birmingham, AL	NS	2.0 (Screen, 1981)	1	1
	Manhattan Shirt Co.[d] Americus, GA	Cotton and polyesters; formaldehyde-based resin, precured	0.090-0.40 (TWA-personal, 1979)	12	4
			0.34-0.37 (TWA-area, 1983)	2	4
			0.27-0.44 (Grab, 1983)	14	5
	E. F. Hathaway Co. Lyons-Foncroft, M	NS; formaldehyde-based resin precured	<0.12-0.22 (TWA-breathing zone, 1981)	20	4
			0.08-0.17 (TWA-area, 1981)	22	1,4
			0.13-0.21 (TWA-area, 1981)	NA[e]	5
			0.32 (Peak, 1981)	NA	5
	E. F. Hathaway Co. Waterville, M	NS; formaldehyde-based resin precured	<0.12-<0.27 (TWA-breathing zone, 1981)	20	4
			0.08-0.20 (TWA-area, 1981)	24	1,4
			0.10-0.88 (TWA-area, 1981)	NA	5
			0.94 (Peak, 1981)	NA	5
	Kingston Shirt Co.[d] Kingston, NC	NS; formaldehyde-based resin precured	<0.080-0.37 (TWA-personal, 1982)	12	4
			0.15-0.47 (TWA-area, 1982)	2	4
	Arrow Shirt Co. Atlanta, GA	NS; formaldehyde-based resin precured, pre-cut	1.02-2.23 (TWA-breathing zone, 1980)	19	4
			0.07-2.07 (TWA-area, 1980)	10	1,4
			0.1-1.0 (Grab, 1980)	10	5
		NS; [illegible], precured, pre-cut	0.034-0.794 (TWA-personal, 1981)	101	4
			0.08-0.48 (TWA-area, 1981)	17	5
	Arrow Shirt Co. Lewistown, PA	NS; formaldehyde-based resin pre-cured, pre-cut	0.15-0.30 (TWA-personal, 1981)	10	4
			0.11-0.48 (TWA-area, 1981)	22	1,4
			0.34-0.58 (TWA-area, 1981)	NA	5
			0.71 (Peak, 1981)	NA	5
2329	Lee County Mfg. Co.	NS	0.400 (Ceiling-area, 1982)	1	NS
	Ballcraft Mfg. Co. Atlanta, GA	NS	0.100 (TWA-personal, 1980)	2	NS
			0.320 (Peak, 1980)	2	NS
			3.000 (Screen, 1980)	1	NS
	Lee Co. Inc. Birmingham, AL	NS	0.000 (Screen, date unknown)	1	NS

Table 6-10. (continued)

SIC code[a]	Company	Fabric type/treatment	Measured formaldehyde concentrations, ppm	Number of measurements	Sampling method[b]
	Todd Uniform Co. Maury City, TN	65% cotton/35% polyester; glyoxal-based resin, pre-cured, pre-cut	0.08-0.54 (TWA-personal, 1982) 0.50 (TWA-area, 1982)	36 2	1,2,7 1,2
2330	New Carolina Industries Weldon, NC	Cotton polyester; finished fabric	0.20-0.63 (TWA-personal, 1980) 0.18-0.42 (TWA-area, 1980) 0.39-1.12 (Grab, 1980)	10 10 13	4 1,4 5
2339	Taylor Co. Birmingham, AL	NS	19.000 (Screen, 1981)	1	NS
2342	Formelex Foundations Inc. Hasbrouck Hts., NY	NS	0.000 (Screen, 1980)	1	NS
2352	Korber Hats Inc. Boston, MA	NS	0.022-0.165 (TWA-personal, 1981)	7	NS
	K Products, Inc. Bismarck, ND	NS	0.038-0.205 (TWA-personal, 1982) 0.460-0.710 (Ceiling-personal, 1982)	2 2	NS NS
2369	Health Tex Inc. Augusta, GA	NS	0.069-0.097 (TWA-personal, 1983)	2	NS
2385	Rogers Mfg. Co. Birmingham, AL	NS	0.430 (TWA-personal, 1983) 1.000 (Screen, 1983)	1 1	NS NS

[a] Descriptions of SIC codes are included in Appendix A.
[b] Sampling methods:
1. P & CAM 125.
2. Modified P & CAM 125.
3. Fritted midget absorbers containing 3-methyl-2-benzothiazolone hydrazone hydrochloride (MBTH) used for 15 minute sampling times.
4. P & CAM 318.
5. CEA Model 555 ambient air monitor, direct-reading instrument.
6. Dräger brand indicator tubes
7. P & CAM 354.
[c] Not specified in the reference.
[d] Glyoxal-based resin, 1,3-dimethylol-4,5-dihydroxy-2-imidazolidinone.
[e] This company can also be classified in SIC code 2331.
[f] In the collection of breathing zone samples, the sampling device is situated in an area representative of the worker's breathing zone.
[g] Not applicable.
[h] This company can also be classified in SIC codes 2329, 2331, and 2339.

not consistent. Consequently, the HCHO levels recorded most likely represent lower levels than actual conditions. The NIOSH method at that time was also used by OSHA.

NIOSH subsequently developed a stable medium for collecting the HCHO and did two indepth industrial hygiene studies. The surveys were done at two large manufacturing sites producing men's dress shirts. HCHO exposure levels were determined for 54 of 72 job titles in two different plants. The number of individuals within each job title whose exposure levels were sampled was based on the total number of employees in that category and reflect a 95 percent confidence level that the highest and lowest exposed individuals were included in the sampling. A summary of the data are presented in Tables 6-11 and 6-12. These tables show that all levels of exposure were less than 0.51 ppm TWA. Also, as Table 6-11 illustrates, the combined range of data was very narrow (0.01-0.39 ppm) for 5 of the 6 departments in the two plants. The range of mean concentrations of all departments (0.13-0.20 ppm) is also very narrow and compares well within the overall combined mean exposure level of 0.17 ppm, which was used for quantitative cancer risk assessment. In addition, the average exposure levels used in EPA's section 4(f) determination (EPA, 1984b), 0.23 ppm (area) and 0.64 ppm (personal) (Versar, 1982), were also used for cancer risk assessment.

Table 6-11. NIOSH Monitoring Data--Ranges by Department

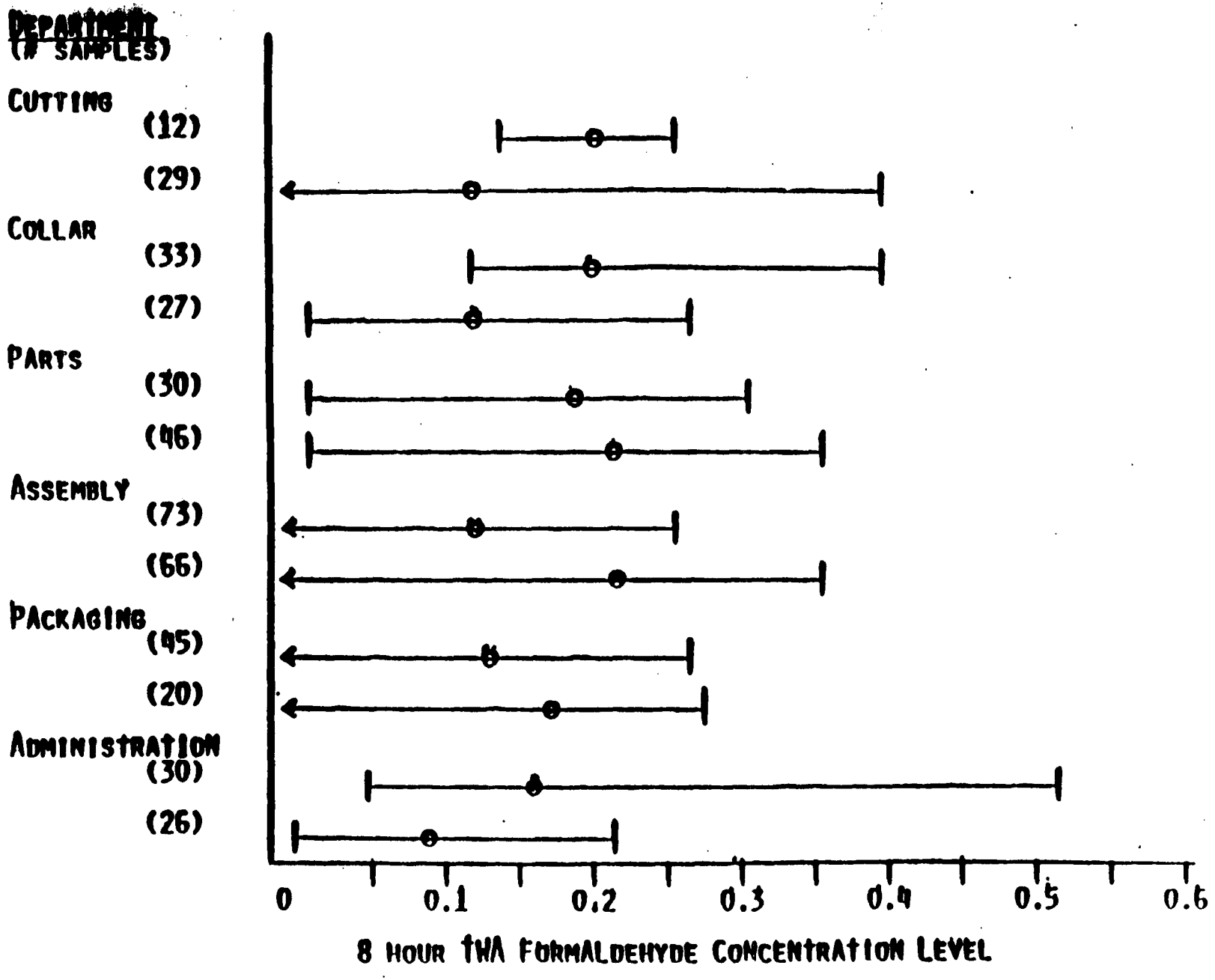


Table 6-12.

FORMALDEHYDE CONCENTRATION LEVELS (PPM)
GARMENT MANUFACTURING

DEPARTMENT	# SAMPLES	RANGE	GEOMETRIC MEAN
ADMINISTRATION	56	0.01 - 0.51	0.13
CUTTING	41	<0.01 - 0.39	0.14
COLLAR	60	0.02 - 0.39	0.16
PARTS	76	<0.01 - 0.35	0.20
ASSEMBLY	139	<0.01 - 0.35	0.17
PACKAGING	65	<0.01 - 0.27	0.14
	(437)	(<0.01 - 0.51)	(0.17)

All of the determinations made in the NIOSH studies were at one point in time and may not reflect the variation of exposure over a longer period. Factors that could promote variation in HCHO levels in these plants include variation in ambient temperature, humidity, type of facric or resin system, and volume of stored materials or completed work.

The exposure range across departments, within plants, as well as between plants, appears to be very tight. Both these plants were large manufacturing sites, producing similar products. Both plants had central ventilation/cooling systems. This type of plant may potentially represent only 10 percent of the total number of manufacturing sites (though up to 25-30 percent of the workforce may work in such plants) (Ward, 1984).

6.6. Summary

The data presented above indicate that HCHO levels in new manufactured homes are generally below 0.5 ppm, with 10-year averages for existing and new HUD Standard homes of 0.19 and 0.15 ppm, respectively. However, some fraction of new homes experience peak levels that could exceed 1.0 ppm for periods of time. It would be expected that as temperature/humidity exceed 75°F/50% RH, HCHO levels would rise as Table 6-3 illustrates. Thus, depending on heating and cooling preferences, HCHO levels in new homes may substantially exceed the reported mean for new homes.

The situation is similar for new conventional homes, although reported mean levels are lower, with long-term means of

0.030 to 0.050 ppm. However, because conventional housing is much more heterogeneous, peak levels in some new homes may substantially exceed reported means. Although temperature and humidity conditions play a large role, construction techniques which tend to limit air exchanges, such as in energy efficient homes, and building product mixes are also of major importance.

Reported HCHO levels during garment manufacture are below 1.0 ppm and in some plants below 0.5 ppm, and the NIOSH data indicate rather tight ranges (none exceeding 0.51 ppm). However, much of the reported monitoring data must be approached with caution due to the technical fault discussed earlier. Building design, ventilation, and temperature/humidity changes may be responsible for daily or seasonal variations.

7. ESTIMATES OF CANCER RISKS

The determination of individual risk can be made through the use of epidemiologic or animal studies. Epidemiologic studies suitable for risk extrapolations are rarely available, however, and are not available in the case of HCHO. Thus, human cancer risk from HCHO must be estimated through use of animal studies. This necessitates extrapolation from high to low doses because, typically, test animals are exposed to concentrations much higher than those expected to be experienced by humans. These extrapolations are carried out by fitting mathematical models to the observed animal data.

7.1. Risk Estimates Based on Squamous Cell Carcinoma Data

Data from two different studies were considered for their appropriateness to this risk assessment, one by Kern et al. (1983) (the CIIT study), the other by Albert et al. (1982) (the NYU study). A study recently received, the Tobe et al. (1985) study, is being peer reviewed and will be compared with the other HCHO studies. Dose-response modeling was applied to the CIIT data for Fischer 344 rats using squamous cell carcinomas of the nasal turbinates as an endpoint. The NYU study provides corroborating evidence of a similar response in another strain of rats (Sprague-Dawley). That study, however, was not considered appropriate for risk estimation since it contains only one exposure concentration, and, based on the CIIT data, one would expect the true dose-response curve in the experimental range curve to be highly nonlinear. Although not statistically

significant, the squamous cell carcinoma response in two B6C3F1 mice of the CIIT study at 15 ppm is suggestive of carcinogenicity from formaldehyde inhalation in another species due to the rarity of this tumor. This data set was not considered for dose-response modeling, however, because of the limited response at the highest dose level. The CIIT study was chosen as the source of data for several reasons: it was an experiment by inhalation, which is the primary route of exposure to man; the quality of the study is considered to be high; and it includes four exposure levels for determining the shape of the dose-response curve (Grindstaff, 1985).

It was decided to estimate the risk of tumor to rats chronically exposed up to time of death without intervention, or to a terminal sacrifice at 24 months. With some adjustments for earlier sacrifice kills discussed below, this was estimated from the CIIT data. The dosing regimen assumed is that of the CIIT study, where exposure was six hours per day for five days per week. For estimation purposes, the animals that lived beyond 24 months included with the animals sacrificed at 24 months.

An adjustment was necessary to correct for animals that died very early in the CIIT study or that were sacrificed prior to 24 months. The rats that died prior to the appearance of the first squamous cell carcinoma at 11 months were not considered at risk. Rats sacrificed at 12 and 18 months would be treated as though they would have responded in the same proportion as the rats that remained alive at the rspective sacrifice times. From

this approach an estimate of the probability of death with tumor within 24 months and an estimate of its variance was obtained. The number of animals at risk, and the number with tumors that would give the same estimates of mean and variance for a 24-month study with no interim kills at 12 and 18 months was determined, and used as the input data for risk analysis. The data adjusted for sacrifice kills obtained in this manner are 0/156, 0/159, 2/153, 94/140 (figures rounded), at nominal dose levels of 0, 2, 5.6, and 14.3 ppm.

Another method, which was not used, would simply omit from the analysis all rats sacrificed prior to 24 months. The data adjusted for sacrifice kills by this method are 0/156, 0/159, 2/155, and 95/141. The two constructed data sets produce a negligible difference in estimated risk at very low doses under the dose-response model discussed below.

Ambient air concentration (ppm) is recommended as the dose metameter at the present time in the absence of evidence suggesting another dose metameter is preferable. It also conforms with EPA past practice. An alternative method suggested by Casanova-Schmitz et al. (1984) and Starr et al. (1984) using data derived from the formation of HCHO-DNA adducts was not used because EPA's interpretation of this data (as discussed previously) leads to a different conclusion than the authors. However, use of this data leads to a reduction of about a factor of 3 at the UCL and 50 at the MLE.

