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

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Office of Pesticides and Toxic Substances
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PREFACE

The Health Risk Assessment of Formaldehyde (HCHO) was prepared to serve as source document for Agency-wide use. This document was developed primarily for use by the U.S. Environmental Protection Agency's (EPA) Office of Toxic Substances to support decision-making regarding possible regulation of HCHO under Section 6 of the Toxic Substances Control Act. Because this document focuses on inhalation exposure to HCHO, this document should not be regarded as a comprehensive assessment of the health effects from oral and dermal exposure. In addition, only two exposure categories are extensively reviewed. Assessment of other categories will be done as needed by other EPA program offices.

In the development of this assessment document, the relevant scientific literature available through February 1, 1986, has been incorporated, except that the epidemiologic section reflects studies available through March 1987. Key studies have been evaluated and the summary and conclusions have been prepared so that the health effects and related characteristics of HCHO are qualitatively identified. Measures of dose-risk relationships relevant to inhalation exposure are also discussed so that the adverse health responses can be placed in perspective with possible exposure levels.

Authors, Contributors, and Reviewers

The Existing Chemical Assessment Division within the Office of Toxic Substances was responsible for preparing this document.

Principal Authors

Richard Hefter, M.S.
Cheryl Siegel Scott, M.S.P.H.
Harry Milman, Ph.D.
Elizabeth Margosches, Ph.D.
Gary Grindstaff, M.S.P.H.
Gregory Schweer, M.S.
Jeanette Wiltse, Ph.D.

Contributing Authors

Mary Argus, Ph.D.
Angela Auletta, Ph.D.
Frederick Dicarlo, Ph.D.
William Farlan, Ph.D.
David Klauder, Ph.D.
Carl Mazza, Ph.D.
George Semeniuk, Ph.D.

Reviewers

The following individuals provided peer review of this document and or earlier drafts of this document.

Irwin Baumel, Ph.D.
Office of Regulatory Support
Office of Research and Development
Washington, D.C.

Steven P. Bayard, Ph.D.
Carcinogen Assessment Group
Office of Health and Environmental Assessment
Washington, D.C.

David L. Bayliss, Ph.D.
Carcinogen Assessment Group
Office of Health and Environmental Assessment
Washington, D.C.

Robert Beliles, Ph.D.
Carcinogen Assessment Group
Office of Health and Environmental Assessment
Washington, D.C.

Vicki L. Dellarco, Ph.D.
Reproductive Effects Assessment Group
Office of Research and Development
Washington, D.C.

Karen East, M.S.
Chemical Review and Analysis Branch
Office of Policy, Planning, and Evaluation
Washington, D.C.

A. M. Jarabek, Ph.D.
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Nancy Pate, Ph.D.
Pollutant Assessment Branch
Office of Air Quality Planning and Standards
Research Triangle Park, NC

Peter Preuss, Ph.D.
Office of Health and Environmental Assessment
Washington, D.C.

Van M. Seabaugh, Ph.D.
Hazard Evaluation Division
Office of Pesticide Programs
Washington, D.C.

Paul White, B.A.
Exposure Assessment Group
Office of Health and Environmental Assessment
Washington, D.C.

EPA Science Advisory Board

The May 1985 draft of this document was independently peer-reviewed in public sessions of the Environmental Health Committee of EPA's Science Advisory Board.

Executive Summary

EPA has conducted an extensive analysis of the experimental and exposure information on formaldehyde in order to characterize the potential risk to humans from exposure to the chemical.

The major non-cancer effects posed by formaldehyde are due to the irritation (i.e., irritation of the eyes, nose, throat and lungs) and cellular changes (i.e., effects on the mucociliary system of the nose). A large number of observations of people in various settings support a conclusion that the generally observed range over which more than 95% of people respond is 0.1-3.0 ppm of formaldehyde. Generally, little risk from non-cancer health effects from exposure to formaldehyde is attributed to cases where exposures are one hundred-fold less than a no- or lowest-observed effect level. Although quantitative estimates of non-cancer risk are not possible, fewer responses are expected to be associated with fewer and less intense exposures.

EPA has classified formaldehyde as a "Probable Human Carcinogen" (Group B1) under its Guidelines for Carcinogen Risk Assessment. Based on a review of epidemiologic studies, EPA has concluded that there is "limited" evidence to indicate that formaldehyde may be a carcinogen in humans. Nine studies reported statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products.

An examination of studies in animals has indicated that there is "sufficient" evidence of carcinogenicity of formaldehyde in animals by the inhalation route. This is based on the induction by formaldehyde of an increased incidence of a rare type of malignant tumor (i.e., nasal squamous-cell carcinoma) in both sexes of rats, in multiple inhalation experiments, and in multiple species (i.e., rats and mice). In these long-term laboratory studies, tumors were not observed beyond the initial site of nasal contact.

Supportive evidence for the carcinogenicity of formaldehyde was obtained from short-term tests designed to measure effects on DNA. Formaldehyde is mutagenic in numerous bacterial test systems and test systems using fungi and insects (Drosophila). It also tranforms cells in culture and causes DNA cross-linking, sister chromatid exchange (SCE) and chromosome aberrations. In addition, formaldehyde has been shown to form adducts with DNA and with proteins in both in vivo and in vitro test systems. Its ability to interfere with DNA repair in human cells has also been shown.

Structure-activity correlations support the prediction of potential carcinogenicity. Formaldehyde is one of several aldehydes which have been shown to have carcinogenic activity in experimental animals. Acetaldehyde, the closest structural analogue of formaldehyde, induces the same type of malignant tumor in the respiratory and olfactory epithelium of the nose of rats as does formaldehyde.

Results from studies in rats by the Chemical Industry Institute of Toxicology were used to estimate the human cancer

risk. The malignant tumor data were used to extrapolate human cancer risk because only this response in formaldehyde-exposed rats was definite and unequivocal in both sexes of rats, was dose-related, and was confirmed in several rat inhalation studies. In the absence of compelling biological evidence on the mechanism of action, as in the case for formaldehyde, EPA's Guidelines for Carcinogen Risk Assessment specify the selection of the linearized multistage procedure for estimating human cancer risk. Using this procedure, the upper bound estimate for excess lifetime risk of developing cancer is $3x10^{-4}$ (Group B1) for apparel workers exposed to formaldehyde at the 0.17 ppm level; $2x10^{-4}$ (Group B1) for residents of mobile homes who are exposed for 10 years to an average level of 0.10 ppm; and $1x10^{-4}$ (Group B1) for residents of some conventional homes who are exposed for 10 years to an average level of 0.07 ppm. The upper bound estimate for an ambient exposure of 1 ug/m^3 (0.00082 ppm) for 70 years (the unit risk) is $1.3x10^{-5}$ (Group B1).

Since some of the existing information supports the use of non-linear risk assessment models to extrapolate cancer risk to humans, and since considerable uncertainty exists in the risk estimates, the real risk may be lower than that projected by the upper bound, linear estimate. The lower bound is always recognized to be as low as zero. However, the predicted excess lifetime cancer risk estimates using an upper bound based on the rat nasal carcinoma data are about equivalent to the excess cancer incidence observed in the epidemiologic studies.

1. Risk Characterization

This risk-characterization presents the major conclusions of EPA's risk assessment of formaldehyde. It reviews the underlying scientific foundation for the findings, describes the strengths and weaknesses of the supporting data, and discusses the uncertainties and potential sources of controversy attending EPA's interpretation of the data and projection of risk. The risk characterization is divided into three sections which discuss the qualitative aspects of the risk assessment, the exposure, and the quantitative risk estimations at current exposure levels. A summary of the health effects of formaldehyde and representative exposure levels is presented in Table 1-1.

1.1. Non-cancer Effects

The major non-cancer effects posed by exposure to formaldehyde are due to the irritating nature of the chemical. These effects are sensory irritation which is readily perceived by the exposed individual and cellular changes which are less evident but still important.

1.1.1. Sensory Irritation

The well documented health effects from acute inhalational exposures are concentration dependent, with individuals responding above a threshold concentration. These effects include irritation of the eyes, nose, throat and lungs, the intensity of which is dependent upon the extent and duration of exposure, and may result in extreme discomfort and inability to function normally at work or in routine daily activities.

TABLE 1-1
HEALTH EFFECTS AND REPRESENTATIVE EXPOSURE LEVELS

Formaldehyde Concentration (ppm)	Health Effects (Exposure time)[a]	Representative Exposure Levels
≤ 0.05		Ambient background
0.1	Human eye irritation begins in some people (minutes-hours)	New mobile homes 10-yr average
0.5	Human mucociliary inhibition and squamous metaplasia, mid-point of range in one study (0.1-1.1 ppm) (years)	
1.0	Human nose and throat irritation begins; most people have eye irritation (minutes-hours)	
2.0	Rat squamous metaplasia and mucociliary system LOEL[b] (months)	
3.0	Human (most) experience nose and throat irritation (minutes)	Current OSHA PEL (8 hr TWA)
	Monkey squamous metaplasia LOEL (weeks)	
5.0	Rat observed 1% cancer incidence (years)	Highest recorded home[c]
	Human lower airway effects begin (minutes-hours)	
15.0	Rat observed 50% cancer incidence (years)	
	Mouse observed 1% cancer incidence (years)	

a Duration of exposure causing the effect is indicated in parentheses.
b LOEL = lowest observed effect level
c Urea-formaldehyde foam insulated home

Due to varying sensitivities, all individuals do not exhibit these acute effects at the same formaldehyde concentration. Thus, the number of persons who respond in a population will increase with increasing concentrations of formaldehyde. A dose-response relationship has not been quantitatively characterized for the general population. However, a large number of observations of people in various clinical and nonclinical settings support a conclusion that the generally observed range over which most people respond (more than 95% response) is 0.1-3.0 ppm of formaldehyde.

Eye irritation occurs first at the lower end of the range; the percentage of individuals that respond increases up to a concentration of formaldehyde of 1.0 ppm, the concentration at which virtually all persons exhibit some degree of eye irritation. Irritation of the nose and throat frequently occurs above 1.0 ppm with most persons responding by 3.0 ppm. Exposures greater than 3.0 ppm are generally intolerable for more than short periods. These acute effects are usually reversible. Tolerance to low levels of formaldehyde can occur in individuals after 1-2 hours of exposure, but symptoms can return if exposure is interrupted and then resumed.

In addition to its direct irritant effects on the respiratory system, formaldehyde has been shown to cause bronchial asthma-like symptoms in humans. Although asthmatic attacks may, in some cases, be due specifically to formaldehyde sensitization or allergy, the evidence for this is inconclusive. Even so, a small number of reports indicate that

formaldehyde may be an inhalant sensitizer causing allergic reactions. There are no sufficiently well controlled studies to establish the extent of such sensitization in the population, nor are induction concentrations of formaldehyde known. However, the concentrations of formaldehyde required to elicit such attacks are higher than would be expected in most non-occupational environments.

1.1.2. Cellular Changes

The primary point of contact of formaldehyde upon exposure by inhalation is the nose. Inhalation of formaldehyde above a threshold level which varies from person to person causes a number of cellular effects which can impair the normal functioning of the nose and are dependent on the concentration and duration of exposure.

A major function of the nose is to prepare the inhaled air for the lungs. This includes warming, moistening, and filtering the inspired air. Dust and many bacteria found in the inspired air are precipitated in the mucus that bathes the mucous membrane and are moved outward by the action of the cilia of the nasal passage. Research indicates that formaldehyde has a number of effects on the workings of this mucociliary apparatus.

Effects on the mucociliary system of laboratory animals have been observed in several short-term exposure studies. In one study, male rats were exposed for 6 hours per day for up to 14 days, to 0.5, 2, 6, or 15 ppm of formaldehyde. At 15 ppm, the stopping of mucous flow (mucostasis) followed by cessation of ciliary activity (ciliastasis) was clearly shown. Only slight

effects were noted in animals being exposed to 6 ppm or 2 ppm. At 0.5 ppm no effects were observed. In other short-term studies formaldehyde caused cell proliferation in the nasal epithelium at doses of 2 ppm and higher. Cell proliferation is a part of the restorative process to repair cellular damage.

In chronic studies, cellular effects, i.e., rhinitis (inflammation of the nasal mucosa), epithelial dysplasia (displacement of one cell type with another one), and squamous metaplasia (replacement of normal mucosal cells with squamous cells), developed in the nasal cavities of rats and monkeys after exposures for 12 months and 26 weeks, respectively, to 2-3 ppm of formaldehyde. After 24 months of exposure, the incidence of squamous metaplasia in rats increased to nearly 100 percent. In both rats and monkeys, a NOEL (no observed effect level) of 1.0 ppm for squamous metaplasia was determined, with a LOEL (lowest observed effect level) of 2.0 ppm in rats and 3.0 ppm in monkeys. The potential relationship between squamous metaplasia and carcinogenesis is presented in section 1.4.2.2.

Evidence of cellular damage in humans is limited. One study in which humans were occupationally exposed from four to nine years (mean = seven years) to formaldehyde in the range of 0.1-1.1 ppm, time-weighted average (TWA) concentration, showed loss of ciliary activity and development of squamous metaplasia. Caution must be used when generalizing from this study because of the small number of exposed persons examined (20) and the possibility of confounding exposure. Five individuals in the formaldehyde-exposed group exhibited nasal cavity changes.

The mucociliary system is an important defense mechanism in the removal of foreign particles and bacteria which enter the upper respiratory system. A reduction in the efficient operation of this defense mechanism, including formation of squamous metaplasia, by exposure to formaldehyde may increase the risk of persons exposed to formaldehyde to develop infections and other respiratory diseases.

1.2. Carcinogenic Effects

EPA has classified formaldehyde as a "Probable Human Carcinogen" (Group B1) under its Guidelines for Carcinogen Risk Assessment. This classification is based on the following:

- o limited evidence of carcinogenicity in humans (i.e., several epidemiologic studies show positive associations between respiratory site-specific cancers and exposure to formaldehyde);
- o sufficient evidence of carcinogenicity in animals (i.e., formaldehyde induced an increased incidence of rare, malignant nasal squamous-cell carcinoma in mice and rats, and in multiple experiments); and
- o additional supportive evidence (i.e., studies demonstrating formaldehyde's mutagenic activity in numerous test systems using bacteria, fungi, and insects, and its ability to transform cells in culture and cause DNA damage in other in vitro assays for mutagenicity. Also, structure-activity analysis indicates that formaldehyde is one of several carcinogenic aldehydes.)

1.2.1. Studies of Humans

The EPA has examined 28 epidemiologic studies relevant to formaldehyde. Three of these studies, two cohort[1] (Blair et al., 1986; 1987 in press; Stayner et al., 1986) and one case-control[2] (Vaughan et al., in press), were well conducted and specifically designed to detect small to moderate increases in formaldehyde-associated human risks. Each of these three studies observed statistically significant associations between respiratory site-specific cancers and exposure to formaldehyde or formaldehyde-containing products. These associations are noteworthy since during inhalation, tissues in the nose, nasal sinuses, buccal cavity (mouth), pharynx,[3] and lungs come into direct contact with formaldehyde. In each of the above three studies, the populations studied were also undoubtedly exposed to other chemicals and these exposures may have contributed to the observed increases in cancer risk. Only the study by Vaughan et al. (1986a,b) controlled for smoking and alcohol consumption.

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[1] A cohort study follows a group of exposed individuals for a specified time period and measures the incidence of site-specific deaths. The observed number of site-specific deaths which occurred in the time period are compared to the number of site-specific deaths which would be expected based on mortality rates of a standard population.

[2] A case-control study identifies cases with the disease of interest and controls who do not have the disease. The cases and controls are compared with respect to past exposure.

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[3] The pharynx is the passage between the nasal cavity and the larynx. The nasopharynx, hypopharynx, oropharynx, and laryngopharynx comprise the pharyngeal region.

The Blair et al. (1986; 1987 in press) cohort study observed significant excesses in lung and nasopharyngeal cancers among U.S. workers occupationally exposed to formaldehyde at 10 industrial sites. Blair et al. (1986), however, argued that the lung cancer excesses provided little evidence of an association with formaldehyde exposure since the lung cancer risk did not increase consistently with either increasing intensity or cumulative formaldehyde exposure. EPA, after reviewing the data, has concluded that the significant excesses in total lung cancer mortality, in analyses either with or without a latency period equal to or greater than 20 years, and together with nasopharyngeal cancer mortality among formaldehyde-exposed workers are meaningful despite the lack of significant trends with exposure. Misclassification of exposure (or lack of specificity between exposure categories) and categorization of deaths into four exposure levels which lowers the power to detect small increases in risk, may have accounted for the observed lack of a significant dose-response relationship. The significance of these findings is reinforced by the fact that the site of the tumors seen in humans (the nasopharyngeal region) is similar to that seen in animals. Blair et al. (1987) performed further analyses of the nasopharyngeal cancers regarding exposure to formaldehyde and particulates. For those workers with particulate exposure, the trend between increasing nasopharyngeal risk and increasing cumulative formaldehyde exposure was not statistically significant, however, the authors concluded that formaldehyde and particulates appeared to be a risk factor for nasopharyngeal cancer.