The multistage model without restrictions on the order of the polynomial in dose was used to extrapolate risks. The formulation of the model for quantal response data was preferred to one including time as a variable. Based on simulation studies conducted under contract to EPA, it was not at all clear that inclusion of time as a variable would provide improved estimation, and there would have been some question about the validity of the results in this case, due to lack of knowledge of the cause of death of experimental animals, and due to adjustments made for sacrifice data (Howe et al., 1984). Risk is summarized as model-derived point estimates and associated upper 95 percent confidence limits in the dose ranges of interest. The latter corresponds to the number from a linearized multistage model procedure.

All currently used mathematical models of dose-response provide oversimplified descriptions of the carcinogenic process. EPA generally recommends the multistage model because of certain desirable properties: (1) it is based on a generally accepted concept that the carcinogenic process usually involves multiple stages, one or more of which may be affected by exposure to the agent being considered; (2) the model class is sufficiently broad as to include both nonlinear and linear members, and is able to describe adequately most observed convex dose response relationships.

Although arguments have been made that there may be a dose level below which the added risk of cancer is zero, there is no

consensus within the scientific community on this topic. Through use of mathematical models of dose-response, there is currently no way to demonstrate either the existence or nonexistence of a threshold. In addition, if any thresholds exist, they are likely to vary among members of the population at risk, and may be modified by other environmental agents. Therefore, use of a dose-response model incorporating a single threshold would provide an estimate of an average population threshold that would have little practical utility. In the absence of clear evidence of a threshold and quantifiable supporting data that could be utilized in risk assessment, it was felt that for dose-response modeling of HCHO it should be assumed that there is no threshold. Such a conclusion is supported by the Consensus Conference on Formaldehyde (1984).

The likelihood of response should be treated as equal in rats and humans for the same exposure regimen and proportion of lifetime exposed. Although differences have been apparent in susceptibility among the species that have been exposed to HCHO, there are no data suggesting that man may be less susceptible than rats.

The estimated risk to rats is based on the CIIT dosing regimen for a period of 24 months, which may need to be adjusted upward to obtain an estimate of risk for lifetime exposure. It may also be necessary to convert the estimated risk to a shorter exposure duration in some cases, or to adjust for a different exposure schedule (i.e., other than six hours per day, five days

per week). However, there is little scientific knowledge that addresses these problems. Consequently, each estimate of lifetime risk from the model (assumed to be equivalent for humans and rats as discussed in the preceeding issue) was multiplied by the proportion of a human lifetime actually exposed. Hypothetically, then, at an exposure concentration producing a lifetime risk of 1/1000, the risk for exposure of half a lifetime was estimated as 1/2000. Similarly, if exposure was for 45 hours per week instead of for 30 as in the CIIT study, the risk estimate would be multiplied by 45/30 = 0.5, giving 3/2000. Exposure of half a lifetime but at 45 hours per week would give .5 times 1.5 times 1/1000 = 1/1333. It should be noted that due to the upward curvature of the dose-response curve the resultant risk will be less than if the scaling factor were applied to dose before substitution into the model if the factor is greater than one, and would be greater if the factor is less than one (in both instances the difference would be less than 2 fold). If the response curve were linear there would be no difference between scaling risk or scaling dose. It is acknowledged that this rule for adjustment is based on very simplified assumptions.

The estimated individual and population risks to humans for the three categories of concern are presented in Table 7-1.

Table 7-1.
ESTIMATED INDIVIDUAL AND POPULATION RISKS BASED UPON SQUAMOUS CELL CARCINOMA DATA FROM CIIT STUDY. POPULATION RISKS (number of excess tumors) APPEAR IN PARENTHESES BELOW INDIVIDUAL RISK ESTIMATES.

Category	Population	Exposure	Maximum Likehihood Estimate of Risk	95 Upper Confidence Limit on Risk
Mobile Home Residents	6,642,000*			
1. Based on current monitoring data		0.19 ppm (112 hrs/wk for 10 yrs)	3×10^{-9} [B1] (<1)	3×10^{-4} [B1] (1993)
2. Based on HUD standard		0.15 ppm (112 hrs/wk for 10 yrs)	1×10^{-9} [B1] (<1)	2×10^{-4} [B1] (1328)
Manufacturers of Apparel	777,000			
1. OSHA standard		3.0 ppm (36 hrs/wk for 40 yrs)	6×10^{-4}	6×10^{-3}
2. Personal sample		0.64 ppm (36 hrs/wk for 40 yrs)	6×10^{-7} [B1] (<1)	1×10^{-3} [B1] (777)
3. Area sample		0.23 ppm (36 hrs/wk for 40 yrs)	9×10^{-9} [B1] (<1)	4×10^{-4} [B1] (311)
4. NIOSH data		0.17 ppm (36 hrs/wk for 40 yrs)	4×10^{-9} [B1] (<1)	3×10^{-4} [B1] (233)
Conventional Home Residents	40,011,000*	0.025 ppm (112 hrs/wk for 70 yrs)	7×10^{-12} [B1] (<1)	3×10^{-4} [B1] (12,003)

* Population estimates are based on anticipated additions to the housing stock between 1985 and 1995 as estimated by Versar (1985b).

7.2. Risk Estimates Based on Polypoid Adenoma Data

There appears to be little credible evidence that polypoid adenomas progress to any of the malignant tumors seen in the Kern et al. (1983) study. However, while the adenomas should not be combined statistically with the squamous carcinomas for hazard identification purposes, they represent an endpoint that can be quantified separately.

Because, it is beyond the capability of the various extrapolation models to fit data with a negative slope, an alternative extrapolation procedure is to drop the two highest doses and use the data from the 2.0 ppm rat exposure group (straight line to zero). However, since the true slope of the dose-response curve is unknown below 2.0 ppm, this approach may vastly overestimate the true risk if the curve is convex, and underestimate it if it is concave. The reason the occurrence of polypoid adenomas has a negative slope probably lies with the fact that the cell type in the respiratory epithelium from which these tumors arise is lost sooner and to a greater extent with increasing dose due to squamous metaplasia. The less respiratory epithelium available the smaller the chance for adenomas to develop.

Risk estimates for polypoid adenomas appear in Table 7-2. For polypoid adenoma as the endpoint instead of squamous cell carcinoma there is no difference between the two procedures described earlier to adjust for animals at risk. The first observation of a polypoid adenoma was in a rat sacrificed at 10

months. Eliminating all rats dead of any cause prior to that time and applying the method used for the carcinoma data leads to 7/159 for the response at 2 ppm with 1/156 at control, the same as if all rats dead prior to an including the 18 month sacrifice were excluded.

Table 7-2.
RISK BASED ON POLYPOID ADENOMA DATA

Category	Dose	Maximum Likelihood Estimate of Risk	95 Upper Confidence Limit on Risk
Mobile Home Residents			
1. based on current monitoring data	0.19 ppm (112 hrs/wk for 10 yrs)	2×10^{-3}	4×10^{-3}
2. Based on HUD data	0.15 ppm (112 hrs/wk for 10 yrs)	1×10^{-3}	3×10^{-3}
Manufacturers of Apparel			
1. Personal sample	0.64 ppm (36 hrs/wk for 40 yrs)	8×10^{-3}	2×10^{-2}
2. Area sample	0.25 ppm (36 hrs/wk for 40 yrs)	3×10^{-3}	5×10^{-3}
3. NIOSH data	0.17 ppm (36 hrs/wk for 40 yrs)	2×10^{-3}	5×10^{-3}
Conventional Home Residents	0.025 ppm (112 hrs/wk for 70 yrs)	2×10^{-3}	4×10^{-3}

7.3. Uncertainty in Risk Estimates

Model-derived risk estimates should be viewed in the proper context. First, the UCL should not be viewed as a point estimate of risk. Generation of the UCL is a statistical method for estimating the range in which the true risk may lie. The true risk is not likely to be higher than the UCL, but it could be lower.

As Table 7-1 illustrates, there is a wide range between the MLE and UCL, approximately 4 or 5 orders of magnitude. This illustrates the statistical uncertainty of the estimates generated due to the input data from the study used, which in this case is highly non-linear. For instance, the individual risks for apparel workers range from 1×10^{-3} [B1] to 6×10^{-7} [B1]. In addition, it has been shown that the MLE is sensitive to small changes in response data when the response is very nonlinear in the experimental range. For instance, the dose giving a risk of 1×10^{-6} (MLE) varies significantly due to small changes in the response data of the Kern et al. (1983) study (Cohn, 1985b). The following illustrates this:

Response at 2 ppm (malignant)	Dose for Risk of 1×10^{-6} (MLE)
1. 0 (actual)	0.67 ppm
2. 1/1,000	0.0022 ppm
3. 1	0.0006 ppm

Consequently, when modeling data that are very non-linear, one should not place great certainty on MLE estimates.

As discussed above, the major contributor to the uncertainty seen in the risk estimates is the steep dose-response seen in the Kern et al (1983) study. There were no carcinomas at 2 ppm, 2 at 5.6 ppm, and 103 at 14.5 ppm, which is a 50-fold increase for only a 2.5 times increase in dose. If changes in respiratory rate are taken into account (the rats at 14.3 ppm are receiving the equivalent of a 12 ppm exposure--use of this data leads to no significant change in estimated risks at exposures of concern) (Grinstaff, 1985), there is a 50-fold increase for only a doubling of the dose.

HCHO's ability to cause rapid cell proliferation, cell killing and subsequent restorative cell proliferation, its ability to interact with single-strand DNA (during replication), interfere with DNA repair, its demonstrated mutagenicity, and the fact that the dose was delivered to a finite area may help explain the abrupt increase in the response. However, none of these factors demonstrate the presence of a threshold or minimal risk at exposures below those that cause significant nonneoplastic responses such as cell proliferation, restorative cell growth, etc. For instance, although HCHO causes varying degrees of cell proliferation in the nasal mucosa of rats due to HCHO exposure, it must be remembered that there is a natural rate of cell turnover in this tissue. While it is low in comparison to HCHO induced increases, it does provide the opportunity for HCHO to react with single-strand DNA during cell replication possibly resulting in a mutant cell which, if proper conditions

are met, could result in a neoplasm. While an event such as this may be rare, it is not unreasonable when one considers that the opportunities for this event to occur are great due to the immense number of cell-turnovers which may lead to defects in some cells of the population of the individuals exposed.

It is often useful to compare the human risks estimated from animal data to those risks observed in the epidemiologic studies. For instance, if one takes the UCL for pathologists exposed to 3.2 ppm HCHO and assumes that all the excess tumors at the UCL would appear as brain tumors, then one would expect to see a 130% increase in brain tumors in this population. However, in the epidemiologic studies which showed significant elevations, increases of approximately 200% are seen. This is true for leukemias as well. The UCL would give a 70% increase whereas an increase of 100% was seen.

The situation for nasal cancer is more complicated because of the inability of the Hayes and Olsen studies to delineate levels of exposure. However, if one chooses an exposure group, such as furniture workers who may be exposed to both wood dust and formaldehyde, one can make some observations. The reported exposures for this group range from 0.1 to 1.3 ppm HCHO as a 8-hour, time-weighted-average. This translates to an increase in nasal cancer risk from 1.5 (50 percent increase) to 11.0 (1000 percent increase) at the UCL. In the Olsen et al. study, an increase in nasal cancer risk of 60 percent is reported for HCHO exposure when the analyses adjusted for wood dust exposure. The

Hayes et al. study reports an 180 percent increase in nasal cancer risk for HCHO exposed persons. Both these increases are not statistically significant due to low power and the small number of cases exposed to only HCHO. In fact, the Hayes et al. study has only 4 percent power to detect the estimated (from the UCl and animal data) risk for an exposure of 0.1 ppm HCHO and 60 percent power for an exposure of 1.3 ppm HCHO. The reported increases in nasal cancer risks in the Olsen et al. and Hayes et al. studies are in the range of those risks which were estimated from the UCL and animal data for furniture workers.

Thus, when individual tumor types are examined it can be seen that the UCL is not indicating greater excesses than seen in certain studies when uncertainties about exposure and the lack of power to detect are considered. Although HCHO's potential carcinogenic effects should not be limited to one site in humans because they are not obliged to breathe through their noses as rats are, the analysis described above does provide a crude check of the risks derived from animal data and those seen in human studies.

Finally, a factor that can have a major bearing on population risk estimates is the quality of the available exposure data. Assumptions made in reporting exposure levels can have a major impact. For instance, it is not uncommon during a monitoring exercise to find a number of samples that are below the detection limit of the analytical technique used. Thus, when a mean exposure level is calculated it should be realized that if

the nondetectable (ND) samples are counted as 0 the calculated mean will understate the actual situation. Conversely, if the ND samples are counted as the limit of detection, the mean will overstate the true situation. Another factor that can skew exposure estimates are changes in non-governmental exposure limit recommendations and the number of years over which the data are collected. Since a number of years of exposure data are often used to calculate means, it is possible that the mean will be weighted by samples taken prior to changes in voluntary exposure limits. Thus, the reported mean could be substantially overestimating the true situation. For instance, in the garment industry, HCHO levels have apparently been falling since the late 70's and early 80's as a result of increased concern and a downward revision of the ACGIH recommendation for HCHO. Consequently, an industry average calculated from data predating 1980 could cause the reported mean to be overstated. This may have a significant impact on the estimated population risks. For the apparel industry there are approximately 800,000 workers exposed to HCHO. The mean personal exposure level used for the section 4(f) determination and this assessment is 0.64 ppm which leads to population risks of <1-777 (MLE-UCL). If the mean area exposure level of 0.23 ppm is used, and there is some evidence that personnel levels may now be approaching this figure, population risk estimates would range from <1-311, which is a 60% reduction at the high end. However, the exposure data for apparel workers are poor in its ability to characterize the

industry, and great confidence cannot be placed on an industry mean as a fair representation of actual exposure levels in the approximately 20,000 sites where workers are exposed.

The data for mobile homes is qualitatively better in its ability to characterize this group because of a greater number of well conducted monitoring surveys. Mobil home exposure studies have been done by HUD, state and local government agencies, and academic researchers. Although data is generally only available to estimate 10 year averages, data from complaint and non-complaint homes produce 10 year averages which range from 0.19 to 0.25 ppm.

7.4. Presentation of Risk Estimates

As discussed in "Data Selection for Quantitative Analysis" above, the recommendation is that risk estimates should be separately derived from squamous cell carcinoma and polypoid adenoma data. However, two positions can be taken concerning the presentation of the risk estimates. One is to present risk estimates separately for squamous cell carinomas and polypoid adenomas and explain the uncertainties associated with each. The other is to add the risk estimates for an overall estimate of carcinogenic risk. These are discussed below.

7.4.1. Separate Risk Estimates Derived From Squamous Cell Carcinoma and Polypoid Adenoma Data

Because two risk estimates are presented, the significance and uncertainties associated with each must be explained.

The squamous carcinomas observed in the Kern et al. (1983) study are frank evidence of carcinogenicity in the rat. The response at 14.3 ppm HCHO was highly significant in both sexes. While not significant at 5.6 ppm, the observation of two squamous cell carcinomas in 240 rats is considered biologically significant, since the historical incidence of squamous cell carcinomas in male and female F-344 rats is 1 in 3,000 rats (NTP, 1985). In addition, significant numbers of squamous carcinomas were observed in rats in two other long-term inhalation studies (Albert et al., 1982; and Tobe et al., 1985). Consequently, there is little uncertainty about the carcinoma results.

There is a positive dose-response relationship for squamous cell carcinomas in the Kern et al. (1983) study. However, because of the nonlinearity of the dose-response relationship, there is a wide divergence between the upper 95 percent confidence limit (UCL) and the maximum likelihood estimate (MLE) of risk. This introduces a large and variable level of uncertainty into the risk estimates (see preceeding section--Uncertainty in Risk Estimates).

The situation for the polypoid adenoma data is not clear. First, the statistical significance is poor. The adenomas are not significant at any dose level for male and female rats separately. Only when the response is pooled at 2.0 ppm is there significance. However, even this is questionable since the response rate in male and female rats is not comparable. At the 5.6 ppm level responses in males and females were significantly

different from one another. Moreover, two of the responses at 2.0 ppm were borderline diagnostic calls between focal hyperplasia and polypoid adenoma (Boorman, 1984), and if these two responses are dropped, significance is lost at 2 ppm. Also, there is a negative dose-response relationship. Although some of this may be due to the replacement of nasal epithelium with squamous epithelium earlier and to a greater extent as dose increases, this is not definite. Thus, it is difficult to characterize the relationship between HCHO exposure and the polypoid adenoma response. Because of the negative dose-response relationship, it was necessary to drop the two highest doses (5.6 and 14.3 ppm) and extrapolate from 2.0 ppm to 0 (a straight line from 2.0 to 0 ppm). Thus, if the true dose-response relationship is concave between 0 and 2.0 ppm, estimated risks will be too low. If upward convex they will be too high (this seems more plausible given the benign and malignant tumor responses in the Tobe et al. (1985) study and the squamous cell carcinoma response in the Kern et al. (1983) study).

As discusssed above, there is a greater level of certainty in the squamous cell carcinoma response and risk estimates derived from them. Conversely, because of the nature of the polypoid adenoma response, its weak statistical significance at best, and the manner of risk estimation, the confidence in this response and associated risk estimates is low.

7.4.2. Calculate Risks Separately But Add The Risks

The rationale for this option is that the polypoid adenomas together with the squamous cell carcinomas observed in the Kern et al. (1983) study are an indication of HCHO's potential human carcinogenicity. Moverover, benign tumors may be expected to appear in the human population (not just in the nasal cavity). It may also be assumed that they have some ability to progress to cancers as a result of the promoting activity of other agents. Consequently, adding the risk estimates from the benign (polypoid adenomas) and malignant (squamous cell carcinomas) data provides an overall estimate of carcinogenic risk to humans.

While such a line of reasoning is plausible, a number of factors must be considered.

First, if the separate risk estimates are added, that estimated estimated from the squamous cell carcinoma data is dwarfed by the estimated adenoma response. For instance, using UCl's the risk to garment workers exposed to 0.64 ppm of HCHO is 1×10^{-3} using squamous cell carcinoma data. The risk based on benign tumors at the same concentration is 2×10^{-2}. Adding the two estimates give a risk of 2.1×10^{-2}. Following the Guidelines (EPA, 1984a) this would be rounded to one significant figure, i.e., 2×10^{-2}. Thus, the contribution to the risk estimate from the frank experimental evidence of carcinogenicity is removed. In addition, the uncertainties unique to estimates of risk based on the squamous cell carcinoma and polypoid adenoma data are not carried clearly forward in a combined estimate of risk.

The second, and major assumption is that there is equivalence between benign and malignant tumors, i.e. a benign tumor will progress to a cancer. This is necessary because the combined risk estimate is nearly entirely weighted by a risk component generated from the benign polypoid adenoma tumor data. Since the estimate is presented as a cancer risk estimate, equivalence (progression) must be assumed. However, the basis for this assumption must be reviewed. Certainly there is much literature on the progression of benign tumors, but equivalence is not automatically assumed, especially when the experimental study (the Kern study) suggests otherwise (see p. 22--Polypoid Adenomas/Other tumors Observed).

It may not be correct to assume that the majority of tumors estimated for the human population will occur in the nasal cavity since humans are not obliged to breathe through their nose. Consequently, it may be worthwhile to look at the nature of benign tumors seen in the nasal cavity of humans and animals as well as in other epithelial tissues in humans.

As previously discussed, the nature and progression of benign tumors in the nasal cavity of rats is poorly understood (see Section 4.2.1.). The polypoid adenomas observed in the Kern et al. (1983) study do not appear to be the benign counterparts of the squamous cell carcinomas or other cancers observed. The situation for humans is similar, although based on clinical experience some generalizations can be made. However, it must be remembered that the clinical cases are the result of diverse

causes and may not share the same course as an HCHO-induced lesion. The following discussion is presented to highlight the uncertainty involved in any discussion of cancer induction.

Two common types of benign lesions seen in the nasal cavity of humans are nasal polyps and inverted sinonasal papillomas which are both polypoid lesions.

Nasal polyps are a common clinical condition in humans and are frequently associated with allergic rhinitis, inflammatory diseases, and other disorders (Paludetti, 1983; Jacobs, 1983; Frazer, 1984; Drake-Lee, 1984). These polyps are not considered to be true neoplasms, but are merely inflammatory hypertrophic swellings (Robbins, 1974).

On the other hand, inverted squamous papillomas are true neoplasms. Inverted squamous papillomas have an incidence that is reported to vary from 0.4 to 4.7 percent of all nasal and sinus neoplasms (Bosley, 1984; Hyams, 1971; Sellars, 1982; Lampertico et al., 1963; Seydell, 1933). Their morphology may vary from that of firm, bulky, opaque polypoid lesions with marked vascularity to having the same appearance as common inflammatory nasal polyps (Bosley, 1984; Perzin et al., 1981). The reported associated frequency of squamous cell carcinoma with inverted papilloma is between 2 to 50 percent (Bosley, 1984; Hyams, 1971; Snyder et al. 1972; Ridolfi et al., 1977; Lasser et al., 1976; Vrabec, 1975; Osborn, 1970; Yamaguchi et al., 1970; Brown, 1964).

Two other types of benign neoplasms are seen in the nasal cavity of humans; fungiform papillomas and cylindrical cell papillomas. Fungiform papillomas are not associated with the development of malignancy while the cylindrical cell papillomas are associated with malignancy in 10 percent of the cases studied (Bosley, 1984).

A number of benign tumors are seen in the oral mucous membrane of humans. Fibromas, papillomas, hemangiomas, lymphangiomas, and less commonly myoblastomas and congenital epulis. However, in contrast approximately 90 percent of oral malignancies are squamous cell carcinomas (Robbins, 1974).

The two most common benign tumors of the human larynx are polyps and papillomas, other less common types run the gamut of every cell type found within the larynx (Robbins, 1974). Squamous papillomas are the most common type of benign tumors seen in the larynx and are the most common of all childhood laryngeal tumors. These are frequently divided into adult and juvenile groups. However, recent work has contradicted some of the classical descriptions used to separate adult from juvenile papillomas (Nikolaidis, 1985).

However, while juvenile papillomas are thought not to, or to rarely, undergo malignant transformation (Nikolaidsis, 1985; and Robbins, 1974) the adult type is regarded as having the potenital to progress to a malignancy (squamous cell carcinoma) (Robbins, 1974). In a study of 83 cases (73 juvenile and 10 adult) of tumors of the larynx, only one adult case was associated with a

squamous cell carcinoma (Nikolaidis, 1985). This suggests a less than one-to-one relationship between papillomas and carcinomas: it should be pointed out that there was surgical intervention and no follow-up.

Although the above does not show that benign tumors caused by HCHO will not progress to a malignant neoplasm, it does show the uncertainty involved in assuming that there is a one-to-one relationship between risk estimates generated from benign and malignant data sets.

7.4.3. Summary

Because of the uncertainties associated with the polypoid adenoma data set, its statistical significance, the manner of risk estimation, and the question of progression to malignant tumors, it is recommended that risk estimates derived from them not be added to estimates derived from squamous cell carcinomas. In addition, it is recommended that greater weight be given to risk estimates derived from squamous cell carcinomas because of the frank expression of carcinogenicity in the rat, they are statistically significant, and there is a positive dose response relationship.

8. ESTIMATES OF NONCANCER RISKS

8.1. Introduction

Although some of HCHO's noncarcinogenic effects are well characterized, there remains the problem of determining the dose-response characteristics of populations for these effects. To determine if dose-response relationships can be drawn from the human data, six cross-sectional and two controlled human studies were selected for review.

8.2. Studies Reviewed

Table 8-1 presents the exposure-response relationships, if any were observed, for those studies identified by Fraenkel, et al. (1985a). From this group of studies, selected ones were extensively analyzed for dose-response relationships. These studies are detailed in Tables 8-2 and 8-3. In addition, several studies which were thought to illicit a possible dose-relationship, but were not identified in Table 8-1 were extensively analyzed. The studies are ones which contain information on both HCHO levels and characterization of response. Studies which examined dermal responses were not selected since exposure is by either patch testing or dermal injection. Results from this route of exposure are often difficult to generalize. The studies selected for Table 8-1 in-depth review were of two types; cross-sectional and controlled (clinical). The cross-sectional studies were of mobile home residents and occupationally exposed workers. In the clinical trials, small groups, fewer than 20, of healthy volunteers were

Table 8-1. SUMMARY OF DOSE-RESPONSE DATA FOR NON-CARCINOGENIC HEALTH EFFECTS OF FORMALDEHYDE#

Investigator	Endpoint	Exposure Schedule	Dose	Response	Statistical Analysis
			RESPIRATORY EFFECTS		
Rader, J. (1974)	Investigated effects of formaldehyde, e.g., all symptoms, nasal sensitivity of conjunctive, sensitivity in nasal-jaw area, dryness, nasal secretion, tear flow	10 subjects divided into 2 groups of 5 were exposed for 1 hour at a time to various concentrations with an interval of at least one day between exposures. The impacts were scored on a standardized intensity scale created by the author.	0.00 ppm 0.1 0.2 0.5 1.0 3.0 5.0	**All Symptoms*** 	
				Specific Symptoms* (Approximate values)**	
				Nasal	None
			0 ppm 0.1 0.2 0.5 1.0 5.0	13 14 35 30 80 250	
				Conjunctival Sensitivity	None
			0 0.1 0.5 1.0 3.0 5.0	15 20 22 30 80 190	
				Nasal-Jaw Sensitivity	None
			0 0.1 0.2 0.5 3.0 5.0	20 21 35 22 85 150	

*Response reported as log of sum average intensity values times frequency of reaction.
**Responses are significantly different than control. No trend analyses were reported. Types of tests not reported.
***Response given as average value of intensity times percent of subjects reporting a symptom. They cannot be assigned unit values or total possible scores. Responses should be considered relative to each dose group.
From Fraenkel, 1985a.

Table 8-1. (Continued)

Investigator	Endpoint	Exposure Schedule	Dose	Response	Statistical Analysis
				Dryness of Throat	None
			0	0
			0.1	15
			0.2	2
			0.5	4
			1.0	4
			3.0	15
			5.0	20
				Nasal Secretion	None
			0	0
			0.1	0
			0.2	2
			0.5	1
			1.0	0
			3.0	20
			5.0	30
				Tear Flow	None
			0	0
			0.1	0
			0.2	0
			0.5	10
			1.0	20
			3.0	40
			5.0	100
Kerfoot, E. J. and T. F. Mooney (1975)	Irritative effects (See Table 1).	Air was sampled which contained formaldehyde gas and paraformaldehyde powers	107 samples were collected with a range from 0.09 to 5.76 ppm. Mean exposure levels from 0.25 to 1.39 ppm.	No dose-response data or prevalence data provided. No quantitative response data provided.	None

Table 8-1. (Continued)

Investigator	Endpoint	Exposure Schedule	Dose	Response				Statistical Analysis
Garry, V. F., et al. (1980)	Upper respiratory irritation	Air samples taken	Exposure levels not given	No dose-response data.				None
			Level of formaldehyde in mobile homes ranged from 0.1 to 3.0 ppm.	Approximate Percent Symptoms Reported				
				Symptoms	[illegible] Adults (18 + years)	[illegible] Children (3-12 years)	38 Newborn (0-2 years)	
				Ear, Nose, Throat	79	80	80	
				Cough, Wheeze	38	64	61	
				Respiratory Problem	38	24	24	
				Diarrhea	22	19	50	
				Headache	50	30	--	
				Nausea and Vomiting	20	15	30	
				Skin rash	--	30	50	
Gamble, J. F. et al.	Changes in pulmonary function on exposure to hexamethylenetetramine-resorcinol (HR)		Mean Concentration (mg/m³)	Acute Effects*		Percent Change**		
		19 HR workers exposed for 8-hour period	0.061	FEV	(liters)	-0.9%		
				FVC	(liters)	-0.2%		
				Peak Flow	(liters/sec.)	-2.7%		
				FEF_{25-75}	(liters/sec.)	-6.7%		p<0.01***
				FEF_{50}	(liters/sec.)	-6.2%		p<0.025
				FEF_{60}	(liters/sec.)	-0.3%		p<0.005
				FEF_{75}	(liters/sec.)	-17.1%		p<0.005
				P_{80}	(liters/sec.)	-0.3%		p<0.05
				CV/VC	(%)	+7.9%		
				N	(ΔN_2)	-0.0%		
		16 HR workers on an unexposed day	0.025	FEV	(liters)	+1.3%		
				FVC	(liters)	+1.4%		
				Peak Flow	(liters/sec.)	+3.0%		
				FEF_{25-75}	(liters/sec.)	+2.0%		
				FEF_{50}	(liters/sec.)	-0.7%		
				FEF_{60}	(liters/sec.)	+3.0%		
				FEF_{75}	(liters/sec.)	-1.2%		
				P_{80}	(liters/sec.)	+4.3%		
				CV/VC	(%)	+2.7%		
				N	(ΔN_2)	-3.6%		

*FEV --forced expiratory volume P_{80} --flows at 80% FVC
FVC --forced vital capacity ΔN --change in nitrogen concentration
CV --closing volume FEF_x --flows at mid-vital capacity
**Percent change refers to difference between before and after work values.
***1-sided t-test with H_0: ΔFF = 0 (i.e., no significant change in pulmonary function).

Table 8-1. (Continued)

Investigator	Endpoint	Exposure Schedule	Dose	Response	Statistical Analysis
Gamble, J. F. et al. (continued)		19 Non-OR exposed workers (control)	0.006	**Acute Effects[a]** — **Percent Change** FEV (liters) +0.4% FVC (liters) +1.7% Peak Flow (liters/sec.) +6.2% FEF_{25-75} (liters/sec.) +3.8% FEF_{50} (liters/sec.) -2.8% FEF_{40} (liters/sec.) -3.2% FEF_{75} (liters/sec.) -5.7% P_{80} (liters/sec.) +0.2% CV/VC (%) +9.6% ΔN ($\%N_2$) -7.4%	No significant changes
		92 exposed workers - E 90 matched non-exposed worker - C 90 randomly selected workers from plant population - O		**Prevalence of Symptoms** Symptom — Group E / C / O Itch 35% 29% 20% Breathing better away from from work 70 41 43 Cough 30 11 19 Shortness of breath 19 17 11 Wheeze 16 9 11 Burning Eyes 43 26 30 Running Nose 27 17 17 Chest Tightness 23 20 9 Dry, Sore Throat 16 13 24 Hoarseness 10 6 12 Phlegm 15 20 8 Persistent cough and phlegm 13 10 4	E significantly ($\alpha = 0.05$) greater than C, O E significantly ($\alpha = 0.05$) greater than C + O E significantly ($\alpha = 0.05$) greater than C + O No statistically significant difference in respiratory symptoms among exposure groups

[a]FEV --forced expiratory volume
FVC --forced vital capacity
CV --closing volume
P_{80} --flows at 80% FVC
ΔN --change in nitrogen concentration
FEF_x --flows at mid-vital capacity
E--exposed workers
C--matched non-exposed workers
O--randomly selected workers from plant population

Table 8-1. (Continued)

Investigator	Endpoint	Exposure Schedule	Dose	Response	Statistical Analysis
Tefrenov, G. G. (1978)	Upper respiratory tract diseases	Occupational exposure	No data provided	Exposed: 20.2%-30.2% exhibited symptoms Control: 13.0% exhibited symptoms of chronic rhinitis, chronic pharyngitis, chronic laryngitis and chronic sinusitis	No statistical analysis
				Motor Function of Nasal Epithelium*	No statistical analysis
				Group — n — mean (minutes) Control — 20 — 16.0 ± 1.3 Workers — 100 — 29.9 ± 1.9	
				Absorptive Function of Nasal Mucosa**	
				Group — n — mean (minutes) Workers without nasal pathology — 39 — 32.3 ± 6.6 Workers with nasal pathology — 14 — 20.4 ± 4.3 Control — 20 — 41.0 ± 4.1	p<0.001 p<0.001
Schoenberg, J. B. and C. A. Mitchell (1975)	Chronic airway obstruction	Occupational exposure	Estimated to range of 7-10 mg/m³ (occasionally 10.6-16.3 mg/m³)	n — Never On-Line — Previous On-Line — Present* On-Line 5 years FEV1.0/FVC — 79.4 ± 1.3 — 79.2 ± 2.7 — 71.2 ± 2.8	p<0.05 for present on-line vs. never on-line group.
			Results not reported in form of dose and response	MEF 50%/FVC — 90.3 ± 4.0 — 88.8 ± 9.0 — 64.0 ± 6.2	p<0.005 for present on-line vs. never on-line group
Hendrick, D. J. and D. J. Lane	Bronchial Asthma	Occupational exposure	No data provided	Wheezing, pulmonary function tests normal	None
Schachter, E. N. et al. (1980)	Acute airway effects	Not available in information provided	Insufficient information in materials provided	Insufficient information	None

*Adjusted to cigarette consumption.
**Measured as time required to move carbon dust from nasal cavity to nasal pharynx.
***Measured as time from inhibition to reappearance of pupillary response after applying homatropine to nasal cavity.