The Stayner et al. (1986) cohort study reported statistically significant excesses in mortality from buccal cavity tumors among formaldehyde-exposed garment workers. The standardized mortality ratio (SMR), a ratio of the observed number of deaths to an age-adjusted number of deaths expected in the group, was highest among workers with a long duration of employment (exposure) and follow-up period (latency). A significant excess in deaths from cancer of the tonsils was also reported, but there were too few deaths to examine any trends with exposure.

Results from the case-control study by Vaughan et al. (1986a,b) showed a significant association between nasopharyngeal cancer and having lived 10 or more years in a "mobile home". Persons for whom this association was drawn had lived in mobile homes that were built in the 1950s to 1970s. This study also reported significant associations between sinonasal cancer and orohypopharyngeal cancer and exposure to resins, glues, and adhesives (SAIC, 1986).[4] No significant trends were found in cancer incidence at any of these sites with respect to occupational formaldehyde exposure; however, the risk estimates for the highest exposure level and cancers of the orohypo- and naso-pharynx appeared elevated. As stated earlier, however, this population, like the two previously discussed, was also undoubtedly exposed to other chemicals which may have contributed to the observed increases in cancer risk.

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[4]Several residential and occupational characteristics were a priori selected as likely surrogates for formaldehyde exposure. Among these were mobile home residency and occupational resins, glue, and adhesive exposure.

EPA previously had reviewed 25 other epidemiologic studies. These studies had limited ability (lower power) to detect small to moderate increases in formaldehyde-related risks due to (1) small sample sizes; (2) small numbers of observed site-specific deaths; and (3) insufficient follow-up. Even with these potential limitations, six of the 25 studies (Acheson et al., 1984a; Hardell et al., 1982; Hayes et al., 1985; Liebling et al., 1984; Olsen et al., 1984; Stayner et al., 1985) reported significant associations between excess site-specific respiratory (lung, buccal cavity, and pharyngeal) cancers and exposure to formaldehyde.

The Olsen et al. (1984), Hayes et al. (1986), and Hardell et al. (1982) studies reported significant excesses of sinonasal cancer in individuals who were exposed to both formaldehyde and wood-dust, or who were employed in particleboard manufacturing where formaldehyde is a component of the resins used to make particleboard. Only the Hayes et al. (1986) and Olsen et al. (1984) studies controlled for wood-dust exposure; the detection limits in both studies, however, exceeded corresponding expected excesses in the incidence of sinonasal tumors and, therefore, no significant excesses were likely to have been observed.

The Acheson et al. (1984a) study conducted in the United Kingdom supports the results of Blair et al. in that, when compared to mortality rates of the general population, significant excesses in mortality from lung cancer were observed in one of six formaldehyde resin producing plants in England. A trend of borderline significance with dose was observed for this one plant. Acheson et al. concluded that the increases in mortality

from lung cancer were not related to formaldehyde exposure since the elevation and trend were not statistically significant when compared with local lung cancer rates. EPA believes that the risks and trends from analyses using local lung cancer rates as the comparison risks appeared sufficiently increased for corroborative use.

The remaining two studies reported significant excesses of buccal cavity cancer among garment workers in 3 plants (Stayner et al., 1985) and excesses of buccal cavity and pharyngeal cancer among formaldehyde resin workers in 1 plant (Liebling et al., 1984). Portions of the Liebling et al. (1984) and Blair et al. (1986, 1987) studies overlapped as did portions of the two Stayner et al. (1985; 1986) studies. However, the non-overlapping portions and improved design of the more recent studies (i.e., Blair et al. 1986, 1987; Stayner et al. 1986) reinforce the conclusions of the earlier studies.

Analyses of the remaining 19 epidemiologic studies have indicated the possibility that observed leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated.

Based on a review of these studies, EPA has concluded that there is "limited" evidence to indicate that formaldehyde may be a carcinogen in humans.[5] Nine studies reported statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products. This is of interest since inhalation is the primary route of exposure in humans. Although the common exposure in all of these studies was formaldehyde, the epidemiologic evidence is categorized as "limited" primarily due to possible exposures to other agents which may have confounded the findings of excess cancers.

1.2.2. Studies in Animals

The principal evidence indicating that formaldehyde causes cancer in animals comes from studies conducted by the Chemical Industry Institute of Toxicology (CIIT) (Kerns et al., 1983) and those by Albert et al. (1982) and Tobe et al. (1985). The CIIT study was a well conducted, multidose inhalation study in rats and mice. In this study, a statistically significant increase in malignant tumors (i.e., squamous cell carcinomas) was seen in the nasal cavities of male and female rats dosed at 15 ppm. In addition, a small increased incidence of squamous cell carcinoma, while not statistically significant, was seen in male mice.

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[5] EPA's Guidelines for Carcinogen Risk Assessment define limited evidence of carcinogenicity in humans as indicating that "...a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded."

Because this type of nasal lesion is rare in mice, these data can be considered to have biological importance. Benign tumors (i.e., polypoid adenomas) were seen in male rats in the CIIT study at all dose levels and in female rats exposed to 2 ppm of formaldehyde. Notably, the dose-response curve for the benign tumors in this study was not linear; the tumor incidence was highest at 2.0 ppm and decreased at higher doses.

Tobe et al. also observed a statistically significant increase in the numbers of squamous cell carcinomas in the same strain of male rats as was used in the CIIT study. Albert et al. reported a statistically significant elevation of the same malignant tumor type in male rats of a different strain. In both the Tobe et al. and Albert et al. studies benign squamous cell papillomas were seen. This observation was in contrast to the CIIT study in which polypoid adenomas were the only benign tumors observed. Hamsters have been tested in long-term inhalation studies (Dalbey, 1982) but no increased incidence of tumors was seen in formaldehyde-treated animals. However, deficiencies in the study design and poor survival limit the interpretation of the results from these studies.

Additional studies in animals that indicate an association between exposures to formaldehyde and cancer are those by Dalbey (1982) in which formaldehyde enhanced the production of tumors induced by a known animal carcinogen (i.e., diethylnitrosamine); Mueller et al. (1978) in which formalin (a water solution of formaldehyde) produced lesions in the oral mucosa of rabbits which showed histological features of carcinoma <u>in situ</u>; and studies by

Watanabe et al. (1954; 1955) in which injections of formalin and hexamethylenetetramine (from which formaldehyde is liberated *in vivo*) produced sarcomas (malignant tumors) and one adenoma (benign tumor) at the site of injection.

Based upon a review of these studies, EPA has concluded that there is "sufficient" evidence of carcinogenicity of formaldehyde in animals by the inhalation route.[6] This finding is based on the induction by formaldehyde of an increased incidence of a rare type of malignant tumor (i.e., nasal squamous-cell carcinoma) in both sexes of rats, in multiple inhalation experiments, and in multiple species (i.e., rats and mice). In these long-term laboratory studies, tumors were not observed beyond the initial site of nasal contact nor have other mammalian *in vivo* tests shown effects at distant sites.

1.2.3. Additional Supportive Evidence

Other relevant information which is considered in carcinogen assessments include results from short-term tests designed to measure effects of a chemical on DNA. Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and *in vitro* cell transformation provide evidence for the potential mechanisms of carcinogenicity. A battery of

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[6] EPA's Guidelines for Carcinogen Risk Assessment define sufficient evidence of carcinogenicity from studies in experimental animals as indicating that "...there is an increased incidence of malignant and benign tumors: (a) In multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, dose-response effects, as well as information from short-term tests or on chemical structure."

tests which measure different endpoints helps to characterize the chemical's response spectrum. In general, the wider the range and the greater the intensity of response of a substance in short-term tests, the more likely it is that the substance may cause cancer.

Formaldehyde is mutagenic in numerous bacterial test systems and test systems using fungi and insects (Drosophila). It also transforms cells in culture and causes DNA cross-linking, sister chromatid exchanges (SCE) and chromosome aberrations. In addition, formaldehyde has been shown to bind with DNA and with proteins in both in vivo and in vitro test systems. Its ability to interfere with DNA repair in human cells has also been shown.

Structure-activity correlations support the prediction of potential carcinogenicity. Formaldehyde is one of several aldehydes which have been shown to have carcinogenic activity in experimental animals. Of those tested, acetaldehyde, is the closest structural analogue of formaldehyde. Like formaldehyde, acetaldehyde damages the respiratory and olfactory epithelium, however, formaldehyde appears to be more potent than acetaldehyde. The main impact of formaldehyde, probably because of its greater reactivity, occurs more in the anterior portion of the nose than that of acetaldehyde. Exposure to either aldehyde leads to the formation of nasal squamous cell carcinoma; acetaldehyde, however, also induces another type of malignant nasal tumor, adenocarcinoma. Polypoid adenoma (benign tumor) were seen following exposure to formaldehyde whereas squamous-cell papilloma (benign tumor) were found following treatment with acetaldehyde. The utility of benign tumors in risk assessment is discussed in sections 1.4., 4.2.1., and 7.4.

1.3. Exposure in Residential and Apparel Manufacturing Settings

EPA's risk assessment focuses on two large populations chronically exposed to low levels of formaldehyde. These populations include: (1) persons who reside in mobile and conventional homes constructed using "significant amounts" of urea-formaldehyde (UF) pressed-wood (i.e, homes in which UF pressed wood is used for floor underlayment and, in some cases, for wall paneling), and (2) apparel workers who are exposed to formaldehyde that is emitted from durable press fabrics.

Available air monitoring data, although not collected under any comprehensive nation-wide survey, indicate that exposure levels in both settings have declined over the last 5 years. This is consistent with the increased commercial use of lower-emitting formaldehyde source material (pressed wood products and durable press resins).

Measurements of formaldehyde levels are strongly affected by a number of factors that add to the overall uncertainty of the data. These factors include the monitoring methods employed, the amount and age of the formaldehyde source material present at the site, the extent of ventilation at the site, and the ambient temperature and humidity. High temperature and humidity, for example, are known to increase emissions of formaldehyde from pressed wood products and durable press fabrics. However, many of the formaldehyde monitoring efforts did not report or document adequately these variables.

1.3.1. Residential Exposure

Most of the monitoring data collected in residences over the

last decade have been in older homes, homes in which urea-formaldehyde foam insulation (UFFI) has been installed, or homes in which the occupants have expressed health complaints. Perhaps more representative of current formaldehyde levels in new mobile and conventional homes are several recent monitoring studies conducted in California, Tennessee and Texas. These studies evaluated homes built after 1980, when builders were using energy-efficient (tighter) construction and most pressed wood producers had begun to use low-emitting resin adhesives.

Recent monitoring results indicate that formaldehyde levels in new (less than one year old) conventional homes generally fall within the range of 0.05 ppm to 0.2 ppm; few measurements exceeded 0.3 ppm. In new mobile homes, formaldehyde levels monitored generally fall within the range of 0.2 ppm to 0.3 ppm with the highest levels measured near 0.4 ppm, the ceiling level targeted by Department of Housing and Urban Development regulations that govern mobile home construction. The larger range of values observed in conventional homes is attributed primarily to the greater variation in design and use of UF pressed wood products in their construction. By contrast, mobile homes have less design variation and, for the most part, generally use pressed wood products more extensively. EPA has developed computer models to estimate initial formaldehyde levels in conventional homes built using significant amounts of pressed wood. Although these models have not been fully validated, they yield expected values that fall within the range of 0.1-0.2 ppm.

EPA estimates that every year approximately 631,000 persons

move into new conventional homes that contain significant amounts of pressed wood. In the same period, about 780,000 persons move into new mobile homes.

Under normal conditions, the amount of formaldehyde released from pressed wood products decreases with time, lowering the levels in these residences. Although numerous studies have investigated the decrease in emissions from uncoated pressed wood in the months immediately after its manufacture, little quantitative information is available on long-term (10-year) formaldehyde emissions from pressed wood. In lieu of long-term emission decay data, EPA derived a decay curve function by combining the results of two large monitoring surveys and statistically determining the best-fit curve to the data as a function of home age. Combined, the two surveys reported almost 1,200 measurements in 400 mobile homes that were constructed during 1970-1980 and ranged in age from one day to nearly 10 years. EPA has used the exponential function derived from these data for quantitative cancer risk assessment purposes to calculate expected 10-year averages for formaldehyde levels in homes built today. The calculated 10-year averages are 0.07 ppm for conventional homes built using significant amounts of UF pressed wood and 0.1 ppm for mobile homes. As these estimates are derived from historical data, a significant source of uncertainty associated with these estimates is the unknown long-term emission characteristics of the UF resins used today to manufacture the pressed wood products used in these homes.

1.3.2. Exposure in Apparel Manufacturing

The U.S. apparel industry employed over 1.1 million workers in 1983. There are approximately 22,600 apparel manfacturing establishments located in every state of the country, and each employs an average of 59 workers.

Monitoring data collected by the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), or otherwise reported in the literature indicate that formaldehyde levels in these facilities were generally below 3.0 ppm prior to 1980. In later years, the levels have generally fallen below the 1.0 ppm level. Recent industrial hygiene studies by NIOSH of two large manufacturing sites that produce mens' shirts indicated that the mean exposure level for both plants was 0.17 ppm.

1.4. Quantitative Risk Assessment

The risk assessment identified two biological effects for which the data are sufficient to evaluate quantitatively. These are acute sensory/cellular effects of the upper respiratory tract and cancer. A combination of results obtained from studies in animals and humans were used to assess the acute sensory/cellular effects while the cancer risk estimates were derived from modeling data obtained from studies in animals.

1.4.1. Non-cancer Risk Assessment

Figure 1-1 illustrates the relationship between the doses associated with sensory irritation and cellular effects in the nasal cavity and the exposure levels for a number of population groups. Instead of using high-to-low dose extrapolation models,

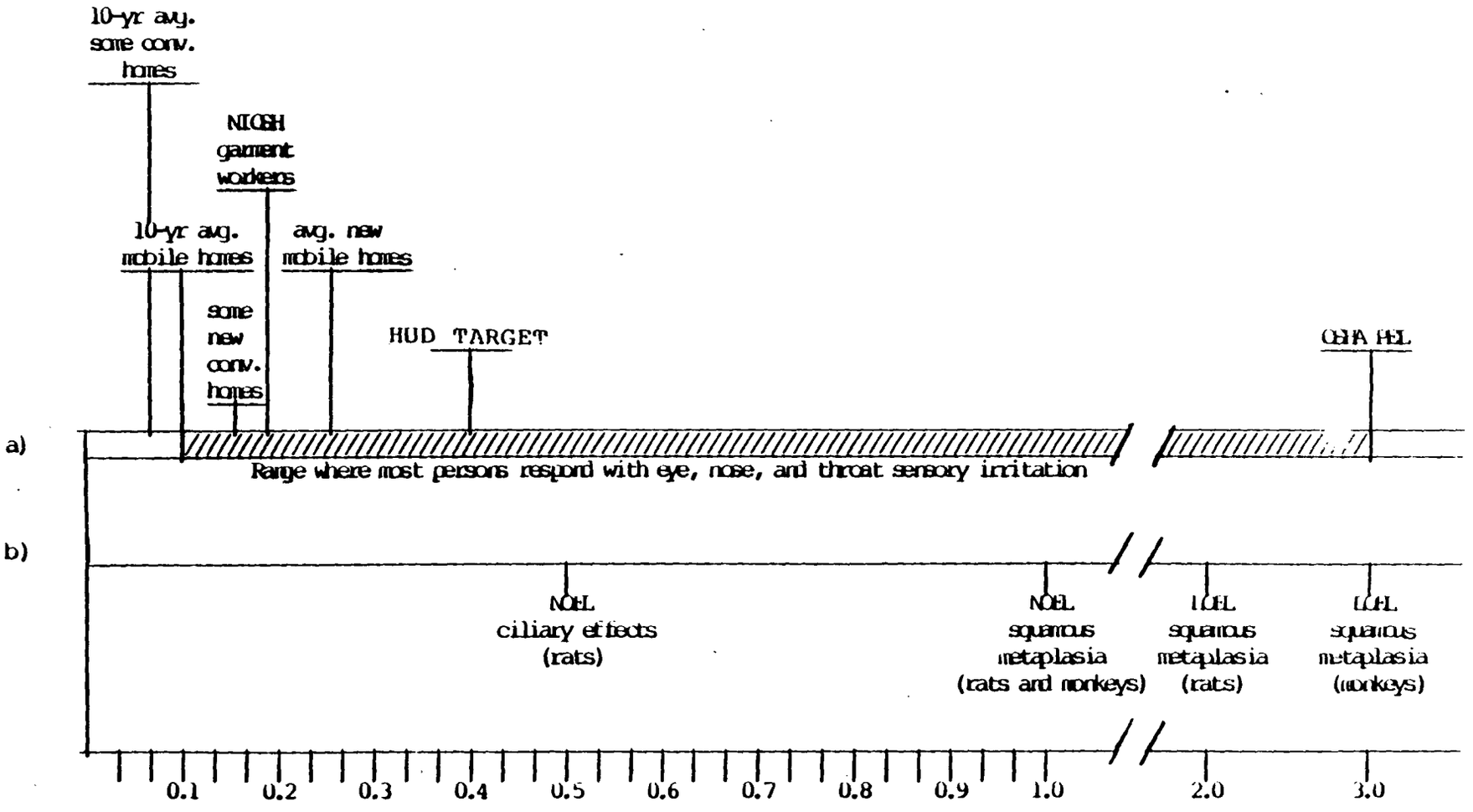

FIGURE 1-1. Relationship between concentrations of formaldehyde causing sensory irritation and cellular effects and milestone exposure levels.

the degree of concern from these effects is approximated by comparing existing exposures to lowest effect levels. Generally, little risk is attributed to cases where exposures are one hundred-fold less than a no- or lowest-observed effect level.