Table 8-1. (Continued)

Author	Endpoint	Exposure Schedule	Dose	Response	Statistical Analysis
			SENSITIVITY		
Harris, D. K. (1953)	Dermatitis: acute papulovesicular eczema	Occupational exposure	Between <10 ppm and 30 ppm	Response not quantified	None
Schwartz, L. et al.	Skin irritation	Patch test evaluated at 24 and 72 hours. Percent of formaldehyde in each fraction not known.	Not quantified Raw cashew shell liquid: 24 hours 72 hours 1st Distillate: 24 hours 72 hours Partially Cured: 24 hours 72 hours	Number Positive Reactions 14/15 14/15 12/15 7/15 7/15 3/15 + 2 late reactions	None
Mortensen, K. E. et al. (1943)	Dermatitis	Unknown	Unknown	355/2370 workers	None
Engel, M. B. and C.D. Calnan (1968)	Dermatitis	1 day to 3 years. Average period of contact before onset was 17 weeks, but in 5 cases rash started within 24 hours of handling adhesive	Not quantified	70% of affected workers had positive reaction to patch test with resin formaldehyde 10% of patients experienced positive reaction to phenol alone 65% of patients experienced positive reaction to resin	None
Horsfall, F. L. (1934)	Delayed contact dermatitis in one patient	Unspecified	Intradermal: 100 ppm 50 25 12.5 0.2 Immersion: 100-0.2 ppm 0.175 ppm	Diameter of Papule 1 Day Persisted Patient / Control 45 / 0 25 / 0 23 / 0 20 / 0 0 / Not tested at this level Positive No controls; no quantitative data provided Negative	None

Table 8-1. (Continued)

Endpoint	Exposure Schedule	Dose	Response		Statistical Analysis
[illegible]	Air samples collected	Log Formaldehyde*			p<0.05
			Burning Eyes		
			Watery Eyes		
			Cough	+(7)	
			Dry Throat	+(3)	
			Phlegm		
			Swollen glands	+(3)	
			Diarrhea	+(3)	
			Headache	+(4)	

*Only symptoms with significant regression coefficients in this table. Exposure parameter was expressed as log formaldehyde concentration and is not presented here. Sign indicates direction of association. Number in parentheses indicates number of months that the association remained significant.

Table 8-2. SUMMARY OF SELECTED CROSS SECTIONAL STUDIES[a,b]

EXPOSURE LEVEL (ppm)	SYMPTOMS	SUBJECT OF STUDY	ESTIMATED PREVALENCE	STUDY	COMMENTS
<0.02-0.78	Cold Symptoms	females (>16 yrs)	2.24[c]	Texas Indoor	Study of mobile homes.
	Headaches	females (5-15 yrs)	4.64[c]	Air Quality	
	Sneezing	females (>16 yrs)	1.91[c]	Study	
	Any nasal abnormality	males & females (>11 yrs)	1.73[c]		
	Sehorrhea	males & females	11.85[d]		
	Pressure in chest	males (>16 yrs)	11.74[c]		
	Sneezing	females (5-15 yrs)	2.86[c]		
	Inflamed mucous membranes	males & females (>11 yrs)	4.49[d]		
0.037	Persistent cough & phlegm	50 non-hexamethylene-tetramine workers in a tire manufacturing plant	10%	Gamble et al.	HR exposed workers had significant reductions in expiratory flow at l lung volumes, indicating increased resistance in small airways when compared to a group of workers from the entire plant.
	Itch		23%		
	Rash	resorcinol	17%		
	Shortness of breath	workers in a	17%		
	Chest sputnum		20%		
	Burning sensation in heart region		11%		

[a] Fraenkel (1985b)
[b] Only those studies where both exposure and prevalence are represented.
[c] Prevalence ratio calculated from the data gathered in the medical interview.
[d] Prevalence ratio calculated from the data gathered in the clinical examination of individuals.

Table 8-2. (Continued)

EXPOSURE LEVEL (ppm)	SYMPTOMS	SUBJECT OF STUDY	ESTIMATED PREVALENCE	STUDY	COMMENTS
0.02–0.05	Persistent cough & phlegm	52 hexamethylene-tetramine	13%		
	Itch	resorcinol workers	35%		
	Rash		23%		
	Shortness of breath		19%		
	Chest sputum		21%		
	Burning sensation in heart region		17%		
0.04–0.09	Eye irritation	34 permanent day	15%	Olsen and	Control group and 34
	Nose, throat irritation	care center staff	23%	Dossing	mobile home day care centers.
0.19–0.44	Eye irritation	70 mobile home day	57%		
	Sinusitis	care center staff	16%		
	Nose, throat irritation		73%		

Table 8-2. (Continued)

EXPOSURE LEVEL (ppm)	SYMPTOMS	SUBJECT OF STUDY	ESTIMATED PREVALENCE	STUDY	COMMENTS
<0.10-2.84	Burning eyes	Residents of mobile homes	25%	Anderson et al.	Study of mobile homes.
	Watering eyes		20%		
	Dry throat		24%		
	Swollen glands		6%		
	Diarrhea		10%		
	Running nose		35%		
	Sneezing		45%		
	Phlegm		25%		
	Wheezing		17%		
	Cough		44%		
	Headache		29%		
	Rash		11%		
0.1-3.0	Ear, nose, throat	Adults	79%	Carry et al.	Mobile homes.
		0-12 yrs	60%		Measurement of formaldehyde
	Cough & wheeze	Adults	38%		vary with month of measurement.
		3-12 yrs	54%		
		0-2 yrs	61%		
	Respiratory problem	Adults	36%		
		0-12 yrs	24%		
	Diarrhea	Adults	22%		
		3-12 yrs	10%		
		0-2 yrs	58%		
	Headaches	Adults	50%		
		3-12 yrs	38%		
		0-2 yrs	0%		
	Nausea & vomiting	Adults	20%		
		3-12 yrs	15%		
		0-2 yrs	38%		
	Skin rash	Adults	0%		
		3-12 yrs	30%		
		0-2 yrs	50%		

Table 8-2. (Continued)

EXPOSURE LEVEL (ppm)	SYMPTOMS	SUBJECT OF STUDY	ESTIMATED PREVALENCE	STUDY	COMMENTS
0.40-0.80[e]	Cough	Present-line		Schoenberg & Mitchell	63 filter manufacturing worke
		>5 yrs	33%		No significant differences
		1-5 yrs	30%		(p>.05) among any of the grou
		<1 yr	40%		in either FVC or $FEV_{1.0}$. The
		Previous on line	12.5%		group, present line more than
		Never on line	6.7%		5 years or more, had a lower
					$FEV_{1.0}$/FVC ratio; and signifi-
					cantly lower (p<0.05) MEF_{50}/F
					than the never-on-line group.
	Phlegm	Present-line			
		>5 yrs	26.7%		
		1-5 yrs	20%		
		<1 yr	26.7%		
		Previous on line	0.0%		
		Never on line	6.7%		
	Dyspnea	Present line:			
		>5 yrs	6.7%		
		1-5 yrs	20.0%		
		<1 yr	20.7%		
		Previous on line	12.5%		
		Never on line	6.7%		

Table 8-3. SUMMARY OF SELECTED CONTROLLED HUMAN STUDIES

Levels of Exposure (ppm)	Symptom	Study Subject	Response	Author
0	Odor perception	Anatomy lab students	13[a]	Rader[b]
	Conjunctival sensitivity	Each group contains six students	25	
	Nose, Throat sensitivity		20	
	Throat dryness		0	
0.1	Odor perception		14	
	Conjunctival sensitivity		15	
	Nose, Throat sensitivity		21	
	Throat dryness		15	
0.2	Odor perception		35	
	Conjunctival sensitivity		35	
	Nose, Throat sensitivity		35	
	Throat dryness		2	
0.5	Odor perception		30	
	Conjunctival sensitivity		18	
	Nose, Throat sensitivity		20	
	Throat dryness		4	
1.0	Odor perception		40	
	Conjunctival sensitivity		30	
	Nose, Throat sensitivity		40	
	Throat dryness		2	

[a]Response represents the log of a weighted average of the concentration x time-factor.
[b]Dose response trend was observed for all complaints.

Table 8-3. (Continued)

Level of Exposure (ppm)	Symptom	Study Subject	Response	Author
3.0	Odor perception		30	
	Conjunctival sensitivity		80	
	Nose, Throat sensitivity		75	
	Throat dryness		15	
5.0	Odor perception		20	
	Conjunctival sensitivity		190	
	Nose, Throat sensitivity		200	
	Throat dryness		10	
0.24	Conjunctival irritation and dryness in nose, throat	Healthy students	2[c] (19%)	Anderson and Molhave
0.40	Conjunctival irritation and dryness in nose, throat		5 (31%)	
0.80	Conjunctival irritation and dryness in nose, throat		15 (94%)	
1.60	Conjunctival irritation and dryness in nose, throat		15 (94%)	

[c] Number of complaints among 16 subjects after a 5-hour exposure to formaldehyde.

exposed to varying concentrations of HCHO and their responses were recorded. Set endpoints were examined such as, odor recognition, conjunctival sensitivity, nose/throat sensitivity, and throat dryness. The cross-sectional studies recorded a wide range of health complaints as Table 8-2 illustrates.

8.3. Limitations of Studies

Even though dose-responses are identified, the studies reviewed have major limitations which prevent their use to infer the magnitude of general population risks.

8.3.1. Study Design Limitations

The data on acute effects come from controlled human studies or cross-sectional studies. The majority of the studies were designed as cross-sectional studies, also known as survey studies, where both a random or nonrandom sampling frame was employed.* In addition, two of these studies' designs did not incorporate a nonexposed or control group (Garry et al. and Anderson et al.). Without a control group, it is impossible to determine the magnitude of a reported symptom.

A cross-sectional study measures the study factor level, in this instance the HCHO level, and disease outcome at the same time. This type of study does not incorporate a follow-up period so that the prevalence of the disease outcome, and not the

*Use of a nonrandom sampling frame prevents extrapolating the results beyond the studied population. Random sampling, on the other hand, allows the making of statistical inferences from the studied population to the general population.

incidence, is obtained.* Cross-sectional studies are often used to generate hypotheses, but they have serious limitations in making causal inferences.

Controlled human studies test etiologic hypotheses and can identify acute effects. The two controlled human studies identified in Table 8-3 did not utilize a randomization scheme. Study participants were self-selected and may not be representative of the general population.

8.3.2. Bias Limitations

Other limitations regard potential bias in the results. The cross-sectional studies do not control for confounding exposures, such as smoking or other occupational exposures and an observed effect may not solely be due to HCHO exposure. Second, many studies report subjective or self-reported symptoms. These symptoms have not been medically verified, and thus results based on subjective measures may be biased by over-reporting or under-reporting. A third problem of the cross-sectional studies concerns the quality of the environmental exposure measurement. HCHO levels vary depending on the season of the year, hour of the day, temperature, and humidity. These factors must be known when evaluating the intensity of the disease endpoint.

8.4. Results

The principal acute effects of HCHO, reported by all studies which were extensively examined (Tables 8-2 and 8-3), are that of

*Prevalence is the number of cases existing with the outcome at a single point in time. Incidence is the number of new cases observed over a period of time.

irritation to eyes, nose, throat, upper respiratory tract and skin.

Evaluation of the results documented in the different papers indicates that these effects exist in varing degrees in people exposed to HCHO. These levels may range between 0.037-3.0 ppm. However, the intensity of these symptoms differ depending on the location of the study (mobile homes, industry, anatomy lab), on ambient air conditions, and on individual characteristics and personal habits.

Four of the studies (e.g., Texas Indoor Air, Anderson et al., Garry et al., and Olson and Dossing) were of occupants in mobile homes. Among the mobile home studies, the symptoms with the highest prevalence across different age groups were headaches, muscle aches, eye symptoms (burning eyes, watery eyes, itchy eyes), nose symptoms, and coughing. Some differences were detected among the different age groups. The youngest groups (0-2 yrs) experienced a higher rate of diarrhea while the adults had a relatively high rate of complaints from headaches. Only the Texas Air Quality study reports significant increases in the prevalence of certain acute effects such as headaches, sneezing, and nasal symptoms among occupants exposed to either 1.0 ppm HCHO or greater, or 2.0 ppm HCHO or greater.

When evaluating these studies, it must be noted that not only ambient conditions within the home, but also seasonal temperature/humidity fluctuations can affect the rates of off gasing (Gamble et al.). Because most mobile homes are tightly

sealed and do not use a continuous influx of outside air, other gases such as carbon monoxide, which were not measured, may contribute to the acute effects experienced by the residents.

Kerfoot and Mooney also reported nose and eye irritation in morticians. These results are qualitative in nature; they indicate that morticians who spent more time embalming than in general funeral work more often complainted of upper respiratory irritation.

In studies of workers in industry, statistically significant increases complaints from acute sensory effects were observed among workers exposed to HCHO. The reported symptoms, itch, rash, breathing better away from work, cough, chest tightness, burning eyes, running nose and burning sensation in the heart region were significantly increased in a group exposed to HCHO when compared to non-HCHO workers. In addition, two studies measured lung function in HCHO resin workers and in filter manufacturing workers. Both studies observed significant decreases in various lung function parameters, but neither study reported the same observation. Exposure levels ranged between 0.02-0.66 ppm. When these two studies controlled for smoking and/or drinking, the observed decreases in lung function measurements remained. The studies do not identify other occupational exposures. It is not known whether the observed effects were due to possible interactions.

Rader tested student volunteers in an anatomy laboratory and found that the concentration levels of HCHO in ambient air are

affected by seasonal changes, time of measurements, room temperature and humidity level. Dose and response showed correlations and there was a statistically significant increase in each of the dosed groups and the control group for the total complaint score* of acute effects. The summed complaint score was for the acute effects: odor perception, conjunctival sensitivity, nose/throat irritation, throat dryness, nasal secretions and tear flow.

Andersen and Molhave assessed the human health effects associated with prolonged exposure to HCHO under controlled thermal and atmospheric conditions. They observed an increasing trend with eye and nose irritation between exposure levels of 0.3 to 2.0 mg/m^3. Human response increased from 19 percent to 94 percent over this exposure range. In addition, mean mucous flow rate decreased at the higher concentrations of HCHO. Changes in airway resistance were significant for nasal pressure drop, vital capacity, a several lung function parameters.

The above studies report eye, nose, throat irritation, and upper respiratory effects with low levels of HCHO exposure, but this information should be judged with caution since in most cases:

- Effects are judged subjectively as symptoms experienced by the subject and not as objective measurements.
- Limitations of the studies include small study sample size, selective study populations low response rates, inadequate control of confounding variables, and

*It must be noted that the complaint score was a sum of the number of complaints times the severity of the response.

inability to distinguish the contributions of HCHO from those of other substances.

8.5. Discussion

Both HUD and OSHA have assessed the acute effects due to HCHO. HUD's assessment was used to support changes in the Manufactured Home Construction and Safety Standards, while OSHA's assessment will be used to support a possible change in OSHA's permissible exposure level for HCHO.

HUD's assessment consisted of an evaluation of the cost-benefit relationships of regulatory alternatives to control HCHO levels in mobile homes. A computer model was developed to assess the relationship between HCHO levels and mobile home age. The cost of illness was calculated for a 20-year exposure period under various assumptions, such as initial HCHO concentrations in homes, type and cost of resulting health effect, and number of homes and persons affected. HUD used the CPSC injury-cost model to estimate an average cost of illness assuming that exposure to HCHO could cause one of several types of health problems (i.e., ingestion of a foreign object, aspiration of a foreign object, dermatitis of the face, or dermatitis of the eyeball). The HUD study did not report the incidence or prevalence of symptoms for persons residing in homes with varying detectable levels of HCHO. HUD's study method assumed that 75 percent of the occupants of a mobile home with HCHO would experience a health problem, but the concentration producing this effect was not derived or estimated.

There were no data presented in the HUD analysis which supports a dose-response relationship between sensory effects and HCHO levels in mobile homes. Data were presented which support a qualitative relationship. However, it is also important to note that HUD's study does not address the question of concentration levels of HCHO in the mobile home and the magnitude of the effect on the resident.

OSHA has produced an assessment of both noncancer irritant and cancer effects. For the noncancerous effects assessment, OSHA relies on data submitted by industry (SOCMA, 1979) and certain assumptions. SOCMA collected information on nose and eye irritation from 17 industries where HCHO exposure occurs and calculated average exposure levels. OSHA only used the endpoint "nose irritation" in their assessment, which SOCMA defined as the ability to detect HCHO odor. However, one must assume that odor recognition correlates with eye, nose, and throat irritation. It may in some individuals, but not in others. For instance, an individual may have a high odor threshold (1.5 ppm), but a low eye irritation threshold. Odor perception (strength) is very subjective. Consequently, odor recognition and strength should only be used as qualitative markers that HCHO levels may be in the range when eye, nose, and throat irritation may occur. Also, the odor respose is very susceptible to fatigue. Fatigue caused by low, initial HCHO levels may mask subsequent increases in HCHO levels, thus further complicating the link between the odor response and irritation.

In summary, HUD's and OSHA's approaches provide some qualitative measure of acute effects from HCHO exposure. However, these techniques do not determine a true dose-response relationship. The Andersen and Mulhave study is the only study that reported a dose-response relationship (Table 8-3). However, this is a clinical study in which only 16 healthy volunteers were used. Selective bias may be present and in no way should this group be presumed to represent the population at large.

Table 8-4 presents response data over a range of exposures for three acute endpoints. As can be seen from the table, reductions in the prevalence of these endpoints from small changes in HCHO levels, say from 0.4 to 0.1 ppm, are difficult to quantify with a high degree of certainty given the limitations of the studies available.

In conclusion, none of the reviewed studies provide adequate data to quantify population risks for the acute effects of HCHO. At best, the studies provide a qualitative estimate of population responses over a wide range of exposure levels.

Table 8-4. EXPOSURE RANGES FOR SELECTED ENDPOINTS

Acute Effect	Exposure Level	Prevelance	Author
Nose Irritation	0.04-0.09	23%[a]	Olsen and Dossing
	<0.01-2.84	45%	Anderson et al.
	0.10-3.00	79%	Garry et al.
	0.19-0.44	73%	Olsen and Dossing
Eye Irritation	0.04-0.09	15%[a]	Olsen and Dossing
	0.10-2.84	57%	Anderson et al.
	0.40-0.80	25%	Olsen and Dossing
Cough and Wheezing	0.02-0.05	13%	Gamble et al.
	<0.10-2.84	44%	Anderson et al.
	0.10-3.00	54%	Garry et al.
	0.40-0.80	33%	Schoenberg and Mitchell

[a] Control group (background level)

9. RISK CHARACTERIZATION

This assessment has discussed studies of many effects of HCHO ranging from the perspective of the chemical's interaction with proteins and DNA to that of overall acute and chronic biological responses. It is inferred that within the existing ranges of exposure of both garment workers and home residents, all or portions of each population are at risk of one or more adverse effects. The uncertainties in estimating the numbers of persons who will have effects of each kind at various levels of exposure have been discussed at length. This section highlights conclusions of the hazard identification, dose-response assessment, and exposure assessment components of the risk assessment, lays out their strengths, weaknesses, and major assumptions, along with their associated uncertainties and gives an overall characterization of the various risks.

9.1. Cancer

Under EPA's proposed cancer risk assessment guidelines, HCHO has been classified as a Group B1-Probable Human Carcinogen. This classification is based on an interpretation of the available human and animal data which indicate that there is limited evidence of HCHO carcinogenicity from epidemiologic studies and a finding of sufficient evidence from animal studies.

HCHO has been found to be carcinogenic (same anatomical site and type of cancer) in two strains of one species, rats, in two, 2-year multidose studies and in two, 2-year single-dose studies. Statistically significant numbers of malignant

neoplasms were seen at one site, nasal cavity, only at about 14 ppm, the highest dose tested. In the CIIT 2-year study the first neoplasms were seen in male rats at month 12 and in female rats at month 15. The same malignant neoplasms were seen in two male mice in the CIIT 2-year study, at the same site, nasal cavity, only at the highest dose, about 14 ppm. Although not statistically significant, these lesions may be biologically significant due to the rarity of nasal tumors in rodents. In addition, a small number of benign polypoid adenomas were seen in rats in the CIIT study at all dose levels. Hamsters have been tested in long-term inhalation studies with negative results. However, study design limitations compromise the results from these studies. Other studies suggest that HCHO may have promotional or cocarcinogenic activity.

The data indicate that HCHO is rapidly metabolized at the site of contact; the tissues receiving the highest dose which would be expected to show the greatest neoplastic response are those at or in close proximity to the site of introduction of the chemical. The long-term animal studies as well as other tests are consistent with this observation.

The mutagenic activity of HCHO has been shown in numerous in vitro tests using procaryotic and eucaryotic cell lines. However, HCHO is a weak mutagen in these tests. In vivo tests in mammals have been negative or equivocal at most.

HCHO is not unique among the chemicals in its structural class in showing carcinogenic activity in animals. Acetaldehyde,

as well as a few other aldehydes, have shown carcinogenic activity in animal tests. The clearest response has been seen with acetaldehyde which is the closest in structure to HCHO.

Although both HCHO and acetaldehyde cause nasal tumors in rats, HCHO produced squamous cell carcinomas in the anterior region of the nasal cavity while acetaldehyde produced adenocarcinomas in the posterior region. As discussed earlier in this document, experimental nasal carcinogens vary in the tumor type, tissue site, and species they affect. Generally, not enough is known to demonstrate a mechanism or pattern for prediction of tumor progression, species susceptibility, and cell type for any particular nasal carcinogen.

Since adequate epidemiologic studies are not available to estimate cancer risk to humans, high to low dose risk extrapolation using animal data was done. For that purpose, the CIIT multidose study in rats was used. The estimated upper bounds for excess lifetime risks range from 3×10^{-4} [B1] to 1×10^{-3} [B1] for apparel workers and 2×10^{-4} [B1] for mobile home residents based on HUD's mobile home standard. The risk for garment workers at the OSHA standard of 3 ppm is 6×10^{-3}. Risk estimates based on benign polypoid adenomas are about an order of magniture greater for the exposures of concern. The principal route of exposure is by inhalation which is the same route as in the animal study used for risk estimation. While the only statistically significant malignant neoplasm seen in the animal study was squamous cell carcinoma of the nasal cavity, the

response in humans may or may not be the same in histology or site because we are not obliged to breathe through the nose as are rats. Other kinds of tumors in the respiratory system and proximate tissues (e.g. the brain) are possible, also possible are tumors at distant sites.

EPA and the Consensus Conference on Formaldehyde agree that HCHO's noncarcinogenic effects (cell killing, irritation) may potentiate its carcinogenicity. Reduction of human exposure to a level that introduces a margin of human safety from these effects may accomplish a significant reduction in risk of carcinogenic effects. Animal studies indicate a NOEL of about 1 ppm for squamous metaplasia. We also cannot rule out the possibility that the potentiating effects of HCHO could operate to increase the risk of persons simultaneously exposed to respiratory carcinogens. Recent epidemiologic studies suggest a synergism between wood dust and HCHO exposure.

The cancer dose-response in the animal study used to estimate human risk is very nonlinear. The Agency has used the multistage model to mimic the observed responses. In keeping with the proposed EPA Cancer Assessment Guidelines, the linear upper 95% CL on the model was used to estimate risks from HCHO exposure, since experimental and mechanistic information did not lead us to select an alternative to that procedure. It should be recognized that the model used is very conservative. Another aspect of the nonlinearity of the experimental data is that it introduces a high level of uncertainty into the extrapolation of

risk to low exposures. For instance, the MLE and 95% UCL derived risks for apparel workers exposed to 0.17 ppm HCHO are 4×10^{-9} [B1] and 3×10^{-4} [B1], respectively. The nearly 5 orders of magnitude difference gives an idea of this uncertainty. In addition, small changes in the input data, if the response is very nonlinear, can have a great impact on the extrapolated MLE estimates.

9.2. Other Effects

Acute effects, irritation of the eyes and upper respiratory system are the most common HCHO effects. Most persons experience discomfort within the range of 0.1 to 3 ppm HCHO. The eyes are generally the most sensitive. For most persons odor recognition occurs at about 1 ppm HCHO and can be a marker for acute effects. More serious effects occur at exposures above 3 ppm.

In addition to its sensory effect on receptors of the eyes, nose, and throat, HCHO also causes inflammation and cellular and tissue damage. Experiments in rats and monkeys indicate that chronic exposures over 1 ppm causes squamous metaplasia and hyperplasia. Also, subchronic exposures of 2 ppm or greater affect the mucociliary clearance system, causing mucostasis and ciliastasis. Ultrastructural changes to cilia may be occurring below 2 ppm. Possible impairment of the nasal mucociliary system (and other mucociliary systems of the respiratory system) by HCHO has been linked to increased episodes of respiratory tract infections in children.

A small number of reports associate HCHO with allergic asthma-like symptoms. However, there are no sufficiently well-controlled studies to establish whether HCHO is an inhalant sensitizer.

On the other hand, HCHO is a well-known dermal sensitizer and irritant. After sensitivity is induced, concentrations which elicit allergic response range from as low as 30 ppm in a patch test to 60 ppm from actual use of formalin. HCHO causes allergic contact dermatitis (Type IV allergy) and probably immunologic contact urticaria (hives or rash) (Type I allergy). Nonallergic contact urticaria has also been reported from multiple exposure.

HCHO has been associated with a number of central nervous system (CNS) disturbances such as memory loss, irritability, and sleep disturbances. However, the human studies linking these CNS effects to HCHO have many technical and design faults which make the results questionable.

A limited number of reports have suggested that HCHO may cause reproductive disorders. However, no clear evidence exists to link HCHO to adverse reproductive outcomes. In addition, based on the available literature it is not likely that HCHO poses a risk as a potential human teratogen.

Garment workers and home residents are at risk from HCHO's acute effects. The HCHO exposures experienced by these two groups fall within the lower end of the range (0.1 to 3 ppm) where most persons experience irritation of the eyes, nose, and throat. However, the distribution of thresholds within the range

for the various effects is not known. Attempts to define the dose-response relationships for these effects have not been successful. However, it is reasonable to assume that some fraction of new homeowners will experience discomfort during the first year of occupancy if adverse temperature and humidity conditions are allowed to exist in the home. An analysis of HUD's manufactured home standard indicates that HCHO levels could approach 1.0 ppm at high temperature and humidity conditions, which is well within the range that some persons may experience discomfort. What fraction will respond is unknown.

In addition to sensory effects, HCHO also is capable of causing cellular changes in the upper respiratory system. Animal studies have shown that HCHO can inhibit mucociliary action after only a few days of exposure to 2, 6 or 15 ppm. Also, chronic studies have shown significant levels of squamous metaplasia in the nasal cavity of rats at 2.0 ppm and in monkeys exposed to 3.0 ppm. The NOEL for squamous metaplasia is estimated to be 1.0 ppm during chronic exposure. Disruption of the nasal mucociliary clearance system (shown in rats at exposures of 2 ppm and greater) is a significant effect because this system is an important defense mechanism which helps clear particulate matter and microbes from the body. The home populations and many garment workers are expected to experience chronic exposures of below 0.5 ppm.

9.3. Summary

The effects of HCHO which cause the most public complaint are irritation of eyes and upper respiratory tract. Cellular effects may be a factor contributing to carcinogenicity as previously discussed. These effects may also worsen the condition of individuals who have other underlying health problems such as asthma or respiratory tract infections, or predispose them to such problems, but it is not known how large a population may be affected. In fact, for none of the several irritation effects of HCHO are available data sufficiently reliable to permit their full impact on the population to be assessed.

From the available reports, we can estimate where the range of thresholds for human response appears to be, but the full health consequences cannot be characterized since the underlying health of individuals and the frequency of their exposure are critical, unknown factors. Table 9-1 summarizes the risks from the cancer and noncancer hazards of HCHO in the populations of concern. Cancer risks are presented as individual risk estimates. For the noncancer effects the margins of safety for each effect are given for the exposures of concern. As Table 9-1 indicates, the current OSHA standard of 3 ppm presents potentially very high cancer risks and virtually no margin of safety for cellular and sensory effects. For garment workers the cancer risk ranges from 3×10^{-4} to 1×10^{-3} based on carcinoma data and 5×10^{-3} to 2×10^{-2} based on adenoma data. Small

Table 9-1.
SUMMARY OF CANCER AND NONCANCER RISKS

Population Segment (exposure level)	CANCER - INDIVIDUAL RISK: Carcinoma Data	CANCER - INDIVIDUAL RISK: Adenoma Data	NONCANCER--MARGINS OF SAFETY: Cellular Effects (Noel 1 ppm)	Eye Irritation (0.05-0.5 ppm)*	Nose/Throat Irritation (1-11 ppm)*	Eye/Nose/Throat Irritation as reported by Consensus Workshop (0.1-3 ppm)*
OSHA std (3 ppm)	UCL 6×10^{-3} MLE 6×10^{-4}	UCL 1×10^{-1} MLE 2×10^{-1}	0.3	0.02-0.2	0.3-4	.03-1
Garment Workers						
NIOSH (0.17 ppm)	UCL 3×10^{-4} MLE 4×10^{-9}	UCL 5×10^{-3} MLE 2×10^{-3}	6	0.3-3	6-65	0.6-18
§4(f) (0.64 ppm)	UCL 1×10^{-3} MLE 6×10^{-7}	UCL 2×10^{-2} MLE 8×10^{-3}	2	0.08-0.8	2-17	0.2-5
Mobile Hm** Residents (at HUD Std. of 0.4 ppm)	UCL 2×10^{-4}	UCL 3×10^{-3}	3	0.1-1	3-28	0.3-8
(0.15 ppm 10-yr av.)	MLE 1×10^{-9}	MLE 1×10^{-3}				
Conventional Home** Residents (0.4 ppm new homes)	UCL 3×10^{-4}	UCL 4×10^{-3}	3	0.1-1	3-28	0.3-8
(0.030 long-term av.)	MLE 7×10^{-12}	MLE 2×10^{-3}				

*Range of individual thresholds.

**Cancer risk based on 10-year and long-term averages as appropriate. Margins of safety based on HUD standard and new home levels as appropriate. HCHO levels higher than 0.4 ppm can be expected due to adverse temperature/humidity conditions, i.e. >77°F/50% RH.

margins of safety are present for cellular and sensory effects except for eye irritation. However, it must be remembered that tolerance to eye irritation exists. Mobile home residents face moderate cancer risks and have some margin of safety for all effects except for eye irritation in some individuals. The situation is essentially the same for conventional home residents. However, as discussed earlier (see Section 6. Exposure Assessment), temperature and humidity conditions have a major impact on indoor HCHO levels and some fraction of new homes may experience HCHO levels greater than 0.4 ppm for varying lengths of time. Consequently, the already small margins of safety would be gone.