1.4.1.1. Sensory Irritation

The onset of sensory irritation in humans exposed to formaldehyde occurs over a wide range of formaldehyde concentrations (i.e., 0.1-3.0 ppm). This range overlaps the expected human exposures identified in this assessment. This means that there is no margin between existing exposures and levels of formaldehyde that are associated with sensory irritation in some humans. Thus, it would seem that some humans may be currently experiencing some degree of sensory irritation to existing levels of formaldehyde in new to moderately new mobile homes and garment manufacturing operations (see Figure 1-1(a)). Due to the large variations in human sensitivity to the irritative effects of formaldehyde, the prediction of response for a population would require a characterization of both the frequency of individual human responses and the severity of effects with increasing exposure. However, available data do not allow the development of a well defined dose-response relationship for these irritation effects. For the exposure conditions presented in Figure 1-1(a), only a small percentage of persons would respond and in all likelihood the eye irritation would be very mild and transitory when an individual enters the home or workplace. The people at greatest risk of experiencing discomfort due to

formaldehyde-induced irritation are new homeowners during the first year of occupancy, particularly under conditions of high temperature and humidity which are typically associated with elevated levels of formaldehyde in these homes.

1.4.1.2. Cellular Effects

Formaldehyde causes cellular changes in the upper respiratory tract. Studies in animals have shown that formaldehyde can inhibit mucociliary action after only a few days of exposure, with a NOEL of 0.5 ppm in rats. Long-term exposure studies have shown squamous metaplasia in the nasal cavities of rats and monkeys. The NOEL for this effect in both species is 1.0 ppm, with LOELs of 2.0 ppm (rats) and 3.0 ppm (monkeys). One study of humans showed nasal cavity effects in some persons exposed in the range of 0.1-1.1 ppm (Edling, et al., 1985).

From these values, it appears that humans and animals may respond similarly (within a factor of 10) to the cellular effects of formaldehyde in the nose. Formaldehyde exposures in mobile and conventional homes and to garment workers fall somewhat below the NOELs and LOELs for cellular effects as determined from studies in animals (Figure 1-1(b)) Since the anticipated exposures in the identified populations are close to those associated with effects in humans and animals, it is expected that home residents and garment workers may be at some risk of experiencing these non-cancer effects.

Although quantitative estimates of risk are not possible, the frequency and severity of response are dose related. Fewer responses are expected to be associated with less frequent and

less intense exposure. In addition, the cellular effects are expected to be reversible once formaldehyde exposure is eliminated.

1.4.2. Cancer Dose-Response Assessment

In principal, data from studies of humans are preferred for making numerical risk estimates. However, as is often the case, the available epidemiologic data on formaldehyde were not suitable for low dose quantitative cancer risk estimation, mainly because of a lack of adequate exposure information in the studies. Accordingly, results from studies in animals were used to estimate low-dose human cancer risk. In addition, even though the epidemiologic studies were not suitable for quantifying a dose-response curve, those studies with observed statistically elevated cancer risks provided some support for the animal-based predicted upper bound risk. This comparison, while yielding valuable information to the assessment, should be viewed with caution since exposure levels in these epidemiologic studies were subject to some variation.

1.4.2.1. Selection of Data

Of the carcinogenicity studies with formaldehyde in animals, EPA has selected the CIIT study in rats as the best study for cancer risk extrapolation. This study was well designed, well conducted, included multiple doses, and used a large number of animals per dose.

Each of the remaining inhalation studies suffered from various limitations which precluded their use in quantitative risk assessment. The CIIT study in mice showed a limited tumor

response only at the highest dose of formaldehyde, while the Albert et al. (1982) study had only a single formaldehyde-exposed group. Although the Tobe et al. (1985) study contained multiple dose groups, a tumor response was seen only at the highest dose, and the number of animals per group was relatively small. Lower cancer risks than those estimated from the CIIT study in rats would have been predicted had the Agency been able to use the CIIT study in mice for risk extrapolation, while higher cancer risks would have been estimated had the results from the Tobe et al. (higher by a factor of ten) or Albert et al. studies been used.

Two types of nasal tumors were observed in the CIIT study in rats, squamous cell carcinomas (malignant tumor) and polypoid adenomas (benign tumor). EPA's risk assessment relied only on the malignant tumor data of the CIIT study to predict human cancer risks because: (1) the malignant tumor response in formaldehyde-exposed rats was definite and unequivocal in both males and females, whereas the frequency of benign tumors reached statistical significance only when the incidences in males and females were pooled; (2) the malignant tumor response in the CIIT study in rats showed an increasing dose-related trend, while the benign tumor response showed a decreasing trend; (3) unlike the benign tumor response which was not confirmed by the other rat inhalation studies, similar malignant tumor types were found both in all rat and mouse inhalation studies with formaldehyde and in a study of acetaldehyde, a close structural analogue of formaldehyde.

The appearance of benign nasal tumors in rats following inhalational exposure to formaldehyde in the CIIT study

contributes to the qualitative weight-of-the-evidence that formaldehyde may pose a carcinogenic hazard, but because of the attendant uncertainties they were not included in the quantitative estimate of human cancer risk. Had the Agency chosen to use the benign tumor response in the quantitative estimation of human cancer risk, the predicted values would have been about ten-fold greater than those reported in Section 1.4.3 using the malignant tumor response alone.

1.4.2.2. Choice of Mathematical Extrapolation Model

Since risks at low exposure levels cannot be measured directly either by experiments in animals or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from results at high doses to expected responses at low doses. The Office of Science and Technology Policy (OSTP) published principles on model selection which states that:

> "No single mathematical procedure is recognized as the most appropriate for low dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists, the models or procedures employed should be consistent with the evidence. When data and information are limited, however, and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incorporate low dose linearity are preferred when compatible with the limited information."

Data relevant to selecting a model for extrapolation of cancer risk associated with exposure to formaldehyde were reviewed; some of the biological information support a direct

relationship between exposure and carcinogenicity while other data are consistent with a non-linear response. The Agency, however, did not conclude that enough information was available to propose an extrapolation model for formaldehyde that was different from the one recommended by the OSTP and EPA's Guidelines for Carcinogen Risk Assessment (i.e., linearized multistage procedure). The Agency has presented various other models for comparative purposes.

Biologic evidence on mechanism of action, which can aid in model selection, largely is inferred from a variety of types of studies. These are limited and suggestive of several mechanisms for formaldehyde. Mutagenicity studies suggest a direct relationship (i.e., a linear one) between exposure to formaldehyde and carcinogenicity. Thus, the ability of formaldehyde to cause point mutations, chromosome aberrations and DNA damage is consistent with the chemical's ability to initiate the carcinogenic reaction.

The steep curvilinearity of the rat nasal carcinoma dose-response data in the CIIT study in rats suggests, however, that cancer development is greatly accentuated above certain concentrations. In keeping with this observation are the results of experiments on DNA synthesis and cell proliferation following short-term formaldehyde exposures and the conversion of normal mucosal cells to squamous cell epithelium (squamous metaplasia) following longer exposures which indicate that certain toxic effects are only noted above certain formaldehyde concentrations. Any relationship between cell proliferation

following formaldehyde exposures and the carcinogenic process is currently unknown. Likewise, although squamous metaplasia may represent a step in the formation of squamous cell carcinoma, its specific role is uncertain. No lesions that may represent stages in a continuum between the squamous metaplasia and carcinoma were identified in the CIIT study.

The CIIT also conducted molecular dosimetry experiments attempting to relate ambient exposures to formaldehyde with tissue-specific levels of formaldehyde-DNA adducts. Use of the data generated by these experiments in risk extrapolation models yields lower estimates of risk, sometimes significantly lower than use of the experimental doses. The CIIT data have been reviewed by EPA scientists and a review panel of non-government scientists to determine whether or not they should be used in the quantitative risk assessment. Both groups concluded that the study had several shortcomings which preclude its use in modifying the doses used in quantitative risk assessment, and they provided three reasons for their conclusion. First, the experimental methodologies must be validated to assure that the experimental assumptions were scientifically sound and that the formaldehyde-DNA-protein complexes were identified properly; second, the single intracellular target used in the study may be inadequate; and third, and perhaps most important, the use of an acute exposure model in the CIIT study may not be appropriate because chronic, not acute exposure is most relevant to risk assessment.

Different extrapolation models fit the observed data reasonably well but there are large differences among them in the risks calculated at low doses. EPA's Guidelines for Carcinogen Risk Assessment state, however, that goodness of fit to the observed tumor data by a given model is not an effective means of discriminating among models. In the absence of compelling biological evidence on the mechanism of action, as in the case for formaldehyde, EPA's guidelines specify that the linearized multistage procedure will be used, with the possible presentation of various other models for comparative purposes. The analysis showed that of the models examined, only the one-hit model produced higher risk estimates (about ten fold higher).

Studies show that non-human primates and rats respond similarly to formaldehyde exposure. Accordingly, an interspecies scaling factor was not used in the risk extrapolation. This position was supported by the Consensus Workshop on Formaldehyde. Consequently, the response of rats and humans was judged to be the same at equivalent exposure levels and durations. However, if a conversion factor, such as nasal surface area, had been used the estimated human cancer risks would have been about an order of magnitude higher.

1.4.3. Numerical Risk Estimates

The risk estimates for the linearized multistage procedure, upper bound (UB) and maximum likelihood estimates (MLE)[7] at various exposure levels are presented in Table 1-2. Risks at any exposure level range from the upper bound to zero. An established procedure does not yet exist for making "most likely" or "best" estimates of risk within the range of uncertainty defined by the upper bound and zero. The upper bound estimate for excess lifetime risk of developing cancer is 3×10^{-4} [Group B1][8] for apparel workers exposed to formaldehyde at the 0.17 ppm level, 2×10^{-4} [Group B1] for residents of mobile homes who are exposed for 10 years to an average level of 0.10 ppm; and 1×10^{-4} [Group B1] for residents of some conventional homes who are exposed for 10 years to an average level of 0.07 ppm. The upper bound unit risk estimate for an ambient exposure of 1 ug/m^3

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[7] The shapes of most models' upper bound estimates tend to parallel the shapes of the models themselves, unless a procedure has been devised to provide otherwise. This is the case for the linearized multistage procedure, which provides a linear upper bound estimate at low dose. The maximum likelihood estimate (MLE), which is the estimate given by a fitted model, takes only the experiment to which the model has been fitted into account. The upper bound estimate, on the other hand, is intended to account for experiment to experiment variability as well as extrapolation uncertainties.

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[8] EPA's Guidelines for Carcinogen Risk Assessment recommend categorizing chemicals in Group B (Probable Human Carcinogen) when "the evidence of human carcinogenicity from epidemiologic studies ranges from almost 'sufficient' to 'inadequate.' To reflect this range, the category is divided into higher and lower degrees of evidence. Usually, category B1 is reserved for agents for which there is at least limited evidence of carcinogenicity to humans from epidemiologic studies."

(0.00082 ppm) for 70 years is 1.3×10^{-5} [Group B1]. The fitted model gives the maximum likelihood estimate curve and, specific to the CIIT study, it has a pronounced S-shape. By contrast, as the linearized multistage procedure's upper bound estimate is traced toward lower doses, its linear nature accomodates increasing variability and extrapolation uncertainty. Both estimates are shown in Table 1-2 to illustrate how the perspectives they give on risk differ. Thus at 3 ppm (which is in the experimental range), the difference between the MLE and the UB is ten-fold, whereas at about one-tenth of that exposure, a 100,000 fold difference is generated.

The lower bound on risk is always recognized to be as low as zero. The upper bound estimate is ordinarily shown to allow for extrapolation uncertainty. It is for this reason, along with adherence to EPA's Guidelines for Carcinogen Risk Assessment, that the upper bound was selected to represent potential human risk. While some of the existing information on formaldehyde is consistent with non-linear interpretations, some support for a linearized upper bound comes from the epidemiologic studies. The excess cancer incidences observed in the epidemiologic studies are about the same as the upper bound on lifetime risk based on the rat nasal carcinoma data.

TABLE 1-2

SUMMARY OF CANCER RISKS ASSOCIATED WITH FORMALDEHYDE EXPOSURE

Population Segement (Exposure Level)	Lifetime Individual Risk
Current OSHA std. (3 ppm)	UB[b] 6×10^{-3} [B1] MLE[c] 6×10^{-4} [B1]
Garment Workers NIOSH (0.17 ppm)	UB 3×10^{-4} [B1] MLE 4×10^{-9} [B1]
Mobile Home Residents (0.10 ppm 10-yr average)	UB 2×10^{-4} [B1] MLE 2×10^{-10} [B1]
Conventional Home[a] Residents (0.07 10-year average)	UB 1×10^{-4} [B1] MLE 6×10^{-11} [B1]
Home/Environment Background Upper Limit (0.05 ppm) 10 yr.	UB 7.0×10^{-5} [B1] MLE 1.0×10^{-11} [B1]
70 yr.	UB 5.0×10^{-4} [B1] MLE 1.0×10^{-10} [B1]

[a] For homes containing substantial amounts of urea-formaldehyde pressed wood (e.g., floor underlayment and/or paneling)

[b] Upper Bound

[c] Maximum Likelihood Estimate

[d] Airborne Unit Risk, 1 ug/m^3 - 70 yrs; Lifetime individual risk, UB = 1.3×10^{-5} [B1]

2. BACKGROUND

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 (14.3 ppm).

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 50 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. The Panel members were also 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 assessed 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.

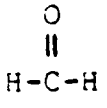
In addition to HCHO's potential cancer risks, HCHO's other effects should be considered in any action to reduce health effects from HCHO. The assessment of the risks from acute respiratory effects was prepared to be considered along with the carcinogenic risk assessment in the overall investigation of 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 PROPERTIES

HCHO is the simplest member of the aldehyde chemical category. It exists in many different forms. Both liquid and gaseous HCHO polymerize readily at ordinary temperatures and can be kept in pure monomeric state only for a limited time. Pure monomeric HCHO is a colorless, pungent gas. Aqueous HCHO, called formalin, is a clear, colorless solution containing about 37 percent by weight of dissolved HCHO in water (room temperature), usually with 6 to 15 percent methanol added to prevent polymerization. Solutions containing over 30 percent by weight become cloudy on standing and precipitate polymer at ordinary temperatures. Concentrated liquid HCHO-water systems containing up to around 95 percent HCHO are obtainable, but the temperature necessary to maintain solution clarity and prevent separation of solid polymer increases from around room temperature to 120°C as the solution concentration is increased. The other forms of HCHO are polymers, the best known of which are para-HCHO and trioxane (trioxymethylene). HCHO is sold and transported only in solution or in the polymerized state.

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



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

Dry HCHO gas condenses on chilling to give a liquid that boils at -19°C and freezes to a crystalline solid at -18°C. Vapor pressure is 400 mm at -33°C. HCHO gas is flammable having a heat of combustion of 4.47 kcal per gram. It forms explosive mixtures with air and oxygen. At atmospheric pressure, flammability is reported to range from 12.1 to 80 volume percent, HCHO-air mixtures containing 65 to 70 percent being the most readily flammable. HCHO is soluble in water, acetone, benzene, diethyl ether, chloroform and ethanol (IARC, 1982). Solutions obtained with the nonpolar solvents are somewhat more stable but also precipate polymer on storage. HCHO solutions have a definite flash point which is lowered by the presence of methanol. The flash point of commercial HCHO 37.5% solution with 14.0% methanol (by weight) is 56°C (132°F). In view of their unique nature, it is recommended that flash point values for HCHO solutions be regarded as approximations and that the solutions be regarded as potentially flammable at least 10°F below the reported figures.

*Includes synonyms for polymeric forms of HCHO.

The partial pressure of HCHO vapor over commercial solutions is also increased by methanol. The partial pressure of HCHO over 37 percent solution containing 9 percent methanol is 4.2 mm at 35°C, whereas a 37 percent solution containing 1 percent methanol has a partial pressure of 2.7 mm under the same conditions (Walker, 1975).

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 Kerns 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. The exposure period was followed by up to six months of nonexposure. Interim sacrifices were conducted at 6, 12, 18, 24, 27 and 30 months. All major tissues from each organ system (approximtely 50 tissues/animal) in the control and high exposure groups were examined histologically. 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 first tumor clinically observed in female rats of the 14.3 ppm group was at 358 days past first exposure and 432 days for males. The adjusted cumulative incidence rate (Kaplan-Meier life table analysis) of squamous cell carcinomas in male and female rats of the 14.3 ppm exposure group at 24 months was 67 and 87%, respectively. Tumors in male mice were discovered at the 24-month sacrifice. The incidence of nasal carcinomas in rats showed a dose-response relationship. See Table 4-1 for a summary of tumor response in rats.

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 Kerns et al. (1983)

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

Although the two squamous carcinomas in mice at 14 ppm were not 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 (Kerns et al., 1983).

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 whereas rats exhibited at 20% decrease. 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 Kerns 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 exhibited a

dose-response relationship with a negative trend. 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 squamous metaplasia was also observed. See Figure 4-1 for frequency and locations (also see Figure 4-3). In rats at 2.0 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 significantly ($p<0.05$) 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). Significant ($p<0.05$) regression of squamous metaplasia was noted at 27 months (post exposure). Similar but more severe and extensive lesions were observed in the 14.3 ppm exposure group in all regions of the nasal cavity. Significant regression of squamous metaplasia was only observed in the posterior portion of the nasal cavity (Levels IV and V). In all exposure groups, epithelial dysplasia was detected earlier than squamous metaplasia.

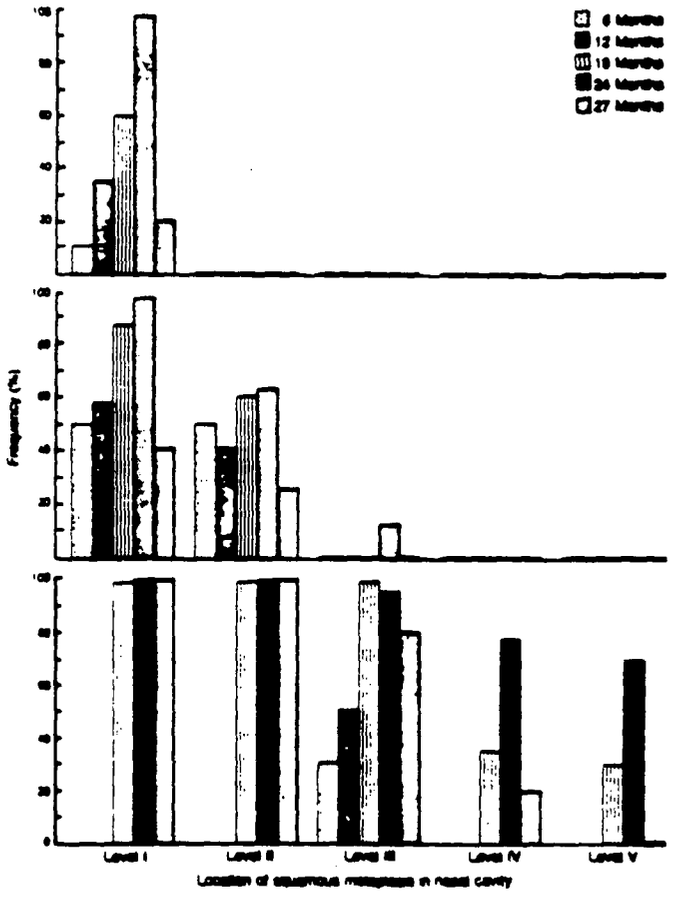


Figure 4-1. Frequency of squamous metaplasia in the nasal cavity of Fischer 344 rats exposed to 2.0 ppm (top), 5.6 ppm (middle), or 14.3 ppm (bottom) of formaldehyde gas for 24 months. Nasal cavity Levels I, II, IV, and V were not evaluated at the 6- and 12-month interim sacrifices in the 14.3 ppm exposure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

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 with serous rhinitis at 18 months in Level II. By 24 months, a majority (<90%) of mice in the 14.3 ppm group had dysplastic and metaplastic changes that were associated with seropurulent rhinitis. At that time period, only a few mice in the 5.6 ppm exposure group had dysplasia, metaplasis or serous rhinitis in Level II. Mice in the 2.0 ppm group were generally free of significant lesions with only a few animals with serous rhinitis at 24 months.

One complication noticed during the Kerns et al. (1983) study was a spontaneous outbreak in rats of sialodacryeo-adenitis. 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 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.

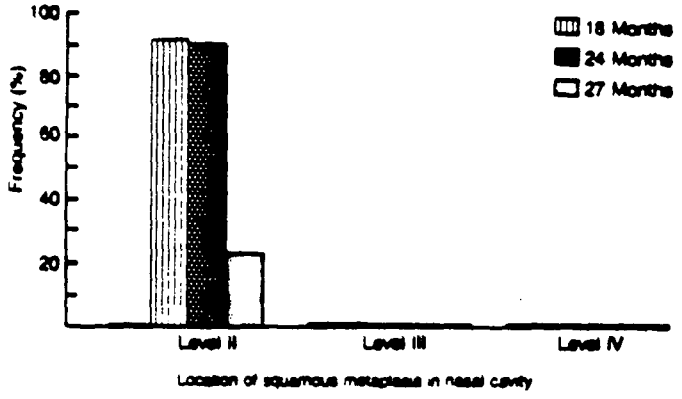


Figure 4-2. Frequency of squamous metaplasia in the nasal cavity of B6C3F$_1$ mice exposed to 14.3 ppm of formaldehyde gas. Figure taken from Kerns et al. (1983).

With regard to HCHO in the exposure chamber in the Kerns study, a panel of experts reviewed the method of generation of HCHO and monitoring and agreed that "the Battelle approach to HCHO vapor generation (heating paraformaldehyde) 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 Kerns (CIIT) 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 Sprague-Dawley 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 (based on authors' comparison of 20 exposure days at 100 ppb of BCME with 500 exposure days at 1 ppb of BCME) 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 uncertainty of comparing different factors involved in dose-rate versus total delivered dose in tumore induction is not resolved, however.

The second Albert et al. (1982) study, in which male Sprague-Dawley 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 of the study (Sellakumar, 1985). Work by Swenberg et al. (1984) in which Sprague-Dawley and Fischer 344 rats were exposed to 0, 10, 20 or 50 ppm of HCL gas for 6 hours per day, 5 days per week, for up to 90 days, indicates that HCL may be considerably less irritating to the upper respiratory tract of rats than HCHO. For those rats exposed for four days and killed 18 hours later, only the 50 ppm group had significant HCL-induced lesions, consisting of focal degeneration, epithelial hyperplasia, and early squamous metaplasia on the dorsal tip of the maxilloturbinate of the most anterior section. Since maximum nasal irritation in rats from HCHO occurs within a few days after exposure begins, the lack of significant nasal irritation from HCL in the 10 and 20 ppm groups indicates that HCL in the Albert study was not sufficiently irritating to draw conclusions regarding the role of irritation in HCHO-related carcinogenesis.

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

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

	Air controls (99 rats)	Colony controls (99 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	38	45	27
Papilloma or polyps	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

*From Sellakumar (1985)

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 Kerns, Albert and Tobe studies, the benign tumor response was markedly different. In the Kerns 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 Kerns, Fischer 344, but the small number used at each dose as compared to Kerns (32 vs. 240) may explain the 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 complete histopathology of nasal tissues was not reported.

In a study by Dalbey (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 life. 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, but survival time was reduced ($p<0.05$) relative to controls. 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 (1982) study with the Kerns et al. (1983) study. One factor that should be considered is that the pathology evaluation in the Dalbey (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 Kerns et al. (1983) study.

Also, the Kerns 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 (1982) study. If one compares the ppm-hrs/week received by rats at 5.6 ppm in the Kerns 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 250 ppm-hrs/wk ÷ 6 hr/day X 5 d/wk = 8.3 ppm). Since only two squamous cell carcinomas were seen in the Kerns et al. (1983) study out of 240 rats at 5.6 ppm, the likelihood of detecting a tumor in the

Dalbey (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%) for HCHO is approximately 32 ppm and for mice it is 3.1 ppm. If one assumes that a HCHO-related 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 (1982) study reduced their respiratory rate, which would further lessen the dose to target tissue.

Although an RD50 value for HCHO 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 Kerns 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. However, in studies by

Kendrick et al. (1976) and Rubin et al. (1978) in which the effects of tobacco smoke inhalation were investigated for rats and hamsters, it was found that at least for tobacco smoke, rats and hamsters had similar reductions in breathing rate and minute volume and in the amount of particulate matter retained in the test animals. Consequently, conclusions regarding the comparison of HCHO-induced respiratory changes in rats and hamsters must await further research.

In the second part of the Dalbey (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 per animal (tracheal tumors) was nearly doubled over DEN-only controls when HCHO was administered 2 days prior to each of 10 weekly DEN treatments, whereas post-HCHO treatment had no measurable effect. Thus, under conditions of the test, HCHO was 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 addition, survival in the HCHO-DEN groups was poor, which further complicates the findings of this part of the Dalbey study.

In a study by Rusch et al. (1983), 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, 0.20, 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 Kerns et al. (1983) study. In the Kerns 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 Kerns et al. (1983) study. This study design was unlikely to show any neoplastic response because of its small number of animals and 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 the experimental protocols used, 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).

In one experiment, Meuller et al. (1978), 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) and produced injection-site sarcomas.

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 and Trochimowicz, 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 and Ward (1983) has been interpreted as showing weak promoting activity of HCHO:acetone solutions on Sencar mouse skin. However, in another study by Krivanek et al. (1983) on CD-1 mice, no promotion was observed when nonirritating applications of HCHO:acetone solutions 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 (EPA, 1986).

In the case of HCHO, the Kerns et al. (1983) study (CIIT study)fits these criteria. 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 Kerns et al. (1983) study is consistent with EPA's Carcinogen Risk Assessment Guidelines (EPA, 1986). Since squamous cell carcinomas were the only statistically significant malignant tumors observed in the study, they are the primary end point 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 Kerns 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.

The PWG was asked to speculate 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

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. Significance determined for each dose level.

*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 Kerns et al. 1983.

Panel of the Consensus Workshop on Formaldehyde (1984). In addition, an analysis of the localization of the tumors observed in the Kerns study by Morgan et al. (1985) revealed that the squamous cell carcinomas generally occurred on the anterior portion of the lateral aspect of the nasoturbinate and adjacent lateral wall (57%) or the mid-neutral nasal septum (26%). In contrast, the polypoid adenomas were confined to a small area of the anterior nasal cavity and were restricted to the margins of the naso- and maxilloturbinates and lateral wall adjacent to these margins. Consequently, it appears unlikely that polypoid adenomas represent the benign counterpart of squamous cell carcinomas.

A small number of other cancers were seen in the Kerns 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."

Since an adenocarcinoma and a morphologically similar carcinoma were seen in the study, the polypoid adenomas may represent the benign counterpart of these lesions. 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." However, a recent analysis by Swenberg and Boreiko (1985) states that polypoid adenomas are likely to be the benign counterpart of adenocarcinomas and may be more common in control animals than previously thought. In the Kerns study, one polypoid adenoma was present in the same section as an adenocarcinoma in the 15 ppm exposure group. In contrast, no adenocarcinomas were found in the 2 or 6 ppm exposure group, even though more polypoid adenomas were found at each of these two exposure levels than at 15 ppm. Even if polypoid adenomas are considered to be the benign counterpart of adenocarcinomas, the conversion rate is low (a conversion ratio of 1:15). 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 Kerns et al. (1983) study only polypoid adenomas were observed. This intraspecies (and intrastrain since Tobe et al. and Kerns et al. used Fischer 344 rats) difference also adds 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.

Because the nature and progression of benign nasal tumors is not well understood, studies on other chemicals can be looked to for elucidation.

Studies by Lee and Trochimowicz (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 (DNP), and 1,2-dibromo-3-chloropropane (DBCP), respectively. In the Reznik et al. (1980) study on DBCP, 78% of the tumors in male and 66% in female F-344 rats 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 with DNP using F-344 rats 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 and Trochimowicz (1982, 1984) using Sprague-Dawley rats 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, squamous carcinomas apparently arise from inverted papillomas rather than exophytic papillomas (Takano et al., 1982).

The experience with other chemicals (see Lee and

Trochimowicz, 1982) and the foregoing illustrate the variability of the types and locations of the tumors found. Also, except in limited cases, the progression of preneoplastic and benign neoplasms to malignant neoplasms is not known with any assurance. 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.

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 for analysis purposes (see Sections 7.2 and 7.4).

4.3. Short-Term Tests: Genotoxicity and Cell Transformation

HCHO affects genetic material in a wide range of test systems (Auerbach et al. (1977); Ragan and Boreiko (1981); Boreiko et al. (1982); Golmacher and Thilly (1983); Ulsamer et al. (1984); Consensus Workshop on Formaldehyde (1984); Dooley et al. (1985); Ma et al. (1985); Scott et al. (1985); Cantoni and Cattabeni (1985), and Stankowski et al. (1986)). Mutagenic activity of HCHO has been demonstrated in viruses, Escherichia

coli, Pseudomonas pluonescens, Salmonella typhimurium, and certain strains of yeast, fungi, Drosophila, grasshopper, and mammalian cells (Ulsamer et al., 1984). HCHO's ability to cause gene mutations, single strand breaks in DNA, DNA-protein cross-links, sister chromatid exchanges (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). In a study by Ragan and Boreiko (1981), treatment of C3H/10T½ cells with HCHO did not result in significant rates of transformation. However, if HCHO treatment was followed by continuous treatment with the tumor promoter 12-0-tetradecanoyl phorbol-13-acetate, significant transformation occurred. 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 its effects on 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 certain bacterial tests it might be considered weak acting, but in a recent NTP Drosophila sex-linked recessive lethal test, HCHO would not be considered a weak acting mutagen (Woodruff et al., 1985). In fact, in some cases HCHO is used as a test standard. In vitro Cytogenetic studies have shown HCHO to be an efficient inducer of sister chromatid exchanges (SCEs) and chromosomal aberrations (Natarajan et al., 1983).

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 to 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, suggesting HCHO could exert its effects by both damaging DNA and inhibiting DNA repair.

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 xeroderma pigmentosum. Exposure of these cell types to HCHO caused similar levels of DNA-protein cross-links and removal of such cross-links in all cell types. The half-life for the cross-links was about 2-3 hours. An examination of the induction and repair of DNA single-strand breaks showed that the production of the breaks was dose dependent, and that there removal occurred at rates similar to the removal of cross-links. In addition, the results indicate that exposure to HCHO causes single-strand breaks without the involvement of excision repair, and that excision repair of HCHO damage may increase the single-strand break 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's inhibiting O^6-methylquanine repair (Grafstrom et al., 1985).