10. REFERENCES

1. Acheson, E.D. 1983. Data presented at the Consensus Workshop on Formaldehyde, October 2 and 3, 1983, Little Rock, Arkansas.

2. Acheson, E.D., Gardner, M.J., Pannett, B., Barnes, H.R., Osmond, C. and Tyalor, C.P. 1984a. The Lancet 1: 611.

3. Acheson, E.D., Barnes, H.R., Gardner, M.J., Osmond, C., Pannett, B. and Taylor, C.P. 1984b. The Lancet 1: 1066.

4. Aekbi, H. and Roggen, G. 1958. Enzymatische demethylierung von dimethyl- C^{14} -aminoantipyrin. Pharm. Acta Helv. 33: 413-428.

5. Ahmed, A.E. and Anders, M.W. 1978. Metabolism of dihalomethanes to formaldehyde and inorganic halide-II. Studies on the mechanism of the reaction. Biochem. Pharmacol. 27: 20-21.

6. Alarie, Y. 1985. Personal communication to Richard Hefter. No studies are known of the respiratory response of hamsters to sensory irritants. However, since hamsters have a trigeminal nerve system, a similar response to sensory irritants as seen in rats and mice would be expected.

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

8. Anderson, H.A., Dally, K.A., and Eckmann, A.D. et al. 1983. The epidemiology of mobile home formaldehyde vapor concentration and resident's health status. Wisconsin Division of Health, Wisconsin State Laboratory of Hygiene, and University of Wisconsin Department of Preventive Medicine.

9. Anderson, H.A., Dally, K.A., Hanrahan, L.P., Eckmann, A.D., Kanarek, M.S., and Rankin, J. 1983. The epidemiology of mobile home formaldehyde vapor concentration and residents' health status. Wisconsin Division of Health. Report to U.S. Environmental Protection Agency, EPA-905/1-83-001.

10. Andersen, I., and Molhave, L. 1984. Controlled human studies with formaldehyde, pp. 154-165. In James E. Gibson (ed.) Formaldehyde Toxicity. Washington: Hemisphere Publishing Corporation, 1983, as cited in Ozga et al.

preliminary assessment of the health effects of formaldehyde. Office of Risk Assessment, Occupational Safety and Health Administration.

11. Battelle Columbus Laboratories. Final Report on a Chronic Inhalation Toxicology Study in Rats and Mice Exposed to Formaldehyde to Chemical Industry Institute of Toxicology, submitted September 18, 1981; revised December 31, 1981.

12. Beall, J.P., and Ulsamer, A.G. 1984. Formaldehyde and Hepatotoxicity: A Review. J. Toxicol. Environ. Health 13: 1-21.

13. Beaumount, J. and Breslow, N. 1981. Power considerations in epidemiologic studies of vinyl chloride workers. Paper presented at the Society for Epidemiologic Research Annual Meeting.

14. Beland, F.A., Fullerton, N.F. and Heflich, R.A. 1984. Rapid isolation, hydrolysis, and chromatography of formaldehyde-modified DNA.

15. Berg, P. 1951. Synthesis of labile methyl groups by guinea pig tissue in vitro. J. Biol. Chem. 190: 31-38.

16. Bertazzi, P.A., Zochetti, C., Pesatori, A., Radice, L. and Vai, T. 1984. Mortality of workers exposed to formaldehyde in resin manufacturing. Presented at the XXI Congress on Occupational Health, Dublin, Ireland, September 1984.

17. Blakely, R.L. 1955. Biochem. J. 61 315.

18. Boorman, G.A. 1984. Letter to Dr. James Swenberg, Chemical industry Institute of Toxicology, Research Triangle Park, North Carolina.

19. Bosley, C.E. and Pruet, C.S. 1984. Inverted Sinonasal Papillomas. Ear, Nose and Throat Journal 63: 509-513.

20. Brendel, R. 1964. Untersuchungen an ratten zur vertraeglichkeit von hexamethylentetramin examethylenetetramine tolerance in rats). Arzneimittelforsch 14: 51-53.

21. Breysse, P.A. 1984. Formaldehyde levels and accompanying symptoms associated with individuals residing in over 1000 conventional and mobile homes in the State of Washington. Stockholm: August 1984, Proc. 3rd Int'l. Conf. Indoor Air Qual. and Climate.

22. Brinton, L.A., Blot, W.J., Becker, J.A., Winn, D,M., Browder, J.P., Farmer, J.C. and Fraumeni, J.F. 1984a. A

case-control study of cancers of the nasal cavity and paranasal sinuses. American Journal of Epidemiology 119: 896-906.

23. Brinton, L.A., Blot, W.J. and Fraumeni, J.F. 1984(b). Nasal cancer in the textile and apparel industries. Submitted for publication.

24. Brkendel, R. 1964. Untersuchungen an ratten zur vertraeglichkeit von hexamethylentetramin [Hexamethylenetetramine tolerance in rats]. Arzneimittelforsch 14: 51-53.

25. Brown, B. 1964. The Papillomatous Tumours of the Nose. J. Laryngol. Otol. 78: 889-905.

26. Brusick, D.J., Myhr, B.C., Stetka, D.G. and Rundell J.O. 1980. Genetic and transforming activity of formaldehyde. Litton Bionetics Report.

27. Buckley, L.A., Jiang, Y.Z., James, R.A., Morgan, K.T. and Barrow, C.S. 1984. Respiratory Tract Lesions Induced by Sensory Irritants at the RD_{50} Concentration. Toxicol. Appl. Pharmacol. 74: 417-429.

28. Buening et al. 1978. Proc. Natl. Acad. Sci. 75: 5358-5361.

29. Carson, J.L., Collier, A.M., and Hu, S.S. 1985. Acquired Ciliary Defects in Nasal Epithelium of Children with Acute Viral Upper Respiratory Infections. N. Engl. J. Med. 312: 463-468.

30. Casanova-Schmitz, M., Starr, T.B. and Heck, H.D'A. 1984. Differentiation Between Metabolic Incorporation and Covalent Binding in the Labeling of Macromolecules in the Rat Nasal Mucosa and Bone Marrow by Inhaled [^{14}C]- and [^{3}H] Formaldehyde. toxicol. Appl. Pharmocol. 76: 26-44.

31. Chang, J.C.F., Gross, E.A., Swenberg, J.A. and Barrow, C.S. 1983. Nasal Cavity deposition histopathology, and cell proliferation after single or repeated formaldehyde exposures in B6C3F1 mice and F-344 rats. Toxicol. Appl. Pharmacol. 68: 161-176.

32. Chang, J.C.F., Steinhagen, W.H., and Barrow, C.S. 1981. Effect of single or repeated formaldehyde exposure on minute volume of B6C3F1 mice and F-344 rats. Toxicol. Appl. Pharmacol. 6: 451-459.

33. Childs, E.A. 1973. Interaction of formaldehyde with fish muscle *in vitro*. J. Food Sci. 38: 1009-1011.

34. CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to formaldehyde. Chemical Industry Institute of Toxicology, December 31, 1981.

35. CIR Expert Panel. 1984. Final Report on the Safety Assessment of Formaldehyde. Journal of the American College of Toxicology 3: 157-184.

36. Cohn, M.S. 1984. Formaldehyde carcinogenic risk assessment: exposure in manufactured housing. In: Comments of the staff of the U.S. Consumer Product Safety Commission to the Department of Housing and Urban Development's Proposed Revisions of the Manufactured Home Construction and Safety Standards (24 CFR Part 3280), April 1984.

37. Cohn, M.S., DiCarlo, F.J., Turturro, A. and Ulsamer, A.G. 1985. Letter to the Editor: Toxicol. and Appl. Pharmacol. 77: 363-364.

38. Cohn, M.S. 1985b. Personal communication on Sensitivity of MLE Estimates.

39. Commoner, B. 1976. "Reliability of Bacterial Mutagenesis Techniques to Distinguish Carcinogenic and Noncarcinogenic Chemicals." United States Environmental Protection Agency Report No. 600/1-76/002. PB 259934. Springfield, VA. National Technical Information Service.

40. Comroe, Jr., J.H. et al. 1974. Defense Mechanisms of the Lungs (Chap. 17). In: Physiology of Respiration, pp. 220-228.

41. Consensus Workshop on Formaldehyde. 1984. Conclusions of the Epidemiology Panel. Little Rock, Arkansas.

42. Consensus Workshop on Formaldehyde. 1984. Final Report: Deliberations of hte Consensus Workshop on Formaldehyde, October 3-6, 1983, Little rock, Arkansas.

43. Conyers, E.P. 1984. Letter and enclosures sent to G. Schweer (USEPA/OTS). Frankfort, KY: Kentucky Department for Health Services, Radiation and Product Safety Branch.

44. Dalbey, W.E. 1982. Formaldehyde and Tumors in Hamster Respiratory Tract. Toxicology 24: 9-14.

45. Della Porta, G. and Cabral, J.G. 1970. Studio della tossicita transplancentare di cancerogenesi in ratti

trattati con esametilentetramina. [Transplacental toxicity and carcinogenesis studies in rats with hexamethylene-tetramine]. Tumori 56: 325-334.

46. Della Porta, G. and Colnaghi, M.I.G. 1968. Noncarcinogenicity of hexamethylenetetramine in mice and rats. Food Cosmet. Toxicol. 6: 707-715.

47. Delzell, E. and Grufferman. 1983. Cancer and other causes of death among female textile workers, 1976-78. Journal of the National Cancer Institute. 71(4): 735-739.

48. Den Engelse, L., Gekbbink, M. and Emmelot, P. 1975. Studies on lung tumors. III. Oxidative metabolism of demethylnitrosamine by rodent and human lung tissue. Chem. Biol. Interact. 11: 535-544.

49. Department of Housing and Urban Development. 1981. An evaluation of formaldehyde problems in residential mobile homes. Final Report. Office of Policy Development and Research, Washington, DC.

50. Drake-Lee, A.B., Lowe, D., Swanston, A. and Grace, A. 1984. Clinical Profile and Recurrence of Nasal Polyps. Journal of Laryngology and Otology 98: 783-793.

51. DuVigneaud, V.T., Varby, W.G, and Wilson, J.E. 1950. Incorporation of the carbon of formaldehyde and formate into the methyl groups of choline. J. Am. Chem. Soc. 72: 2819-2820.

52. Eccleston, M. and Kelly, D.P. 1973. Assimilation and toxicity of some exogenous C compounds, alcohols, sugars and acetate in the methane-oxidizing bacterium Methylococcus capsulatus. J. Gen. Microbiol. 75: 211-221.

53. Egle, J.L. 1972. Retention of inhaled formaldehyde, propionaldehyde, and acrolein in the dog. Arch. Environ. Health 25: 119-124.

54. Einbrodt, J.J., Prajsnar, D. and Erpenbeck, J. 1976. Der formaldehyde und ameisensaeurespiegel im blut und urin beim menschen nach formaldehyd-exposition. [Effect of formaldehyde exposure on people in school and living areas.] Zentralbl. Arbeitsmed. Arbeitsschutz Prophyl. 26(8): 154-158.

55. Environmental Protection Agency. 1981. Priority Review Level 1: Formaldehyde.

56. Environmental Protection Agency. 1984a. Proposed Guidelines for Carcinogen Risk Assessment. 49 FR 46294.

57. Environmental Protection Agency. 1984b. Formaldehyde; Determination of Significant Risk; Advance Notice of Proposed Rulemaking and Notice. 49 FR 21870-21898.

58. Fayerweather, W.E., Pell, S. and Bender, J.R. 1982. Case-control study of cancer deaths in DuPont workers with potential exposure to formaldehyde. In: Formaldehyde: toxicity, epidemiology, and mechanisms. JJ Clary, JE Gibson, RS Waritz, eds. New York; Marcel Dekker, Inc.

59. Feldman, M. Ya. 1975. Reactions of Nucleic Acids Research and Molecular Biology (J.N. Davidson and W.E. Cohn, eds.), Vol. 13, pp. 1-49. Academic Press, New York.

60. Feron, V.J. 1979. Effects of Exposure to Acetaldehyde in Syrian Hamsters Simultaneously Treated with Benzo(a)pyrene or Diethylnitrosamine. Prog. Exp. Tumor Res. 24: 162 (Karger, Basel).

61. Feron, V.J. 1984. Summary Tumor Results-Acetaldehyde. Proided to Dr. H. Milman, U.S. EPA, Washington, DC.

62. Feron, V.J., Kruysse, A., Til, H.P. and Immel, H.R. 1978. Repeated Exposure to Acrolein Vapour: Subacute Studies in Hamsters, Rats, and Rabbits. Toxicology 9: 47-57.

63. Feron, V.J., Kruysse, A. and Wouterson, R.A. 1982. Respiraory Tract Tumors in Hamsters Exposed to Acetaldehyde Vapour Alone or Similtaneously to Benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol. 18: 13.

64. Fleig, I., Petri, N., Stocker, W.G. and Thiess, A.M. 1982. Cytogenetic Analyses of Blood Lymphocytes of Workers Exposed to Formaldehydein Formaldehyde Manufacturing and Processing. J. Occup. Med. 24: 1009-1012.

65. Fox, A.J. and Collier, P.E. 1976. Low mortality rates in individual cohort studies due to selection for work and survival in the industry. Journal of Preventive and Social Medicine 20: 225-230.

66. Fraenkel, A.H., Johnson, A., and Rench, J.D. 1985a. Task 93 --Formaldehyde Dose-Response Estimations for Noncancer Outcomes. EPA Contract No. 68-01-6721. Battelle, Washington, D.C.

67. Fraenkel, A.H., Johnson, A., and Rench, J.D. 1985b. Task 93 --Formaldehyde Dose-Response Estimations for Noncancer Outcomes. EPA Contract No. 68-01-6721. Battelle, Washington, D.C.

68. Frazer, J.P. 1984. Allergic Rhinitis and Nasal Polyps. Ear, Nose, and Throat Journal 63: 172-176.

69. Friedlander, B.R., Hearne, T. and Newman, B. 1982. Mortality, cancer, incidence, and sickness-absence in photographic processors: an epidemiologic study. Journal of Occupational Medicine 24(8): 605-613.

70. Fujii, T., Asada, Y. and Tonomura, K. 1974. Assimilative pathway of methanol in Candida sp. incorporation of ^{14}C-bicarbonate into cell constituents. Agric. Biol. Chem. 38: 1121-1127.

71. Gamble, J.F., McMichael, A.J., Williams, T. and Battigelli, M. 1976. Respiratory function and symptoms: An environmental-epidemiological study of rubber workers exposed to a phenol-formaldehyde type resin. Am. Ind. Hyg. Assoc. J., 37: 499-513.

72. Garry, V.F., Oatman, L, Pleus, R., and Gray, D. 1980. Formaldehyde in the home: Some environmental disease perspectives. Minn. Med., 63: 107-111.

73. Gastwirth, J.L. 1983. Combined tests of significance in EEO cases. Presented at the 1983 Annual Meeting of the ASA in Toronto, Canada.

74. Gescher, A., Hickman, J.A. and Stevens, M.F.G. 1979. Oxidative metabolism of some N-methyl containing xenobiotics can lead to stable progenitors of formaldehyde. Biochem. Pharmacol. 28(21): 3235-3238.

75. Girman, J.R., Geisling, K.L., and Hodgson, A.T. 1983. Sources and concentrations of formaldehyde in indoor environments. Presented at the 75th Air Pollution Control Association Annual Meeting, New Orleans, L.A. June 20-25, 1982. Washington, DC: Energy and Environmental Division, U.S. Department of Energy. Contract No. DE-AC03-765F00098.

76. Goldberg, I. and Mateles R.I. 1975. Growth of Pseudomonas C on C, compounds: enzyme activities in extracts of Pseudomonas C cells grown on methanol, formaldehyde, and formate as sole carbon sources. J. Bacteriol. 122: 47-53.

77. Goodman, J.I. and Tephly T.R. 1971. A comparison of rat and human liver formaldehyde dehydrogenease. Biochem. Biophys. Acta 252: 489-505.

78. Grafstrom, R.C., Curren, R.D., Yang, L.L. and Harris, C.C. 1985. Genotoxicityof Formaldehyde in Cultured Human Bronchial Fibroblasts. Science 228: 89-90.