However, the results of a study by Snyder and Van Houten (1986) question the finding of Grafstrom et al. (1983) that HCHO inhibits UV-induced, unscheduled DNA synthesis. They found that the inhibition only occurs when thymidine is used as a precursor, which suggests an uptake artifact. Also, their results indicate that HCHO has no significnat effect on the rate of repair of x-ray-induced strand breaks or those by bleomycin. Consequently, Snyder and Van Houten believe that it is likely that HCHO has no significant effect on the sealing of most DNA breaks in human fibroblasts; their work did not support a conclusion that the ligation step of excision repair is preferentially sensitive to HCHO.

In a study by Craft and Skapek (1986) using human lymphoblasts, it was found that when these cells were exposed in vitro to HCHO using single or multiple treatment regimens, a difference in the cumulative induced mutant fraction was observed. Single treatment exposures (0-150 uM X 2 hr) resulted in a nonlinear increase in induced mutant fraction. The multiple

exposure experiment using either three treatments of 50 uM X 2 hr, five treatments of 30 uM X 2 hr, or ten treatments of 15 uM X 2 hr, all treatments administered on alternative days, resulted in additive (linear) increases in mutant fraction.

The multiple treatment regimen produced a lower rate of mutations compared to an equivalent single dose; an induced mutant fraction of $2.2 \pm 0.2 \times 10^{-6}$ for the five 30 uM exposures vs. $4.8 \pm 0.4 \times 10^{-6}$ for the single 150 uM treatment.

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 and Buck, 1984). Whether Casanova-Schmitz et. al. measured covalent binding of HCHO to macromolecules has

been questioned. See section 4.5.2 for a further discussion of this issue.

Various studies have been undertaken to determine whether HCHO has genotoxic effects 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 specify, 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 sister chromatid exchanges (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 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 observed 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 a study reported 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. Mierouskiene' and Lekevicius (1985) have reported a statistically significant increase in chromosome aberrations in a group of 50 workers exposed to phenol, styrene, and HCHO. The control group consisted of 25 individuals which had no occupational exposure to chemical substances. The finding of increased chromosome aberrations was independent of age, exposure length, and smoking habit. In a study by Bauchinger and Schmid (1985) using lymphocytes from 20 males exposed to HCHO and unexposed males employed by a paper factory, a significantly increased incidence of dicentrics or dicentrics and ring chromosomes was observed for 11 exposed workers employed as supervisors. Their total mean exposure time was 2.5 times longer than for the 9 exposed paper machine operators. SCE values were not significantly different for smoking and nonsmoking HCHO workers when compared with the control group.

No genetic effects in humans were seen in studies by Fleig et al. (1982), Ward 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. In the Ward 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.

Finally, Connor et al. (1985) examined the mutagenicity of urine from HCHO-exposed autopsy service workers. An exposed group of 19 and a control group of 20 were matched by sex, age, and use of tabacco, alcohol, and recreational drugs. Urine

samples were tested using S. typhimurium TA100 and TA98 with and without S9 activation. Except for a sample from a smoker in the control group and three samples from an individual receiving metronidazole therapy, most samples produced little or no increase in revertants using either strain. However, a significant number of the samples from the exposed group were toxic to TA100 and TA98. Similar findings have been reported for aluminum workers (exposed and control) and in nursing personnel. The toxicity from the three studies appear to be identical, but the toxicant has not been identified (Connor et al., 1985).

As noted above, the literature reports conflicting data concerning chromosomal effects in humans. However, the weight of these data seems to indicate little potential for these effects in the workplace, but this judgement must be tempered by the limitations of the studies.

4.4. Other Effects/Defense Mechanisms

4.4.1. Introduction

The cancer response observed in the Kerns 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 the nature of the effects themselves, and how they may relate to results seen in long-term animal tests of HCHO, by examining three subject areas: sensory irritation; cell-proliferation; and the mechanics of the mucous layer "defense" system.

4.4.2. Sensory Irritation

In the Kerns 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, 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 the 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. Also, it should be noted that respiratory rate suppression could change over the course of a chronic study (Dallas et al. 1985).

In the case of the Kerns 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.

The evidence indicates that mice are more sensitive or better able to respond 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 Kerns 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 tobacco smoke is similar (as discussed in the section on animal tests, two factors may account for the absence of an observed effect in hamster; limited pathology work in the study, and a low test dose.

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.

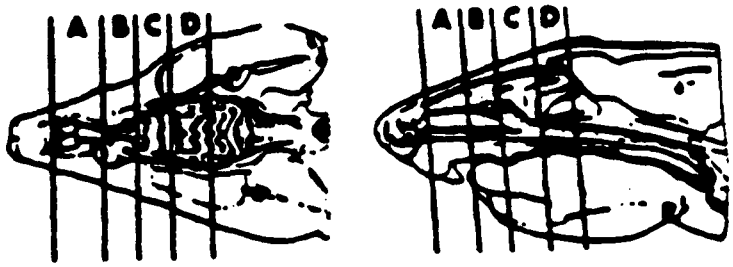


Figure 4-3. Drawing indicating the level of sections from the nasal passages of rats and mice. Figure taken from Swenberg et al. 1983.

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 (LEVEL B)*

Post-Exposure Time of Pulse	% Labelled Cells**	
	O/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 mucociliary 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. Perhaps the ability of mice to reduce their breathing rate at high HCHO concentrations played a role.

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 Kerns 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 for metaplasia.

In the Kerns 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 these effects are important determinants in HCHO induced carcinogenicity and that they help explain the nonlinearity of the cancer response. Another factor suggested to contribute to the possibility of a nonlinear response is the role of the mucous layer in trapping and removing HCHO. This hypothesis is that when its removal capacity is exceeded or its flow impeded, 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 Kerns 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 rough comparison can be made. The incidence of squamous metaplasia in level 2 (level B in Figure 4-3) 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, incidence of squamous metaplasia alone does not appear to explain the extreme nonlinearity observed. A major limitation of this comparison is that it does not account for the severity and extent of the lesions which presumably increased at higher concentrations.

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 and hexamethyphosphoramide (HMPA) are cytotoxic and cause cancer in rats. Data on these chemicals may provide some insight.

If one examines the incidence and severity of the noncarcinogenic lesions seen in the Woutersen (1985) 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 anatomical region that had a high incidence of noncancer lesions that was 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 (1984)

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 and Trochimowicz (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 Kerns 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 for HCHO to interact with single-strand DNA during cell replication or to promote an initiated cell. Consequently, prudence would dictate that situations which cause cell proliferation or lesions should also be avoided. This includes short-term peaks especially if cell proliferation and cytoxicity contribute to the carcinogenic process. Also, it must be remembered that there is a natural background rate of cell turnover 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 in individuals 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 or the absence of a carcinogenic response. For instance, the well-known carcinogen urethan causes skin tumors (papillomas and squamous cell carcinomas) in mice, but not epidermal hyperplasia or inflammatory reactions (Iversen, 1984).

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 ability to cause ciliastasis and cell mortality at elevated concentrations. In addition, it has been postulated that below certain HCHO concentrations (1-2 ppm) the mucous layer can trap and remove much inhaled HCHO, thus preventing it from reaching underlying cells. However, once the mucous layer is saturated, HCHO can then begin to affect the underlying cells as described in the section above. When this occurs, the mucociliary clearance system is seriously compromised which allows a greater amount of HCHO to reach the respiratory epithelium. If the mucous layer removed most 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. The discussion below describes the effects caused by HCHO on the mucociliary system and its role in protecting the nasal mucosa.

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, 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 impinged 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. (1983, 1984, 1986) 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

accompanied by ciliastasis was evident in a number of anatomical regions of the rat nasal cavity. In another study by Morgan et al. (1986), male rats were exposed for 6 hours per day for 1, 2, 4, 9, or 14 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. 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 mucostasis, 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 mucostasis 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 Kerns et al. (1983) study. Recent work by Bogdanffy et al. (1985) demonstrated the ability of HCHO to bind with proteins in human and rat nasal mucus and bovine serum albumin. Incubation of HCHO in vitro with these materials indicated that binding is rapid and that the main binding constituent in nasal mucus is albumin. Consequently, some fraction of inhaled HCHO would be expected to be bound and removed, thus protecting the underlying epithelium.

Whether the mucous layer has some finite capacity to absorb, retain, bind, and metabolize 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 can 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 Kerns 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). However, the finding is complicated by the fact that labelled extracellular as well as intracellular protein was measured and the fact that the overall results of this study have been questioned. Consequently, the relative proportions of these two constituents may not be able to be compared at each dose level. A discussion of the formation of DNA-HCHO adducts as studied in this experiment may be found in section 4.5.2.4.

Finally, no data exist to show that other than a constant proportion of HCHO reaches the respiratory epithelium at concentrations below 2.0 ppm, levels that are generally not acutely toxic to the underlying cells. At higher concentrations, above the acute toxicity threshold, it is reasonable to expect that higher, nonconstant proportions of HCHO reach the underlying cells because of damage to and eventual destruction of the mucociliary clearance system.

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 Kerns 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 suggest that it does play a role. Although data show that HCHO reacts 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. 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 Kerns 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 target tissue dose is plotted rather than concentration.

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 Kerns et al. (1983) study. However, an examination of the data described in the sections above (1) does not support the concepts that the action of the mucous layer presents a barrier to HCHO or that it causes a nonlinear relationship between air concentrations and the amount reaching target cells at levels below overt acute toxicity, (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). Nasal deposition in rats in excess of 98% has been reported (Dallas et al., 1985). 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, and 0.20 umol/g for liver. Inhalation of 6 ppm HCHO for 6 hrs/day for 10 days did not significantly alter the nasal mucosa, brain, and liver HCHO concentrations. A study by Bogdanffy et al. (1985) demonstrated that nasal mucus reacts rapidly with HCHO, and suggests that the main binding constituent in nasal mucus is albumin.

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 (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 <u>in vitro</u> diffusion studies using rabbit skin indicate that free HCHO cannot be detected enzymatically.

In a study by Bartnik et al. (1985), the percutaneous absorption of HCHO was determined by applying [^{14}C] HCHO-containing cream (0.1% HCHO) to the backs of rats. Over 70% of the radiolabel was found in the treated skin, 2.3% in urine, 1.8% in the carcass, 0.7% in feces, and 1.3% in CO_2 after 48 hours. Thus total percutaneous absorption was 6.1% of the applied dose. However, some fraction of this number may represent methanol or formic acid which was present in the radiolabelled sample (2 and 3%, respectively). Similar results were obtained by Robbins et al. (1984) using rabbits to which ^{14}C-labelled HCHO was applied as a solution under an occluded patch. Concentrations up to 37 ug HCHO per patch did not significantly alter the proportion absorbed. When ^{14}C-labelled DMDHEU containing cloth was applied to the backs of rabbits under various occlusion/perspiration conditions, only insignificant amounts of the radiolabel penetrated the epidermis. Even under the most severe test condition, only 2.5% of the radiolabel was transferred from the cloth to the animal of which 80-90% was found in the skin directly under the patch.

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 formate levels (Einbrodt et al., 1976). Gottschling et al. (1984) studied a group of veterinary medical students exposed to HCHO. An examiniation of

pre- and post-exposure urine samples did not indicate a formic acid shift. 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. Reaction with Glutathione

The intracellular level of glutathione (GSH) affects the metabolism and toxicity of HCHO. In a study by Ku and Billings (1984), the relationship between HCHO metabolism and toxicity and GSH concentration in isolated rat hepatocytes was investigated. When hepatocytes were pretreated with diethyl maleate (DEM) to deplete GSH, the initial rate of HCHO disappearance was decreased approximately 50%. The concentration of HCHO used (5.0 mM) was not toxic to DEM-treated or untreated cells. Thus cell viability was not a factor. HCHO was also shown to decrease GSH intracellular concentration in a dose and time-dependent manner. DEM treatment followed by HCHO addition caused a similar reduction in GSH concentrations even though DEM pretreatment resulted in varying GSH concentrations. In studies measuring the cell toxicity of HCHO, it was found that DEM pretreatment greatly decreased cell viability, whereas HCHO treatment alone did not after 60 minutes. When DEM was added to incubations containing HCHO, toxicity was increased at all incubation times. Only at 120 minutes was there substantial toxicity in the HCHO only treatment group. DEM/HCHO treatment increased lipid peroxidation at HCHO concentrations which decreased cell viability in other studies. DEM alone had no affect on lipid peroxidation. To determine if the enhanced toxicity is due to DEM treatment and

consequent reductions in GSH concentrations, L-methionine was added to DEM/HCHO treated cells. L-methionine treatment reduced reduction in GSH concentration and prevented HCHO stiumulation of lipid peroxidation and loss of cell viability. Thus, enhanced toxicity can be traced to the effects of DEM on GSH concentrations. As a further check on this hypothesis, the addition of free radical scavengers, ascorbate, BHT, and -tocopherol protected the cells from HCHO induced toxicity in DEM-pretreated cells. On the contrary, the addition of scavengers had no effect on HCHO-induced toxicity in the absence of DEM treatment, which suggests a non-free-radical mode of toxicity.

In studies using isolated, perfused rat lungs and livers, Ayres et al. (1985) reported dose-related reductions in GSH concentrations. However, the concentrations needed to significantly reduce GSH levels are many times higher than those expected in the environment. Studies by Heck et al. (1980) and Casanova-Schmitz et al.(1984) indicate that carcinogenic concentrations of HCHO in the rat (15 ppm) did not reduce nonprotein sulfhydryl levels in rat nasal tissue or produce plasma HCHO levels approaching the lowest HCHO concentration causing GSH depletion in isolated lung/ liver. Thus, GSH depletion does not appear to be a critical factor in HCHO-related toxicity (Ayres et al., 1985).

The role of GSH depletion on the formation of DNA-protein cross-links (DPX) has been reported by Casanova-Schmitz and Heck

(1984, 1985). It was found that when GSH levels were depleted by phorone, increases in interfacial (IF) DNA (a measure of DPX) and the concentration of DPX in isolated DNA were observed. The yield of DPX was reported to increase nonlinearly with HCHO concentration for both normal and GSH depleted rats. In addition, DPX yields were greater at low HCHO concentrations in GSH depleted rats indicating that the metabolism of HCHO at low concentrations may be more effective (the significance of the reported nonlinearity in the formation of DPX is discussed in section 4.5.2.4). However, a study by Lam et al. (1985) reported that the concentration of nonprotein sulfhydryls in rat nasal mucosa was not significantly reduced at 6 or 15 ppm HCHO, which indicates that HCHO's toxic effects at these levels are not related to GSH depletion.

4.5.2.3. 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 and Jones (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.

In a study of the disposition of HCHO in mice, Billings et al. (1984) found that 70-75% of i.p. injections of 6 mg/kg or 100 mg/kg of ^{14}C-HCHO was exhaled as CO_2 within 4 hours, with an additional 10% exhaled at the end of 24 hours. When the rates of CO_2 excretion between mice dosed with 100 ug/kg HCHO or 100 mg/kg formate were examined, it was found that the rate of CO_2 excretion in mice given HCHO was slower than the formate-dosed mice. Since formate is an intermediate in HCHO oxidation, the authors speculated that HCHO might accumulate in tissues. However, subsequent testing did not bear this out. Robbins et al. (1984), using rabbits found the following distribution of radioactivity 48 hours after intravenous injection of ^{14}C-HCHO: blood 1.58%; skin/muscle/organs 3.26%; urine 4.14%; and 37.03% in CO_2.

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.

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.