79. Grafstrom, R.C., Fornace, A., Jr. and Harris, C.C. 1984. Repair of DNA Damage Caused by Formaldehyde in Human Cells. Cancer Research 44: 4323-4327.

80. Grafstrom, R.C., Fornace, A.J., Jr., Autrup, H., Lechner, J.F. and Harris, C.C. 1983. Formaldehyde Damage to DNA and Inhibition of DNA Repair in Human Bronchial Cells. Science 220: 216-218.

81. Gralla E.J., Heck, H d'A., Hrubesh, L.W. and Meadows, G.W. 1980. A report of the review of the formaldehyde exposure made by the CIIT ad hoc analytical chemistry investigative team held at the Battelle Memorial Columbus (Ohio) Laboratory. Raleigh, NC: Chemical Industry Institute of Toxicology. CIIT Docket No. 62620.

82. Grindstaff, G.F. 1985. Revised Cancer Risks for Formaldehyde. Memorandum to Richard Hefter.

83. Harrington, J. and Oakes, D. 1984. Mortality Among British Pathologists. Br J Ind Med 41: 188-191.

84. Harrington, J. and Shannon, H. 1975. Mortality study of pathologists and medical laboratory technicians. British Medical Journal 4: 329-332.

85. Hawthorne, A.R., Gammage, and Dudney, C.S. et al. 1984. Oak Ridge National Laboratory. An indoor air quality study of forty east Tennessee homes. Draft report. Washington, DC: U.S. Department of Energy #FTP/A-001701. ORNL-5965.

86. Hayes, R.B., Raatgever, J.W. and deBruyn, A. 1984. Tumors of the nose and nasal sinuses: A case-control study. Presented at the XXI Congress on Occupational Health, Dublin, Ireland, September 1984.

87. Heath, C.W. 1982. The leukemias. In: Cancer epidemiology and prevention. D. Schottenfeld, J.F. Fraumeni Jr., eds. Philadelphia: W.B. Saunders Co.

88. Heck, H. d'A. 1982b. CIIT Activities 2: 3-7.

89. Heck, H. d'A and Casanova-Schmitz. 1983. Reaction of Formaldehyde in the Rat Nasal Mucosa. In: Formaldehyde: Toxicology-Epidemiology-Mechanisms. Clay, J.J., Gibson, J.E., and Waritz, R.S., Eds. Marcel Dekker, Inc., New York.

90. Heck, H. d'A, Casanova-Schmitz, M., Dodd, P.B., schachter, E.N., Witek, T.J. and Tosun, T. 1985. Formaldehyde (CH_2O) Concentrations in the Blood of Humans and Fischer-344 Rats

Exposed to CH_2O Under Controlled Conditions. Am. Ind. Hyg. Assoc. J. 46: 1-3.

91. Heck, H. d'A, White, E.I. and Casanova-Schmitze. 1982a. Biomed. Mass Spectrom. 9: 347-353.

92. Hemminki, K., Falck, K. and Vainio, H. 1980. Comparison of Alkylation Rates and Mutagenicity of Directly Acting Industrial and Laboratory Chemicals. Arch. Toxicol. 46: 277.

93. Hernberg, S., Westerholm, P., Schultz-Larsen, K., Dogerth, R., Kuosma, E., Englund, A., Hansen, H.S. and Mutanen, P. 1983. Nasal and sinunasal cancer. Scand. J. Work. Environ. Health 9: 315-326.

94. Herron, J. and Penzhorn R. 1969. Mass spectrometric study of the reactions of atomic oxygen with ethylene glycol and formaldehyde. J. Phys. Chem. 73: 191-196.

95. Hodges, H.E. 1984. Letter with enclosures to USEPA, Office of Toxic Substances. Nashville, TN: Tennessee Department of Health and Environment, Air Pollution Control Division.

96. Horton, A.W., Tye, R. and Stemmer, K.L. 1963. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. J. Natl. Cancer Inst. 30: 31-43.

97. Howe, R.B., Crockett, P.W. and Crump, K.S. 1984. Weibull-A and Probit-A Fortrain Programs Implementing Weibull and Generalized Probit Models with Additive Background Response Rates for the Analysis of Animal Bioassay Data. Battelle, Washington, DC.

98. HPMA. 1984. Hardwood Plywood Manufacturers' Association. Comments before the USEPA, May 23, 1984, Formaldehyde: Determination of significant risk, NAPR, and notice. Docket No. OPTS 62033. Reston, VA: Hardwood Plywood Manufacturers' Association.

99. Huennekens, F.M and Osborn, M.J. 1959. Folic acid coenzymes and 1-carbon metabolism. Adv. Enzymol. 21: 369-446.

100. Hyams, V.J. 1971. Papillomas of the Nasal Cavity and Paranasal Sinuses A Clinico-Pathologi Study of 315 Cases. Ann. Otol. 80: 192-206.

101. IARC Monograph. 1982. Some Industrial Chemicals and Dye Stuffs. IARC 29: 345-389.

102. IRMC. 1984. Draft Report of the Risk Assessment Subgroup of the IRMC-Formaldehyde Work Group.

103. IRMC. 1984a. Report of the Subcommittee on Formaldehyde Sensitization.

104. IRMC. 1984b. Report of the Subgroup on Systemic Effects--Formaldehyde.

105. Jacobs, R.L., Freda, A.J. and Culver, W.G. 1983. Primary Nasal Polyposis Annals of Allergy 51: 500-505.

106. Kane, L.E. and Alarie, Y. 1977. Sensory Irritation to Formaldehyde and Acrolein During Single and Repeated Exposures in Mice. Am. Ind. Hyg. Assoc. J. 38: 509-521.

107. Kane, L.E., Barrow, C.S. and Alarie, Y. 1979. A Short-Term Test to Predict Acceptable Levels of Exposure to Airborne Sensory Irritants. Am. Ind. Hyg. Assoc. J. 40: 207-229.

108. Keil, J.E. and Weinrich, M.C. 1982. Compendium of epidemiologic and related methods. Class handout, University of South Carolina.

109. Kensler, C.J. and Battista, S.P. 1963. Components of cigarette smoke with ciliary-depressant activity. New Engl. J. Med. 269(22): 1161-1166.

110. Kerfoot, E.J., and Mooney, T.F. 1975. Formaldehyde and paraformaldehyde study in funeral homes. Am. Ind. Hyg. Assoc. J., 36 533-537.

111. Kern, W.D., Pavkov, K.L., Donofrio, D.J., Gralla, E.J. and Swenberg, J.A. 1983. Carcinogenicity of Formaldehyde in Rats and Mice After Long-Term Inhalation Exposure. Cancer Research 43: 4382-4392.

112. Kitchens, J.F, Casner, R.E., Edwards, G.S., Harward, W.E, III and Macri, B.J. 1976. Investigation of selected potential environmental contaminants: formaldehyde. Washington, DC: U.S. Environmental Protection Agency. EPA-560/2-76-009.

113. Klenitzky, J.S. 1940. On experimental cancer of the uterine cervix. Bull. Biol. Med. Exp. 9: 3-6.

114. Konopinski, V.J. 1983. Residential formaldehyde and carbon dioxide. Indiana State Board of Health, Indianapolis, IN. 329-334.

115. Krivanek, N.D., Chromey, N.C. and McAlack, J.W. 1983. Skin Initiation Promotion Study with Formaldehyde in CD-1 Mice. In: Formaldehyde: Toxicology-Epidemiology-Mechanisms. J.J. Clary, J.E. Gibson, and R.S. Waritz, Eds., Marcel Dekker, New York.

116. Kuschner, M., Laskin, S., Drew, R.T., Capiello, V. and Nelson, N. 1975. The inhalation carcinogenicity of alpha halo ethers. III. Life-time and limited period inhalation studies with bis (chloromethyl) ether at 0.1 ppm. Arch. Environ. Health 30: 73-77.

117. Laduron, P. and Leysen, J. 1975. Enzymatic formaldehyde production from 5-methyltetrahydrofolic acid: prior step to alkaloid formation. Biochem. Pharmacol. 24: 929-932.

118. Lampertico, P., Russell, W.O. and Macomb, W.S. 1963. Squamous Papilloma of Upper Respiratory Epithelium. Arch. Path. 75: 293-302.

119. Lasser, A., Rothfeld, P.R., and Shapiro, R.S. 1976. Epithelial Papilloma and Squamous Cell Carcinoma of the Nasal Cavity and Paranasal Sinuses. Cancer 38: 2503-2510.

120. Lee, K.P. and Trochimowicz, H.J. 1982. Induction of Nasal Tumors in Rats Exposed to Hexamethylphosphoramide by Inhalation. J. Natl. Cancer Inst. 68: 157-164.

121. Lee, K.P. and Trochimowicz, H.J. 1984. Morphogenesis of Nasal Tumors in Rats Exposed to Hexamethylphosphoramide by Inhalation. Environmental Research 33: 106-118.

122. Levine, R.J., Andjelkovich, D.A. and Shaw, L.K. 1984. The mortality of Ontario undertakers and a review of the formaldehyde-related mortality studies. Journal of Occupational Medicine 26(10): 740-746.

123. Malorny, G., Rietbrock, N. and Schneider, M. 1965. Die oxydation des Formaldehyds zu ameisensaeure im Blut, ein Beitrag zum Stoffwechsel des Formaldehyds. [Oxidation of formaldehyde to formic acid in blood, a contribution to the metabolism of formaldehyde.] Naunyn Schmiedebergs Arch. Exp. Pharmakol. 250: 419-436.

124. Marsh, G. 1983. Proportional mortality among chemical workers exposed to formaldehyde. British Journal of Industrial Medicine 39: 313-322.

125. Marsh, G. 1983. Mortality among workers from a plastic producing plant: A matched case-control study nestled in a retrospective cohort study. Journal of Occupational Medicine 25(3): 219-2030.

126. Mashford, P.M. and Jones, A.R. 1982. Xenobiotics 12: 119-124.

127. Matanoski, G. 1980. Data presented at the 49th meeting of the Interagency Collaborative Group or Environmental Carcinogenesis, February 6, 1980, Bethesda, Maryland.

128. McMartin, K.E., Martin-Amat, G., Makar, A.B. and Tephly, T.R. 1977. Methanol poisoning. V. Role of formate metabolism in the monkey. J. Pharmacol. Exp. Therap. 201: 564-572.

129. McMartin, K.E, Martin-Amat, G., Noker, P.E. and Tephly, T.R. 1979. Lack of role for formaldehyde in methanol poisoning in the monkey. Biochem. Pharmacol. 28: 645-649.

130. Meittinen, O.S and Wang, J. 1981. An alternative to the proportionate mortality ratio. Americal Journal of Epidemiology 116: 144-148.

131. Meuller, R., Raabe, G. and Schumann, D. 1978. Leukoplakia induced by repeated deposition of formalin in rabbit oral mucosa: Long-term experiments with a new "oral tank." Exp. Pathol. 16: 36-42.

132. Meyer, B., and Hermanns, K. 1984a. Formaldehyde indoor air problems. Seattle Washington: University of Washington. Proc. Air Poll. Control Assoc. Annual Meeting, 1984, San Francisco, CA. APCA paper 84-35.2.

133. Meyer, B., and Hermanns, K. 1984b. Diurnal variations of formaldehyde exposure in mobile homes. Berkeley, CA: Lawrence Berkeley National Laboratory, Report #18573.

134. MHI. 1984. Manufactured Home Inst. Comments pertaining to the advance notice of proposed rulemaking on formaldehyde under section 4(f) of the Toxic Substances Control Act.

135. Molina, E. 1942. Poisson's exponential binomial limit. New York: D. Van Nostrand Company, Inc.

136. Morgan, K.T., Patterson, D.L. and Gross, E.A. 1983a. Formaldehyde and the Nasal Mucociliary Apparatus. In: Formaldehyde: Toxicology-Epidemiology-Mechanisms. Clary, J.J., Gibson, J.E., and Waritz, R.S., Eds. Marcel Dekker, Inc., New York.

137. Morgan, K.T., Patterson, D.L. and Gross, E.A. 1983b. Localization of Areas of Inhibition of Nasal Mucociliary

Function in Rats Following in Vivo Exposure to Formaldehyde. Am. Rev. Respir. Dis. 127: 166.

138. Morgan, K.T., Patterson, D.L. and Gross, E.A. 1984a. Froc Palate Mucociliary Apparatus: Structure, Function, and Response to Formaldehyde Gas. Fundam. Appl. Toxicol. 4: 58-68.

139. Morris, E.D. and Niki, H. 1971. Mass spectrometric study of the reaction of hydroxyl radicals with formaldehyde. J. Chem. Phys. 55: 1991-1992.

140. Moschandreas, D.J., Stark, J.W.C., McFadden, J.E., and Morse, S.S. 1978. Geomet, Inc. Indoor air pollution in the residential environment, Vol. I, Data Analysis and Interpretation. Washington, DC: U.S. Environmental Protection Agency. EPA-600/7-78-229a.

141. Myers, G.E. 1984. The effect of temperature and humidity on formaldehyde emission from UF-bonded boards: a literature critique. Madison, WS: Dept. of Agr. Forest Service, Forest Products Laboratory.

142. NAHB. 1984. National Association of Home Builders. 4-F comment: builder survey--concerning use of prefinished plywood paneling and particleboard underlayment in new homes.

143. National Research Council, Committee on Aldehydes, Board on Toxicology and EnvironmetnalHalth Hazards. 1981. Health Effects of Formaldehyde (CH7), In: Formaldehyde and Other Aldehydes. Washington, DC, National Academy Press.

144. National Toxicology Program. 1982a. Technical Report Series--1,2-Dibromoethane. NTP-TR 210.

145. National Toxicology Program. 1982b. Technical Report Series--1,2-Dibromo-3-Chloropropane. NTP-TR 206.

146. National Toxicology Program. 1985. Technical Report Series: Propylene Oxide. NTP-TR 267.

147. NPA. 1984. National Particleboard Association. 4-F comment: Comments of the National Particleboard Assoc. on advance notice of proposed rulemaking on formaldehyde under section 4(f) of the Toxic Substances Control Act.

148. Nebergall, W.H., Schmidet, F.C. and Holtzclaw, H.F. Jr. 1972. General chemistry. Lexington, MS: DC Heath and Co.

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

150. Newbold, R.P., Tume, R.K. and Horgan, D.J. 1973. Effect of feeding a protected safflower oil supplement on the composition and properties of the sarcoplasmic reticulum and on postmortem changes in bovin skeltetal muscle. J. Food Sci. 38: 821-823.

151. Nikolaidis, E.T., Trost, D.C., Buchholz, C.L. and Wilkinson, E.J. 1985. The Relationship of Histologic and Clinical Factors in Laryngeal Papillomatosis. Arch. Pathol. Lab. Med. 109: 24-29.

152. Obe, G. and Ristow, H. 1977. Acetaldehyde Not Ethanol Induces Sister Chromatid Exchanges in Chinese Hamster Cells In Vitro. Mutat. Res. 56: 211.

153. Occupational Safety and Health Administration. 1984. Preliminary assessment of the health effects of Formaldehyde. November 5, 1984.

154. Olson, J.H., and Dossing, M. 1982. Formaldehyde Induced Symptoms in Day Care Centers. Am. Ind. Hyg. Assoc. J. 43: 366-370.

155. Olsen, J.H. and Jensen, O.M. 1984. Case-control study on sinonasal cancer and formaldehyde exposure based on a national data linkage system for occupation and cancer. Presented at the Society for Epidemiologic Research, 17th Annual Meeting, Houston, Texas, June 13-15, 1984. Am J Epidemiology 120: 459.

156. Osborn, D.A. 1970. Nature and Behavior of Transitional Tumors in the Upper Respiratory Tract. Cancer 25: 50-60.

157. Palese, M. and Tephly, T.R. 1975. Metabolism of formate in therat. J. Toxicol. Environ. Health. 1: 13-24.

158. Patel, R.N. and Hoare, D.S. 1971. Physiological studies of methane and methanol-oxidizing bacteria: oxidation of C-1 compounds by Methylococcus capsulatus. J. Bacteriol. 197: 137-192.