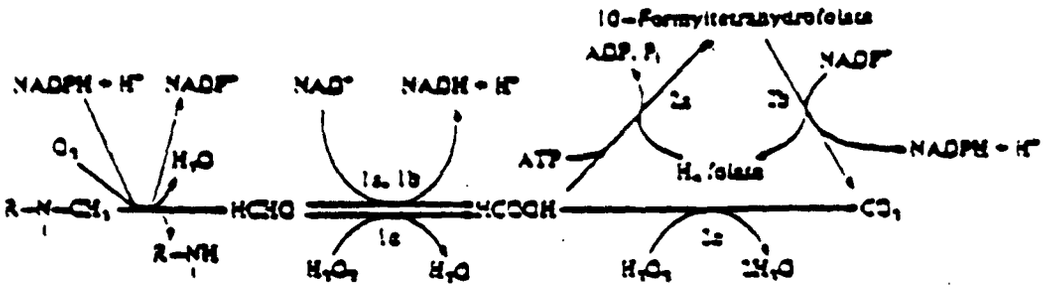
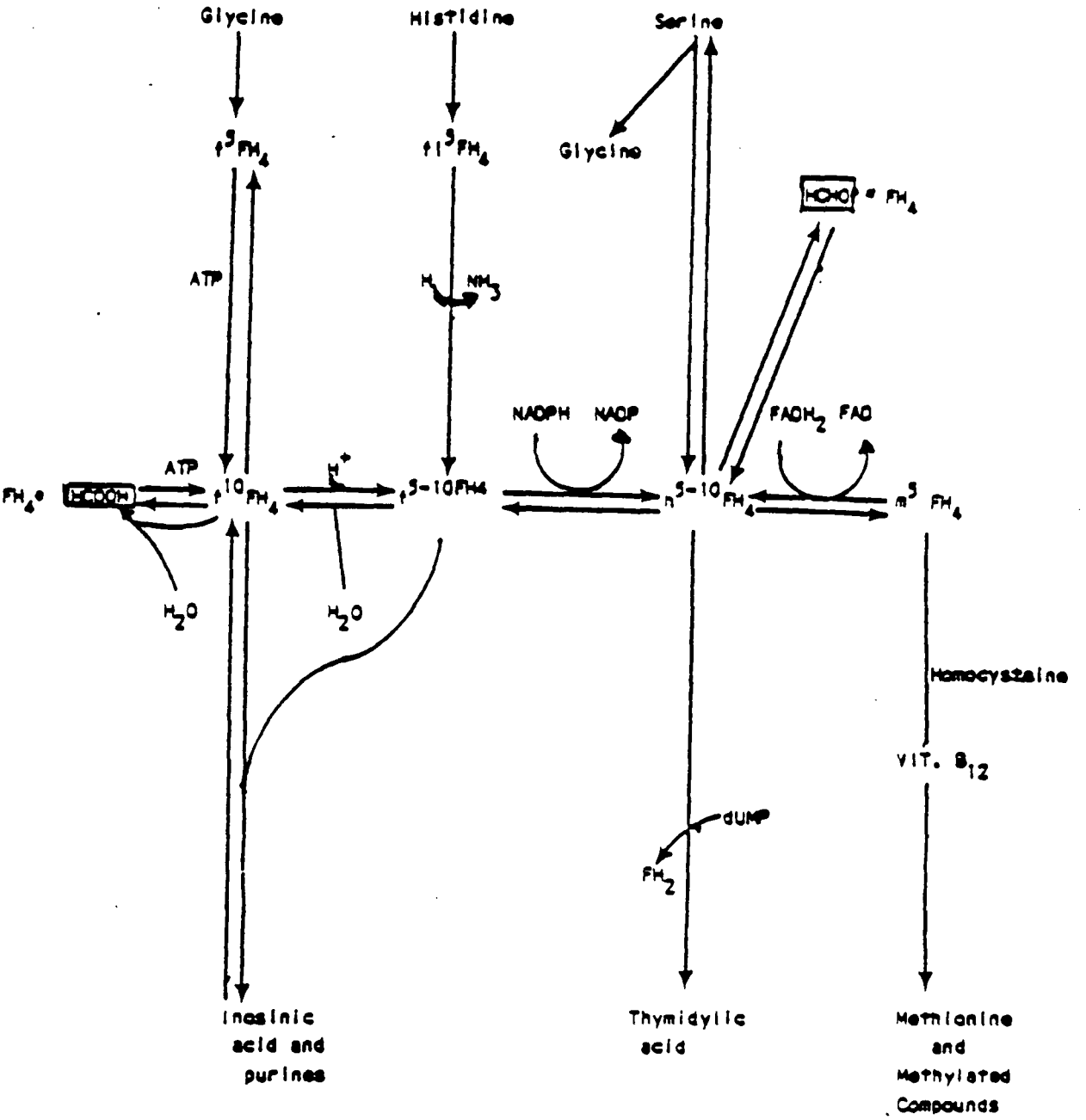


Figure 4-4. Simplified reaction sequence from drug N-demethylation (cytochrome-P-450-dependent monooxygenase) to HCHO, formate, and CO_2 production (from Waydhas et al., 1978). Reactions are: 1a, HCHO dehydrogenase (GSH); 1b, aldehyde dehydrogenase; 1c, catalase (peroxidatic mode); 2a, 10-formyltetrahydrofolate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

4.5.2.4. Reactions with Macromolecules

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, RNA and DNA (Ulsamer et al., 1984; Casanova-Schmitz and Heck, 1983, 1984; Consensus Workshop on Formaldehyde, 1984; Mizenina et al., 1984; Solomon and Varshavsky, 1985; Schouten, 1985; Foekens, 1985).

A recent study by Casanova-Schmitz et al. (1984) has reported the difference between metabolic incorporatin 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 difference between metabolic incorporation and covalent binding was determined by the use of a phenol extraction procedure. This procedure allows the separation of macromolecules into phases after centrifugation (aqueous (AQ), organic, and interfacial (IF) phases). DNA can be recovered from both the AQ and IF phases. The convalently bound DNA is recovered from the IF phase. In this way, the authors claim that the relationship between metabolically labelled DNA and cross-linked DNA can be determined. 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 (intra- and extracellular) 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 and Buck, 1984).

The Casanova-Schmitz study has been reviewed by Cohn et al., 1985, EPA, and the Science Advisory Board (SAB) (1985). Its implications for quantitative cancer risk assessment have also been addressed. Cohn et al. came to the conclusion that the data were interesting but preliminary in nature and thus not useable as input to quantitative risk assessment. The SAB is composed of a group of non-EPA scientists who advise the Administrator of EPA regarding the scientific adequacy of agency risk assessments, testing and assessment guidelines, research proposals, etc. The Agency agreed with the SAB to seek a review of the study by an independent group of scientists. The group's report to EPA (Report No. TR-835-20, Expert Review of Pharmacokinetic Data: Formaldehyde) is provided in Appendix 1 and is summarized by the group as follows:

1. Some doubt still remains as to the validity of the assumptions which form the basis for distinguishing metabolically incorporated and crosslinked (or adducted) CH_2O, i.e., $^{3}H/^{14}C$ in DNA.

2. Experimental methods and controls were adequate with respect to monitoring the CH_2O administration and analysis of dual-labeled materials. However, the chloroform/iso-amylalcohol/phenol extraction for DNA and DNA crosslinked to proteins was not validated in terms

of the identities of materials separated nor the overall efficiency and consistency of extraction. The occurrence of underlying variability of incorporation due to kinetic isotope effects on the disposition of tritiated CH_2O can neither be assessed nor discounted.

3. Sufficient documentation is still unavailable to state unequivocably that all the crosslinked DNA-protein complexes occur in the IF-DNA fraction.

4. There remains a need for an effective biochemical dosimeter to measure the dose of CH_2O delivered to the cells of the nasal epithelium. The data provided by Casanova-Schmitz et al. are not considered a sufficiently well-validated measure of this parameter.

5. The nonproportionality of the calculated concentration of bound ^{14}C (CH_2O)-DNA as a function of the administered dose is documented adequately. Whether the nonproportionality truly reflects crosslink formation or is due to the small sample size, to a constant loss in the recovery of IF-DNA, or to artifactual disturbances in the $^{3}H/^{14}C$ ratio remains to be elucidated.

6. The increase in concentration of bound ^{14}C with the concentration of CH_2O is well documented, as is the increase in the difference in the $^{3}H/^{14}C$ ratio between IF-and AQ-DNA. The power of separate comparisons for the 0.3 and 2 ppm doses is low because of small sample size relative to the coefficient of variation. This limits the potential for inferences about no-response levels and low-dose extrapolations.

7. The study of Casanova-Schmitz et al. is an important first step toward quantitative assessment of the intracellular level of CH_2O in the nasal mucosa of the rat following inhalation exposure. At its present level of validation, however, it does not provide a basis for such quantitation. Furthermore, the selection of an acute study model may not be appropriate to the assessment of chronic toxicity.

In response to the report, the Chemical Industry Institute of Toxicology (CIIT) submitted detailed comments which strongly disagree with the expert groups conclusions. CIIT's comments are provided in Appendix 1. As with many emerging areas of investigation there are bound to be disagreements among

scientists. This is one of those cases. Additional work underway at CIIT using primates may resolve areas of disagreement. Until the issues raised concerning the Casanova-Schmitz study are resolved, this study will not be used as a basis for an alternate measure of HCHO exposure.

4.5.2.5. 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. HCHO is also produced from a wide range of xenobiotics (Dahl and Hadley, 1983). Cytochrome P-450-dependent N-demethylation of drugs can contribute HCHO. 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*. The role of HCHO in xenobiotic transformation has also been studied (Kucharczyk et al., 1984).

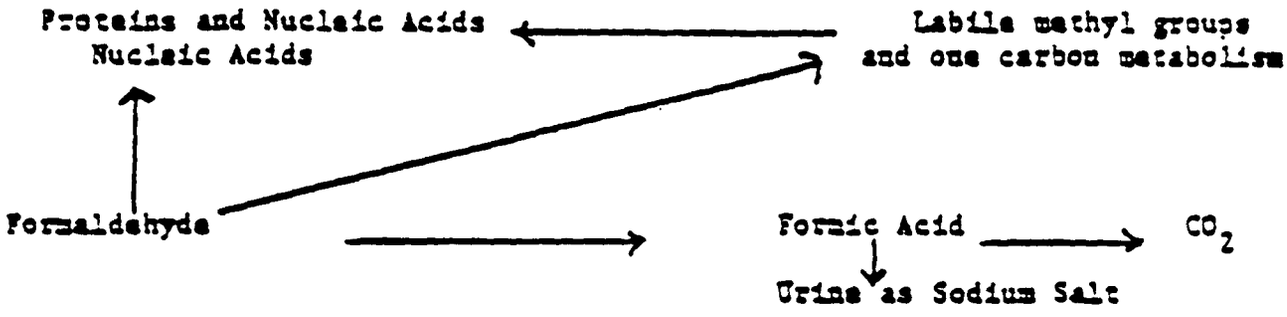
Whereas the conversion of HCHO to CO_2 occurs in a similar manner in the different species studied, the relative importance of each reaction differs among species and tissues. Thus, the rat is able to convert formate to CO_2 at more than twice the rate

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 (this may be a function of the analytic technique and not necessarily the absence of free HCHO), 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 occurs, 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 with assurance at this time. However, Casanova-Schmitz et al. (1984) have made an important contribution in this area. Egle's work (1972) suggests that the respiratory tract tissues would receive the greatest dose. Although effects at other body sites cannot be ruled out, the weight of the evidence indicates that effects at sites distant from the area of exposure would not be expected.

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 HCHO-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, 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). A group of 210 male hamsters, which were further divided into six subgroups of 35 each, 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. A group of 210 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, groups of 35 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 inhibited the 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. Following the 52-week treatment period, there was a 29-week recovery period after which all hamsters were killed 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 Woutersen et al. (1985) 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 27 months. There were 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.

Table 4-12.
Nasal and Laryngeal Cancer in Rats Treated with Acetaldehyde by Inhalation for 27 Months (Woutersen et al. 1985)

Site and Tumor Type	Incidence [a]							
	Males				Females			
	Acetaldehyde (ppm)				Acetaldehyde (ppm)			
	0	750	1500	3000	0	750	1500	3000
Nose								
Papilloma	0/49	0/52	0/53	0/49	0/50	1/48	0/53	0/53
Adenocarcinoma	0/49	16/50[b]	30/53[b]	20/49[b]	0/50	6/48[c]	26/53[b]	20/53[b]
Carcinoma *in situ*	0/49	0/49	0/53	1/49	0/50	0/48	3/53	5/53
Squamous cell carcinoma	1/49	1/49	10/53[b]	14/49[b]	0/50	0/48	5/53	17/53[b]
Metastasizing squamous cell carcinoma	0/49	0/49	0/53	1/49	0/50	0/48	0/53	0/53
Larynx								
Carcinoma *in situ*	0/49	0/49	0/53	0/49	0/50	0/48	1/53	0/53

[a] Incidence is expressed as the number of animals with tumors over the number of animals examined.

[a] $p \leq 0.01$

4.7. Epidemiologic Studies Reviewed

4.7.1. Introduction

The EPA has reviewed the available cohort and case-control studies related to formaldehyde. Many of these studies have been released within the past three years. Only one study is currently ongoing which relates to evaluating human risks associated with formaldehyde exposure a case-control study of nasal cancers by the Centers for Disease Control. Only cohort and case-control designed studies were analyzed for this review since they yield the best quality of information for judging causality. Table 4-13 identifies these studies. Although these studies are of optimal designs for evaluative purposes, many studies suffer from limitations that can potentially influence their conclusions. Major drawbacks are: (1) the inference of formaldehyde exposure levels from industrial hygiene data; (2) the inability to completely separate the contributions of HCHO from the contributions of other occupational or personal exposures; (3) small sample sizes for the cohort studies; (4) small numbers of observed site-specific deaths; and (5) insufficient follow-up.

One outcome of the design limitations is low statistical 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,

*The power of a study is the ability to detect true association of the exposure and disease. If a study is likely to conclude that the exposure is not associated with a disease, when in fact an association existed, it has a low power for detecting that association.

Table 4-13

Summary of Studies Relevant To Formaldehyde

	Type of Study	Author	Study Group	Referent Group	Exposure Data
1.	SMR	Matanoski (1982)	Pathologists	a) U.S. white male age and calendar year-specific mortality rates; b) members of the American Psychiatric Association	Absent
2.	SMR	Harrington and Shannon (1975)	Pathologists	Ireland, Wales or Scotland male age and calendar year specific mortality rates	Absent
3.	SMR	Harrington and Oakes (1982)	Pathologists	Ireland age-sex and calendar year-specific mortality rates	Absent
4.	SMR	Levine et al. (1984)	Ontario morticians (male)	U.S. white male age and calendar year-specific mortality rates	Inferred[a]
5.	SMR	Stroup et al. (1984)	Anatomists	a) Psychiatrists; b) U.S. white male age-specific mortality rates	Inferred[a,b]
6.	SMR	Wong (1983)	Chemical workers	U.S. age-sex and calendar year-specific mortality rates	Absent
7.	SMR	Tabershaw Associates (1982)	Chemical workers	U.S. age-sex and calendar year-specific mortality rates	Absent
8.	SMR	Acheson et al. (1984a)	Chemical workers	Male mortality rates of England/Wales	Present
9.	SMR	Marsh (1983)	Chemical workers	U.S. age-race-sex and calendar year specific mortality rates	Absent
10.	SMR	Bertazzi et al. (1984)	Formaldehyde resin workers	National and local male specific mortality rates	Inferred[a]
11.	SMR	Blair et al. (1986, 1987)	Formaldehyde producers or users	U.S. ae-race-sex and calendar year specific mortality rates	Present
12.	SMR	Stayner et al. (1986)	Garment workers	U.S. age-race-sex and calendar year-specific mortality rates	Present
13.	PMR	Walrath and Fraumeni (1983)	N.Y. embalmers and funeral directors	U.S. age-race and calendar year-specific proportions of deaths	Inferred[a,b]
14.	PMR	Walrath and Fraumeni (1984)	California embalmers	U.S. age-race and calendar year-specific proportions of deaths	Inferred[a,b]
15.	PMR	Marsh (1983)	Chemical workers (male)	U.S. age-race-sex and calendar year-specific proportions of deaths	Absent
16.	PMR	Liebling et al. (1984)	Formaldehyde production chemical workers	U.S. white male age and calendar year-specific proportions of deaths	Absent
17.	PMR	Stayner et al. (1985)	Garment workers	U.S. age-race and calendar year-specific proportions of deaths	Inferred[a,b]

Table 4-13 (cont.)