159. Paludetti, G., Maurizi, M., Tassoni, A., Tosti, M. and Altissim, G. 1983. Nasal Polyps: A comparative Study of Morphologic and Etiopathogenetic Aspects. Rhinology 21: 347-360.

160. Perzin, J.H., Lefkowitch, J.H. and Hui, R.M. 1981. Bilateral Nasal Squamous Carcinoma Arising in Papillomatosis. Cancer 48: 2375-2382.

161. Pilat, P. and Prokop, A. 1976. Time course of the levels of oxidative intermediates during methanol utilization by Candida boidinii Bh. J. Appl. Chem. Biotechnol. 26: 445-453.

162. Poirier, M.C., True, B. and Laishes, B.A. 1982. Formation and Removal of (Guan-8-YL)-DNA-2-Acetylaminoflourene Adducts in Liver and Kidney of Male Rats Given Dietary 2-Acetylaminofluorene. Cancer Res. 42: 1317-1321.

163. Proctor, D.F. 1982. The Mucociliary System (Chap. 10). In: The Nose: Upper Airway Physiology and the Atmospheric Environment. Proctor/Anderson (eds.). Elsevier Biomedical Press, pp. 245-278.

164. Pruett, J.J., Scheuenstuhl, H. and Michaeli, D.L. 1980. The incorporation and localization of aldehydes (highly reactive cigarette smoke components) into cellular fractions of cultured human lung cells. Arch. Environ. Health. 35: 15-20.

165. Rader, J. 1974. Irritative Effects of Formaldehyde in Laboratory Halls, Analytical and Experimental Investigations. Dissertation for M.D. Degree. Institute of Pharmacology and Toxicology, University of Wurzberg, Federal Republic of Germany.

166. Rapoport, I.A. 1948. Mutation Under the Effect of Unsaturated Aldehydes. Dokl. Akad. Nauk. S.S.S.R. 61: 713 (in Russian).

167. Report of the Federal Panel on Formaldehyde. 1982 Environ. Health Perspect: 43: 139-168.

168. Reznik, G., Reznik-Schuller, H., Ward, J.M. and Stinson, S.F. 1980. Morphology of Nasal-Cavity Tumours in Rats After Chronic Inhalation of 1,2-Dibromo-3-Chloropropane. Br. J. Cancer 42: 772-781.

169. Ridolfi, R.L., Lieberman, P.H., Erlandson, R.A. and Moore, O.S. 1977. Schneiderian Papillomas: A Clinicopathologic Study of 30 Cases. Am. J. Surg. Pathol. 1: 43-53.

170. Rietbrock, N. 1969. Kinetik and Wege des Methanolumsatzes. [kinetics and pathways of methanol metabolism.] Naunyn Schmiedebergs Arch. Pharmakol. Exp. Pathol. 263: 88-105.

171. Ristow, H. and Obe, G. 1978. Acetaldehyde Induces Cross-links in DNA nad Causes Sister-chromatid Exchanges in Human Cells. Mutat. Res. 58: 115.

172. Robbins, S.L. 1974. Pathologic Basis of Disease. W.B. Saunders Co., Philadelphia, pp. 845-849, 885-892.

173. Rothman, K.J. and Boice, J.D. 1982. Epidemiologic analysis with a programmable calculator, 2nd Edition. Boston: Epidemiology Resources, Inc.

174. Rusch, G.M., Clary, J.J., Rinehart, W.E. and Bolte, H.F. 1983. A 26-Week Inhalation Toxicity Study with Formaldehyde in the Monkey, Rat, and Hamster. Toxicol. Appl. Pharmacol. 68: 329-343.

175. Sakaguchi, K., Saiika, K., Kurane, R. and Murata, M. 1975. Assimilation of formaldehyde and other C_1-compounds by Gliocladium deliquescens and Paecilomyces varioti. Agric. Biol. Chem. 39: 1695-1702.

176. Schlesselman, J.J. 1982. Case-control studies. New York: Oxford Press, Chapters 2 and 6.

177. Schoenberg, B.S. 1982. Nervous system. In: Cancer epidemiology and prevention. D. Schottenfeld, J.F. Fraumeni, Jr., eds. Philadelphia: W.B. Saunders Co.

178. Schoenberg, J.B., Mitchell, C.A. 1975. Airway disease caused by phenolic (phenol-formaldehyde) resin exposure. Arch. Environ. Health, 30: 574-577.

179. Schottenfeld, D. and Fraumeni, J.F., Jr. 1982. Cancer Epidemiology Prevention, pp 46-47, W.B. Saunders Co.

180. Schutte, W., Frank, C.W., Hoffman, J., Sailer, S., and Scarpellino, C. 1981. Final report to the Formaldehyde Institute. Iowa City, Iowa. University of Iowa.

181. Sellars, S.L. 1982. The Inverted Nasal Papilloma. J. Laryngol. Otol. 96: 1109-1112.

182. Seydell, E.M. 1933. Fibro-Epithelial Tumors of the Nose (Papillomata) and Their Relationship to Carcinoma. Ann. Otol. 42: 1081-1103.

183. Singh, J., Walcott, R., St. Pierre, C., Coffman, M.A., Ferrel, T.W., Opthoff, D., and Montgomery, D. 1982. Clayton Environmental Consultants Inc. Evaluation of formaldehyde problem in mobile homes - testing and evaluation. Washington, DC: Office of Policy Development and Research, U.S. Department of Housing and Urban Development. Contract No. HC-5222, Volume 3.

184. Slaga, T.J., Sivak, A. and Boutwell, R.K. 1978. Mechanisma of tumor promotion and cocarcinogens. Raven Press. NY.

185. Snyder, R.N. and Perzin, K.H. 1972. Papillomatosis of the Nasal Cavity and Paranasal Sinuses (Inverted Papilloma Squamous Papilloma) A Clinicopathologic Study. Cancer 30: 668-690.

186. SOCMA: Booz, Allen, and Hamilton. 1979. Preliminary study of the costs of increased regulation offormaldehyde exposure in the U.S. workplace. Prepared for Synthetic Organic Chemical Manufacturers Association. Scarsdale, New York.

187. Spangler, F. an dWard, J.M. 1983. Skin Initiation-Promotion Study with Formaldehyde in Sencar Mice. In: Formaldehyde: Toxicology-Epidemiology-Mechanisms. J.J. Clary, J.E. Gibson and R.S. Waritz, Eds. Marcel Dekker, New York.

188. Spear, R. 1982. Formaldehyde Study Shows Gene Effect in Anatomy Students. The New Physcian 6: 17.

189. Starr, T.B. and Buck, R.D. 1984. The Importance of Delivered Dose in Estimating Low-Dose Cancer Risk From Inhalation Exposure to Formaldehyde. Fundam. Appl. Toxicol. 4: 740-753.

190. Starr, T.B., Gibson, J.E., Barrow, C.S., Boreiko, C.J., Heck, H. d'A., Levine, R.J., Morgan, K.T., and Swenberg, J.A. 1984. Estimating Human Cancer Risk From Formaldehyde: Criticla Issues. Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina.

191. Stayner, L., Smith, A.B., Reeve, G., Blade, L., Elliott, L., Keenlyside, R. and Halperin, W. 1984. Proportionate mortality study of workers exposed to formaldehyde in the garment industry. Presented at the Society for Epidemiologic Research 17th Annual Meeting, Houston, Texas, June 13-15, 1984. Am J Epidemiology 120: 458-9.

192. Stewart, H.L., Dunn, T.B., Snell, K.C. and Deringer, M.K. Tumors of the Respirator Tract. In: V.S. Turosou (ed.), Pathology of Laboratory Animals, Vol. 2, pp. 251-288. Lyon, France: IARC, 1979.

193. Stroup, N., Blair, A., and Erickson, G. 1984. Brain cancer and other causes of death in anatomists. Presented at the Society for Epidemiologic Research 17th Annual Meeting, Houston, Texas, June 13-15, 1984. Am J Epidemiology 120: 500

194. Strittmatter, P. and Ball, E.G. 1975. Formaldehyde dehydrogenase, a glutathione-dependent enzyme system. J. Biol. Chem. 213: 445-461.

195. Swenberg, J.A., Barrow, C.S., Boreiko, C.J., Hick, H. I'A., Levine, F.J., Morgan, K.T., and Starr, T.B. 1983. Nonlinear biological responses to formaldehyde and their implications for carcinogenic risk assessment. Carcinogenesis 4: 945-952.

196. Swenberg, J.A., Dryoff, M.C., Bedell, M.A., Popp, J.A., Huh, N., Kirstein, U. and Rajewsky, M.F. 1984. O^4-Ethyldeoxythymidine, but not O^6-Ethyldeoxyguanosine, Accumulates in Hepatocyte DNA of Rats Exposed Continuously to Diethylnitrosamine. Proc. Nat'l. Acad. Sci. USA 81: 1692-1695.

197. Swenberg, J.A., Gross, E.A., Martin, J., and Popp, J.A. 1983. Mechanisms of formaldehyde toxicity. In: J.E. Gibson (ed.), Formaldehyde Toxicity. Hemisphere Publishing Corp., Washington.

198. Tabershaw Associates. 1982. Historical prospective mortality study of past and present employees of the Celanese chemical and plastics plant located in Bishop, Texas. Tabershaw Associates, Rockville, Maryland.

199. Takano, T., Shirai, T.S., Ogiso, T., Tsuoa, H., Baba, S. and Ito, N. 1982. Sequential Changes in Tumor Development Induced by 1,4-Dinitrosopiperazine in the Nasal Cavity of F344 Rats. Cancer Research 42: 4236-4240.

200. Thomson, E.J., Shackleton, S. and Harrington, J.M. 1984. Chromosome Aberrations and Sister-Chromatid Exchange Frequencies in Pathology Staff Occupationally Exposed to Formaldehyde. Mutation Res. 141: 89-93.

201. Thorndike, J. and Beck, W.S. 1977. Production of formaldehyde from N5-methyltetrahydrofolate by normal and leukemic leukocytes. Cancer Res. 37: 1125-1132.

202. Tola, S., Hernberg, S., Collan, Y., Linderborg, H. and Korkala, M.L. 1980. A case-control study of the etiology of nasal cancer in Finland. Int. Arch. Occup. Environ. Health 46: 79-85.

203. Tobe, M., Kaneko, T., Uchida, Y., Kamata, E., Ogawa, Y., Ikeda, Y. and Saito, M. 1985. Studies of the Inhalation Toxicity of Formaldehyde. National Sanitary and Medical Laboratory Service (Japan), pp. 1294.

204. Traynor, G.W., and Nitschke, A. 1984. Field survey of indoor air pollution in residences with suspected combustion-related sources. August 1984. Stockholm: Proc. 3rd Int'l. Conf. Indoor Air Quality and Climate.

205. Tuttle, W.W. and Schottelius, B.A. 1969. Gas Exchange-Respiration. In: Textbook of Physiology. The C.U. Mosby Company, St. Louis.

206. UFFI/ICC. 1981. Urea Formaldehyde Foam Insulation Information and Coordination Centre. The report on the national testing survey to the board of review by the UFFI/ICC. Canada.

207. Ulsamer, A.G., Beall, J.R., Kang, H.K., Frazier, J.A. Overview of Health Effects of Formaldehyde. 1984. In Saxsena, J. (ed.), Hazard Assessment of Chemicals--Current Developments. New York, Academic Press, Inc. 3: 337-400.

208. University of Texas, School of Public Health. 1983. Final report. Texas indoor air quality study. Houston, TX: University of Texas.

209. Uotila, L. and Koivusalo, M. 1974. Formaldehyde dehydrogenase from human liver; purification, properties, and evidence for the formation of glutathione thiol esters by the enzyme. J. Biol. Chem. 249: 7653-7663.

210. Usdin, V.R. and Arnold, G.B. 1979. Transfer of formaldehyde to guinea pig skin. Gillette Research Institute Report. Contract No. 78-391.

211. Versar. 1982. Final Draft Report--Exposure Assessment for Formaldehyde. Versar, Inc. Springfield, VA.

212. Versar. 1985a. Conventional and Mobile Home Production and Occupation Projections Over the Next Ten Years in Support of Formaldehyde Exposure Task (14). Memorandum to Greg Schweer, Richard Hefter, U.S. EPA, Washington, DC.

213. Versar. 1985b. Maximum Levels of Formaldehyde Exposure in Residential Settings. EPA Contract No. 68-02-3968, Task No. 14. Versar, Inc., Springfield, VA.

214. Vital Statistics of the U.S. 1974. 1970 Volume II-Mortality, Part A. United States Department of Health, Education and Welfare. Health Resources Administration 75-1104.

215. Vrabec, D.P. 1975. The Inverted Schneiderian Papilloma: A Clinical and Pathological Study. Laryngoscope 85: 186-220.

216. Walker, J.F. 1975. Formaldehyde, 3rd ed. New York: Robert E. Kriegar Publishing Co.

217. Walrath, J. 1983. Abstract: Mortality among embalmers. 1983b. American Journal of Epidemiology 118(3): 432.

218. Walrath, J. and Fraumeni, J. 1983. Mortality patterns among embalmers, International Journal of Cancer 31: 407-411.

219. Ward, E. 1984. Memorandum: Formaldehyde Interim Exposure Report. U.S. EPA, Washington, DC.

220. Ward, Jr., J.B., Hokanson, J.A., Smith, E.R., Chang, L.W., Pereira, M.A., Whorton, Jr., E.B. and Legator, M.S. 1984. Sperm Count, Morphology and Fluorescent Body Frequency in Autopsy Service Workers Exposed to Formaldehyde. Mutation res. 130: 417-424.

221. Watanabe, F., Matsunaga, T., Soejima, T. and Iwata, Y. 1954. Study on aldehyde carcinogenicity. Part I. Experimentally induced rat sarcomas by repeated injection of formalin. Gann 45: 451-452.

222. Watanabe, F. and Sugimoto, S. 1955. Studies on aldehyde carcinogenicity. Part II. Seven cases of transplantable sarcomas of rats developed in the area of repeated subcutaneous injections of urotropin (hexamethylene-tetramine). Gann 46: 365-367.

223. Waydhas, C., Weigl, K. and Sies, H. 1978. The disposition of formaldehyde and formate arising from drug N-demethylations dependent on cytochrome P-450 in hepatocytes and in perfused rat liver. Eur. J. Biochem. 89(1): 143-150.

224. Weisburger, J.H. and Williams, G.M. 1980. Chemical carcinogenesis. In: Weisberger J.H., Holland, J.F. and Frei E (Eds). Cancer Medicine. 2nd ed. Lea and Febiger, Philadelphia.

225. Widdicombe, J.G. 1977. Defense Mechanisms of the Respiratory System (Chap. 9). In: Respiratory Physiology II. University Park Press, Baltimore, pp 291-315.

226. Wilkins, R.J. and MacLeod, H.D. (1976). Formaldehyde induced DNA-protein cross-links in Escherichia coli. Mutations Research 36, 11-16.

227. Wong, O. 1983. An epidemiologic mortality study of a cohort of chemical workers potentially exposed to formaldehyde. In: Formaldehyde: toxicity. J.J. Clary, J.E. Gibson, R.S. Waritz, eds. New York: Hemisphere Publishing Corp.

228. Woutersen, R.A., Appelman, L.M., Feron, V.J. and Van Der Heijden, C.A. 1984. Inhalation Toxicity of Acetaldehyde in Rats. II Carcinogenicity Study: Interim Results After 15 Months. Toxicology 31: 123-133.

229. Woutersen, R.A., Appelman, L.M., Wilmer, J.W.G.M., Spit, B.J., and Falke, H.E. 1984b. Subchronic (13-week) Inhalation Toxicity Study with Formaldehyde in Rats (Appendices), pp. 1-88. Submitted to Dr. Harry A. Milman, U.S. EPA, Washington, DC.

230. Yamaguchi, K.T., Shaapshay, S.M., Incze, J.S., Vaughan, C.W. and Strong, M.S. J. Otolaryngol. 8: 171-178.