Type of Study	Author	Study Group	Referent Group	Exposure Data
18. PMR	Delzell and Grufferman (1983)	Textile workers	U.S. age and calendar year-specific proportions of white female deaths	Absent
19. Case-Control	Fayerweather et al. (1982)	Chemical workers	One male employee matched for age, adjusted service date, plant location and pay class	Present
20. Case-Control	Brinton et al. (1984a)	Nasal and paranasal sinus cancer cases in NC 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	Present
21. Case-Control	Tola et al. (1980)	Nasal and paranasal sinus cancer cases in Finland	One non-respiratory cancer control matched for age and sex	Present
22. Case-Control	Hemberg et al. (1983)	Nasal and sinonasal cancer cases in Finland, Sweden, and Denmark	One colorectal cancer control matched for age-at-diagnosis, sex and country	Present
23. Case-Control	Hardell et al. (1982)	Nasal and nasopharyngeal cancer cases in Sweden	Referent group identified from previous study (Hardell et al., 1981)	Present
24. Case-Control	Olsen et al. (1984)	Nasal and sinonasal cancer cases in Denmark	Colon, rectum, prostate or breast controls matched for age-sex-year of diagnosis	Present
25. Case-Control	Hayes et al. (1986)	Nasal and sinonasal cancer cases in Holland	Living and deceased population controls	Present
26. Case-Control	Roush et al. (1985)	Sinonasal and nasopharyngeal cancer in Connecticut	Controls sampled from Connecticut death certificates	Inferred[b]
27. Case-Control	Partenen et al. (1985)	Respiratory cancer cases from a retrospective cohort of male woodworkers	Three controls selected from the cohort and matched for age	Present
28. Case-Control	Vaughan et al. (1986a,b)	Sinonasal and pharyngeal cancer in Washington	Controls sampled from population matched for age and sex	Present

[a]Exposure levels are inferred from industrial hygiene studies of similar workers.
[b]Exposure levels are inferred from number of years employed in occupation.

magnitude of the increase, background incidence of the disease, desired statistical significance, and type of analysis.

Several newly released studies have strengthened our knowledge regarding the potential carcinogenicity of HCHO. These new studies have contributed stronger evidence and suggest that HCHO may be a human carcinogen. In particular 9 studies (Acheson et al., 1984a; Blair et al., 1986, 1987; Hardell et al., 1982; Hayes et al., 1986; Stayner et al., 1985; and Vaughan et al., 1986b) show among different groups statistically significant associations between site-specific respiratory cancer and exposure to HCHO-containing products. Three of these studies (Blair et al., 1986; Blair et al., 1987, Stayner et al., 1986; and Vaughan et al., 1986a,b) were specifically designed to detect moderate elevations in human risk. In addition, 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 remain when other professional or like socioeconomic groups are used as referents.

4.7.2. Review of Studies Overview and Discussion

Twenty-eight studies (Table 4-13) of populations that may have been exposed to HCHO have been reviewed. Appendix 2 contains a description of each of the studies. These studies were of cohort or case-control designs. Results were expressed as Standardized Mortality Ratios or Proportionate Mortality Ratios ** or as odds ratios***. Eleven studies were of chemical or industrial workers and seven studies were of medically-related professions. For medically-related professions, e.g., morticians, embalmers, anatomists, and pathologists, the exposure was to formalin. This group has diverse chemical exposures, but formalin is one exposure which is common. Ten other case-control studies examined occupational etiologies of sinonasal cavity and pharyngeal cancers. Exposure in these studies was examined directly by quantitating HCHO levels or indirectly through

**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 SMR analysis uses death rates of a general population to derive the expected number of deaths. Proportionate Mortality Ratios (PMR) are measures in which the cause-specific proportions of mortality among the exposed (observed deaths) are compared to the expected proportion of deaths among the unexposed (general population). In the PMR study, large excesses of deaths due to one cause can deflate the remaining proportions and can, thus, bias comparisons of the other causes of deaths.

***The odds ratio (OR), 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.

particular occupations where HCHO exposure has been known to occur.

The sparsity of individual exposure data made it difficult to separate formaldehyde from the other occupational or residential exposures. Table 4-14 shows that twelve studies have exposure data for individual members of the study; 6 of these studies (Acheson et al., 1984a; Blair et al., 1986; Stayner et al., 1986; Fayerweather et al., 1982; Partanen et al., 1985; and Vaughan et al., 1986) have enough information to examine an exposure-response gradient. Other studies inferred exposure by citing previous industrial hygiene data of similar occupational groups. This review used exposure estimates identified in EPA (1984b) of similar occupations as a surrogate for those epidemiologic studies where exposure levels were not identified. It is not known whether the individuals under study did or did not have formaldehyde exposures at the levels identified in EPA (1984b). Table 4-14 presents exposure estimates for occupations identified in this review.

Each of the 28 studies has been evaluated with respect to bias, confounding, and chance. Excesses, both statistically significant and not statistically significant, in site-specific mortality have been emphasized in this review. Deficits were also noted. Deficits are hard to interpret except when examining therapeutic treatments. Findings that are not statistically significant are important in light of the small numbers of site-specific neoplastic deaths expected or observed in many of the studies (usually fewer than 5 deaths). Low statistical power is

Table 4-14

Formaldehyde Levels to Which Occupational Groups Might Be Exposed

Occupation	Average Formaldehyde Level (ppm)	Reference
Embalmers	0.3 - 0.9	Levine, 1984
	0.2 - 0.9	NIOSH, 1980
	0.1 - 5.3	Kerfoot and Mooney, 1
	1.37 - 1.70	EPA, 1984b
Anatomists	0.07 - 0.14	Stroup, 1984
Pathologists	0.85[a], 3.2[b]	EPA, 1984b
Resin Manufacturing	2.2 - 3.3	Bertazzi et al., 198
	0.24[a], 1.40[b]	EPA, 1984b
Textile Manufacturing	0.70[a], 0.42[b]	EPA, 1984b
Apparel Manufacturing	0.64[a], 0.23[b]	EPA, 1984b
Wood Furniture Manufacturing	0.10[b], 1.30[b]	EPA, 1984b
Particleboard Manufacturing	0.33[a], 0.31[b]	EPA, 1984b

[a] Personal sample
[b] Area Sample

characteristic of several studies. The power of a study is the ability to detect a certain level of risk. Insufficient follow-up and small sample sizes in the cohort studies compound to low power through insufficient person-years and through cancers not yet having appeared. Thus, elevations in specific-site cancers in individual cohort studies which are not consistently observed across all studies should not be totally discounted because they are not statistically significant. Likewise, the absence of rare cancers, e.g., nasal, in all cohort studies (except Blair et al., 1986) may be a reflection of power. A similiar situation may be observed in the case-control studies. Small numbers of cases for any given exposure lowers the detection power. Thus, associations with a specific neoplastic site may not be consistently observed across like exposures.

The question of the validity of multiple comparisons always arises in an examination of many studies and sites. Twenty-eight studies have been reviewed and to account for multiple comparisons by dividing a commonly accepted p-value by the number of comparisons yields a stringent rejection value. This rejection value will not be employed for this review since its use would have the impact of diminishing the statistical power in the 28 studies to detect a true positive. As previously identified, many of these studies already suffer from low statistical power.

Tables 4-15 through 4-17 present power calculations for the reviewed studies. Each table summarizes, by study design, observed and expected numbers of deaths for neoplasms of the

Table 4-15

Power Calculations for SMR Studies

Study	Size	Cancer Site	Observed	Expected	SMR	Least Detectable Relative Risk[a] with Power 80%	90%
Matanoski (1982) pathologists	1336	buccal cavity and pharynx	NG[b]	NG	---	---	---
		lung	NG	NG	---	---	---
		colon	NG	NG	---	---	---
		brain	5	1.7[c]	296	3.9	4.7
		lymphopoietic	7	9.5[c]	74	2.0	2.3
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---
pathologists	1439	buccal cavity and pharynx	NG	NG	---	---	---
		lung	6	8.1[c]	74	2.1	2.3
		colon	NG	NG	---	---	---
		brain	1	1.2[c]	82	4.5	5.6
		lymphopoietic	5	6.2[c]	81	2.2	2.5
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---
Levine et al. (1984) morticians	1477	buccal cavity and pharynx	1	2.1	48	3.8	4.4
		lung	19	20.2	94	1.4	1.7
		colon	NG	NG	---	---	---
		brain	3	2.6	115	3.0	3.6
		lymphopoietic	8	6.5	124	2.3	2.6
		leukemia	4	2.5	160	3.2	3.7
		nasal	0	0.2	---	12.0	16.5
Harrington and Shannon (1975) pathologists	2079	buccal cavity and pharynx	NG	NG	---	---	---
		lung	11	27.9	*39	1.5	1.6
		colon	NG	NG	---	---	---
		brain	NG	NG	---	---	---
		lymphopoietic	8	4.0	*200[d]	---	---
		leukemia	1	1.6	63	4.2	5.1
		nasal	0	NG	---	---	---

Table 4-15 (cont.)

Harrington and Oakes (1984) male pathologists	2307	buccal cavity and pharynx	NG	NG	---	---	---
		lung	9	22.0	*41	1.6	1.8
		colon	NG	NG	---	---	---
		brain	4	1.2	*331	---	---
		lymphopoietic	2	3.0	67	3.0	3.5
		leukemia	1	1.1	*91	5.1	6.1
		nasal	0	0.1[e]	---	---	---
Stroup (1984) anatomists	2239	buccal cavity and pharynx	1	6.8	*15	2.2	2.4
		lung	12	43.0	*28	1.4	1.5
		colon	20	18.5	108	1.6	1.8
		brain	10	3.7	*271	---	---
		lymphopoietic	18	14.4	125	1.8	2.0
		leukemia	10	6.7	148	2.2	2.5
		nasal	0	0.4	---	8.0	10.5
		brain					
		leukemia	11	1.9[a]	*579	---	---
			8	3.8[a]	*212	---	---
Wong (1983) chemical workers	2067	buccal cavity and pharynx	NG	NG	---	---	---
		lung	3	11.6	95	1.9	2.0
		colon	6	NG	---	---	---
		brain	2	1.6	188	4.3	5.0
		lymphopoietic	0	4.4	136	2.6	3.0
		leukemia	2	0.6	308	7.2	9.0
		nasal	0	NG	---	---	---
Tabershaw Associates (1982) formaldehyde exposed chemical workers	867	buccal cavity and pharynx	NG	NG	---	---	---
		lung	3	5.2	58	2.4	2.7
		colon	NG	NG	---	---	---
		brain	1	0.7	135	5.8	7.3
		lymphopoietic	3	2.0	152	4.0	4.7
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---

Table 4-15 (cont.)

Acheson et al. (1984a)	7716	buccal cavity and pharynx	5	4.3	116	2.6[f]	3.0[f]
chemical workers		lung	205	196.0	105	1.1[f]	1.1[f]
		colon	NG	NG	---	---	---
		brain	5	12.5	40	1.9	2.1
		lymphopoietic	20	26.3	76	1.6	1.7
		leukemia	9	11.4	79	1.8	2.0
		nasal	0	1.1	---	4.7	5.6
BIP plant		lung	166	141.0	118	1.5[f]	1.4[f]
		nose	0	0.7	---	6.1	7.7
Bertazzi et al. (1985)	4462	buccal cavity and pharynx	NG	NG	---	---	---
formaldehyde		lung	5	3.7	136	2.8	3.2
exposed		colon	NG	NG	---	---	---
resin workers		brain	NG	NG	---	---	---
		lymphopoietic	3	1.1	273	5.0	6.0
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---
Blair et al.[g] (1986)	26561	buccal cavity and pharynx	18	19	96	1.6	1.7
formaldehyde		nasopharynx	6	2	*300	---	---
exposed		lung	201	192	111	1.1[f]	1.1[f]
manufacturing and production		colon	42	48	87	1.4	1.5
workers		brain	17	21	81	1.6	1.8
		lymphopoietic	56	62	91	1.4	1.4
		leukemia	19	24	80	1.5	1.7
		Hodgkin's disease	14	10	142	2.0	2.2
		nasal	2	2.2	91	3.4	4.0
With 20 years latency[h]		lung[i]	148	110	*135	---	---
		nasopharyngeal	3	1	300	4.3	5.3
Stayner et al. (1986)	11030	buccal cavity and pharynx	6	3.9	155	2.6	3.0
garment workers		buccal cavity	4	1.2	*343	---	---
		pharynx	2	1.8	113	---	---
		colon	NG	NG	---	---	---
		brain	5	7.0	71	2.5	2.6
		lymphopoietic	18	19.8	91	1.7	1.9
		leukemia	9	7.9	114	2.5	2.4
		connective tissue	4	1.1	*364	---	---
		nasal	0	0.6	---	7.2	9.0

* $p < 0.05$

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

[b] NG, observed or expected number of deaths not given in paper.

[c] Age-specific mortality rates of psychiatrists used as the comparison group

[d] Power was not calculated for sites where statistically significant elevations were observed.

[e] As described in Levine et al. (1984)

[f] Because the expected number of deaths was large, least detectable relative risks were obtained by the approximation of Beaumont and Breslow (1981).

[g] SMR for the Blair et al. study are for analyses based on white males with time-weighted average exposure of >0.1 ppm formaldehyde.

[h] White males with cumulative formaldehyde exposure greater than 0 ppm-years.

[i] Observed and expected numbers of deaths are for white male wage workers.

Table 4-16

Conditional Power Calculations for PMR Studies[a]

Study	Size	Cancer Site	Observed	Expected	PMR	Least detectable PMR with power[b] 80%	90%
Walrath and Fraumeni (1983)	1132	buccal cavity and pharynx	8	7.1	113	230	250
NY embalmers and funeral directors		lung	72	66.8	108	130	140
		colon	29	20.3	*143[c]	---	---
		brain	9	5.8	156	240	280
		lymphopoietic	25	20.6	121	160	170
		leukemia	12	8.5[d]	140	210	240
		nasal	0	0.5[d]	---	860	1060
Walrath and Fraumeni (1984)	1050	buccal cavity and pharynx	8	6.1	131	220	260
California embalmers		lung	41	42.9	96	140	151
		colon	30	16.0	*187	---	---
		brain	9	4.7	*193	---	---
		lymphopoietic	19	15.5	123	170	190
		leukemia	12	6.9	*175	---	---
		nasal	0	0.6[d]	---	720[d]	880[d]
Marsh (1983)	2490	buccal cavity and pharynx	0	0.8	---	530	660
resin manufacturing workers		lung	NG	NG	---	---	---
		colon	NG	NG	---	---	---
		brain	NG	NG	---	---	---
		lymphopoietic	2	2.3	86	350	400
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---
Liebling et al. (1984)	24	buccal cavity and pharynx	2	0.2	*870	---	---
formaldehyde resin workers		lung	NG	NG	---	---	---
		colon	NG	NG	---	---	---
		brain	NG	NG	---	---	---
		lymphopoietic	1	0.5	217	860	1060
		leukemia	NG	NG	---	---	---
		nasal	0	NG	---	---	---

Table 4-16 (cont.)

Stayner et al.	256	buccal cavity	3	0.4	*750	---	---
garment		lung	11	12.2	90	180	200
workers		colon	NG	NG	---	---	---
		brain	1	2.1	48	580	440
		lymphatic and hematopoietic	10	6.1	163	220	250
		leukemia/aleukemia	4	2.4	168	550	580
		nasal	0	NG	---	---	---
Delzell and Grufferman	4462	buccal cavity and pharynx	18	18.0	100	170	180
textile		lung	106	117.8	90	120[e]	130[e]
workers		colon	115	115	100	120[e]	130[e]
		brain	17	18.9	90	170	180
		lymphopoietic	121	64.2	188	130	140
		leukemia	45	37.5	120	145	150
		nasal	NG	NG	---	---	---

* $p<0.005$

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

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

[c] Power was not calculated for those sites where statistically significant elevations were observed.

[d] As published in Levine et al. (1984).

[e] Because the expected numbers of deaths was large, least detectable PMR's were obtained by the approximation of Beaumont and Breslow (1982).

Table 4-17

Power Calculations for Case-Control Studies[a,b]

Study	Size	Cancer Site	Exposure Ratio = P_o	Odds Ratio	Least Relative Odds to detect with power[c] 80%	90%
Fayerweather et al. (1982)	481 cases/	lung, bronchus	formaldehyde:			
cancer deaths	481 controls	and trachea	males workers (20%)	0.74	2.0	2.2
in chemical	(1:1) match)	lymphopoietic		0.72	3.5	4.1
workers		prostate		3.20	4.4	5.5
		brain		0.45	11.6	16.8
Brinton et al. (1983)	160 cases/	nasal cavity	textile workers:			
nasal and paranasal	290 controls	and sinuses	females (17.4%)	1.8	2.5	2.8
sinus cases in NC and VA	(1:2 match)					
nasal and nasopharyngeal	541 controls	nasopharyngeal	manufacture:	*5.8	---	---
cases in Sweden			males (0.8%)			
Olsen et al. (1984)	839 cases/	nasal cavity	formaldehyde:			
nasal cancer	2465 controls	and sinuses	females (0.1%)	*2.8	15.0	18.0
cases in Denmark			males (4.2%)	2.8	---	---
			textile dust:			
			females (2.5%)	1.3	2.8	3.2
			males (1.9%)	0.7	2.4	2.7
Hayes et al. (1984)	144 cases/	nasal cavity	formaldehyde: (Classification A)			
nasal and nasal	353 controls	and sinuses	males with no or low			
sinsus cases in	(1:2 match)		level wood dust			
the Netherlands			exposure (6.2%)	2.8	3.4	3.7
			males with high			
			level wood dust			
			exposure (50%)	1.9	6.9	8.0
			formaldehyde: (Classification A)			
			males, controlled	*1.9	---	---
			for high wood dust exposure			

Table 4-17 (cont.)

Partenen et al. (1985) nested respiratory cancer case-control study	55 cases/ 169 controls	respiratory system	formaldehyde:			
			ever exposed (26.6%)	1.4	2.5	2.8
			level of exposure			
			0.1 - 1.0 ppm (16%)	1.5	2.7	3.1
			> 1.0 ppm (7.7%)	1.4	3.4	3.9
Vaughan et al. (in press) sinonasal and pharyngeal cases in the U. S.	53 cases/ 552 controls	nasal cavity and sinuses	occupational formaldehyde:			
			cumulative exposure			
			5 - 9 years (6.3%)	1.1	4.0	4.8
			10 + years (10.9%)	0.3	2.7	3.3
			occupational: resins, glues and adhesives			
			low exposure (6.5%)	2.0	3.2	3.7
			high exposure (2.3%)	*3.8	---	---
			domestic: mobile home residence			
			1 + years (12.0%)	1.7	2.7	3.3
	27 cases/ 552 controls	nasopharyngeal	occupational formaldehyde:			
			no. of years exposed			
			1 - 9 (25.0%)	1.2	3.2	4.0
			10 + (10.3)	1.6	4.5	5.6
			occupational: stains, varnishes, solvents			
			low exposure[e]	0.9		
			high exposure[e]	*4.0	---	---
			domestic: mobile home residence			
			1 - 9 years (12.0%)	2.1	3.7	4.7
			10 + years (3.7%)	*5.6	---	---
	174 cases/ 552 controls	oro-hypo-pharyngeal	occupational formaldehyde:			
			no. of years exposed			
			1 - 9 (25.0%)	0.6	1.7	1.9
			10 + (10.3%)	1.2	2.1	2.4
			occupational: resins, glues, adhesives			
			low exposure[e]	1.3		
			high exposure[e]	*3.9	---	---

Table 4-17 (cont.)

stains, varnishes, solvents			
low exposure[e]	1.0		
high exposure[e]	*3.0	---	---
domestic:			
mobile home residence			
1 - 9 years (12.0%)	1.0	2.0	2.2
10 + years (3.7%)	0.9	2.9	3.3

*$p<0.05$

[a] Power calculations for Tola et al. (1980), Roush et al. (1985) and Hernberg et al. (1983) could not be calculated due to the unknown exposure ratio (p_o) among the controls.

[b] Power was not calculated for studies where statistically significant elevations were observed.

[c] 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), Hayes et al. (1984), and Hardell et al. (1982).

[d] Matching ratio not identified by Hardell et al. (1982).

[e] Prevalence of the exposure among the controls not cited by Vaughan et al. (As reported in SAIC, 1986).

hematopoietic site cancer as an example, Table 4-15 shows that Levine et al. (1984) could detect, with 80 percent power, a relative risk of 2.3 or greater and with 90 percent power, a relative risk of 2.6 or greater.

The above seven sites were selected for several reasons. First, because the exposure is generally by inhalation and nasal tumors were seen in the chronic rat study (Kerns, 1983), the respiratory system is a reasonable place to look for effects. Nasal tumors, buccal cavity tumors, and pharyngeal tumors were included because man, unlike the rat, is not an obligatory nose breather and inhaled formaldehyde would initially contact these areas. Last, the Epidemiology Panel, Consensus Workshop on Formaldehyde (1984) and Levine et al. (1984) report significant excesses in brain, leukemia, and colon cancer mortality when results across studies were combined.

Epidemiologists use five criteria for judging whether an association is causal. These criteria are: 1) strength of the association, 2) consistency across studies, 3) temporally correct association (disease occurs after exposure), 4) specificity of the association, and 5) coherence with existing data. The reviewed epidemiologic studies are of a cohort or case-control design, designs which examine health consequences of previous exposure, thus permitting point 3 to be satisfied.

The Blair et al. (1986), Blair et al. (1987), Vaughan et al. (1986a,b), and Stayner et al. (1986) were designed to detect moderate increases in formaldehyde-related risks. The Blair et al. (1986) and Vaughan et al. (1986) studies observed significant

associations with nasopharyngeal cancer and apparent exposure to formaldehyde, in either the occupational or residential environment. Vaughan et al. (1986) reported a significant association between the incidence of nasopharyngeal cancer and living 10 or more years in a mobile home. This study also reported statistically significant associations between sinonasal cancer and oro-hypopharyngeal cancer and exposure to resins, glues, and adhesives (SAIC, 1986). Mobile home residency and occupational resins, glues and adhesives exposure were a priori selected as likely surrogates for formaldehyde exposure. No statistically significant associations were found between cancer incidence at any of these sites with respect to occupational formaldehyde exposure as assessed using an occupational linkage system. The risk estimates, however, for the highest exposure level and cancers of the oro-hypopharynx and nasopharynx appeared elevated. These results for the occupational formaldehyde exposure most likely were biased towards the null hypothesis since a large proportion of the case interviews were with the next-of-kin, respondents less likely to report or remember all jobs the case had ever held.

Blair et al. (1986, 1987) observed excesses of lung and nasopharyngeal cancer mortality among U.S. workers exposed to formaldehyde in 10 plants. The highest risks were observed for lung cancer among men with a 20-year latency and for nasopharyngeal cancer among men with exposure to formaldehyde-containing particulates. An apparent dose trend was observed between nasopharyngeal cancer mortality and exposure to

formaldehde and particulates (Blair et al., 1987); no clear trends were observed between lung cancer mortality and formaldehyde level (Blair et al., 1986). Blair et al. (1986) argued the data provide little evidence that lung cancer mortality is associated with formaldehyde exposure at levels experienced by workers in this study, although they concluded that simultaneous exposure to formaldehyde and particulates appear to be a risk factor for nasopharyngeal cancer. Blair et al. (1987) additionally state that further investigation is needed regarding the dose-dependent association between nasopharyngeal cancer mortality and exposure to formaldehyde and particulates. The significant excesses in total lung cancer mortality, in analysis either with or without a latency period equal to or greater than 20 years, and in nasopharyngeal cancer mortality among ever-exposed workers are meaningful. Inhalation is the primary route of exposure for this cohort. Second, misclassification of exposure, the lack of specificity between the narrow exposure categories, may account for the lack of a statistically significant trend between lung cancer mortality and formaldehyde level. Blair et al. (1986) relied upon historical industrial hygiene data, process changes, and human recall to reconstruct past exposure to formaldehyde. The observed wide variations in historical industrial hygiene data for any given job and the reliance upon human memory may have contributed to misclassification.

Stayner et al. (1986) reported significant mortality excesses from neoplasms of the buccal cavity, connective tissue, and tonsils among formaldehyde-exposed garment workers. The risk

ratio for buccal cavity cancer was significantly elevated among workers with a long duration of employment (exposure) and follow-up period (latency). Although it is not presented in Stayner et al. (1986), EPA calculations showed a statistically significant trend between buccal cavity cancer mortality and increasing duration of employment. A significant excess in deaths from cancer of the tonsils (located in the oropharynx) was also reported, but there were too few deaths (only 2) to examine any trends with exposure.

The significant associations between formaldehyde exposure and excesses in site-specific buccal cavity and respiratory cancers support observations from EPA's previous review of the epidemiological literature. These other studies had limited ability to detect formaldehyde-related risks due to lower power. Even with this potential limitation, 6 studies (Olsen et al., 1984; Hardell et al., 1982; Hayes et al., 1986; Acheson et al., 1984a; Liebling et al., 1984; and Stayner et al., 1985) reported significant associations between excess site-specific respiratory or buccal cavity and pharyngeal cancer and exposure to formaldehyde.

The Hayes et al. (1986) and Olsen et al. (1984) studies report significant excesses of sinonasal cancer and exposure to both formaldehyde and wood-dust. Both studies controlled for simultaneous wood-dust exposure, and by doing so, the detection limits exceeded excesses in expected sinonasal neoplastic risk. Hardell et al. (1982) reported a significant excess in sinonasal cancer and employment in particleboard manufacturing.

The other 3 studies examined mortality among workers occupationally exposed to formaldehyde-containing products. Acheson et al. (1984a) observed a significant elevation in lung cancer among formaldehyde resin workers in 1 plant in the U.K. Acheson et al. (1984a) observed at this plant a marginally significant trend with dose. Acheson et al. (1984a) concluded that the increased lung cancer mortality and positive trend were not related to formaldehyde exposure since analyses using local cancer rates as the comparison were not statistically significant. EPA believes that the risks and trends from analyses using local lung cancer rates as the comparison appeared sufficiently increased for corroborative use. EPA notes, however, it was not known how many of the formaldehyde-exposed lung cancer deaths were included in the deaths of the local comparison group. This would lead to a reduction in power since the same death could be counted in both the numerator and denominator.

The 2 other studies (Stayner et al., 1985 and Liebling et al., 1984) reported statistically elevated SMR's for buccal cavity cancer among garment workers and for buccal cavity and pharyngeal cancers among formaldehyde resin workers in 1 plant. Portions of the Liebling et al. (1984) and Blair et al. (1986, 1987) studies overlapped as did portions of the two Stayner et al. (1985; 1986) studies. The nonoverlapping portions and improved design of the more recent studies (i.e., Blair et al., 1986; Blair et al., 1987; Stayner et al., 1986) reinforce the conclusions of the earlier studies.

The studies of embalmers, anatomists and pathologists reported deficits in mortality from site-specific respiratory cancers. Although individual characteristics are not known, this observation may be a reflection of decreased smoking habits among these professional groups in comparison to the general population. Since expected deaths are based on general population site-specific mortality, the number of expected deaths may be biased upwards with the resultant SMR being lower. The lack of lung cancer excesses in these studies may additionally reflect the lower statistical power to detect moderate increases in site-specific respiratory cancer mortality.

Site-specific excesses in lymphopoietic, leukemia, colon, and brain neoplasms have been observed in five studies (Harrington and Shannon, 1975; Harrington and Oakes, 1984; Stroup, 1984; Walrath and Fraumeni, 1983; Walrath and Fraumeni, 1984), but these excesses were not statistically significant across all studies. This lack of consistency may reflect lack of a causal relationship or may reflect limited power to observe excesses at specific sites because of small sample sizes, insufficient follow-up, different exposure levels, and different routes of exposure in the individual studies. The Epidemiology Panel of Consensus Workshop on Formaldehyde (1984) summarized the observed and expected numbers of site-specific cancers from both SMR and PMR studies and noted statistically significant excesses in mortality from brain cancer and leukemia among embalmers, pathologists, and anatomists. Levine and co-workers (1984) used

this same method and, additionally, noted a statistically significant excess in mortality from colon cancer.

The same conclusions were reached through the use of another approach by summarizing all SMR and all PMR site-specific findings according to Fisher's combined probabilities method (Sokal and Rolf, 1969). Fisher's combined probabilities can be used on different sets of data that test the same scientific hypothesis and where for one reason or another a joint statistical analysis is not optimal. This methodology does not assume all studies are equal. Again, Fisher's combined probabilities may not be an ideal test. Its use on discrete or count data tends to bias the results toward non-significance (Gastwirth, 1983). A detailed description of the procedures and analyses are presented in EPA, 1984b. Table 4-18 presents the summarized results. Thus, where site-specific mortality has been reported, it can be concluded from SMR studies that brain cancer mortality is significantly elevated ($p<0.05$) among pathologists, anatomists, and embalmers, and from PMR studies that leukemia and brain cancer mortalities are significantly elevated ($p<0.05$) for these professions. Likewise, from PMR studies, colon and lymphatic and hematopoietic cancer mortalities are significantly elevated ($p<0.05$) for manufacturing workers.

To further examine power, the human data were compared to estimates of the upper bound risk that were calculated based on the malignant tumors in Kerns (1983). This comparison assumes the excess risk calculated from the animal low-dose extrapolation is the excess above a risk of one for the study population

Table 4-18

Fisher's Combined Probability(p) for SMR and for PMR Studies

Cancer Site	Study Design	Study Population	Fisher's pa
Buccal cavity and pharynx	SMR	Embalmers, Anatomists, Pathologists	0.64
		Manufacturing Workers	0.40
	PMR	Embalmers, Anatomists, Pathologists	0.36
		Manufacturing Workers	0.10
Lung	SMR	Embalmers, Anatomists, Pathologists	0.99
		Manufacturing Workers	0.35
	PMR	Embalmers, Anatomists, Pathologists	0.54
		Manufacturing Workers	0.83
Colon	SMR	Embalmers, Anatomists, Pathologists	<0.35
		Manufacturing Workers	0.22
	PMR	Embalmers, Anatomists, Patholoists	<0.01
		Manufacturing Workers	0.48
Brain	SMR	Embalmers, Anatomists, Pathologists	<0.01
		Manufacturing Workers	0.95
	PMR	Embalmers, Anatomists, Pathologists	0.02
		Manufacturing Workers	0.75
Lymphatic and hematopoietic	SMR	Embalmers, Anatomists, Pathologists	0.08
		Manufacturing Workers	0.56
	PMR	Embalmers, Anatomists, Pathologists	0.17
		Manufacturing Workers	<0.01
Leukemia	SMR	Embalmers, Anatomists, Pathologists	0.17
		Manufacturing Workers	0.26
	PMR	Embalmers, Anatomists, Pathologists	0.04
		Manufacturing Workers	0.10

[a]Probability of $-2 \sum_{j=1}^{k} \ln p_j$ distributed as a chi-square with 2k degrees of freedom (Sokal and Rolf, 1969). Small values indicate a statistically significant elevation over 100.

relative to the U.S. population (Margosches and Springer, 1983). Hence, human site-specific neoplastic relative risks are calculated by adding the percentage increase in site-specific tumors to a relative risk of one.

Two major assumptions are made to carry out this prediction. First, the number of human cancer site-specific deaths approximates lifetime incidence. Second, site-to-site concordance between animals and humans does not necessarily hold, and only one site is examined at a time.

Table 4-19 presents the upper bounds on predicted human relative risk for seven neoplastic sites. Based on Table 4-19, we would expect to see a relative risk of around 1.26 for buccal cavity and pharyngeal neoplasms for funeral service workers (morticians and embalmers). It must be noted that the predicted relative risks vary greatly with the mortality. The rarer the cause of mortality the higher the predicted relative risk will be. Comparing the occupation-associated predicted human relative risks with the least detectable risks identified in Table 4-15 to 4-17, we see that very few of the SMR and PMR studies had 90%, or even 80%, power to detect this upper bound predicted human nasal sinus and cavity risk. Most of case-control studies had 80% power to detect such excess nasal cavity and sinus risks, if average exposure to formaldehyde for the cases was around 1.3 ppm. Note, the reviewed studies had over 90% power to detect a predicted upper bound on nasal cavity and sinus relative risk (RR=101.0) that was based on animals bearing either nasal cavity and sinus squamous cell carcinomas or polypoid adenomas if

Table 4-19

Predicted Human Relative Risks for Selected Occupations[a]

Cancer Site	Funeral Service Workers (1.70 ppm)[b]	Apparel (0.64 ppm)[b]		Manufacturing Resin (1.40 ppm)[b]	Furniture (1.30 ppm)[b]	(0.10 ppm)[b]	Particle Board (0.33 ppm)	Textile (0.70 ppm)
Buccal cavity and pharynx	1.26[c]	1.23[c]	(5.65)[d]	1.53[c]	1.44[c]	1.03[c]	1.11[c]	1.26[c]
Lung	1.02	1.02	(1.38)	1.04	1.04	1.00	1.01	1.02
Colon	1.05	1.04	(1.90)	1.10	1.09	1.01	1.02	1.05
Brain	1.24	1.22	(5.44)	1.51	1.42	1.03	1.11	1.24
Lymphopoietic	1.05	1.05	(2.04)	1.12	1.10	1.01	1.03	1.06
Leukemia	1.13	1.12	(3.41)	1.28	1.23	1.01	1.06	1.13
Nasal cavity and sinus	6.45	5.83	(101)	12.45	10.65	1.60	2.42	6.50

a This procedure is described by Margosches and Springer (1983). It is based on an assumption that excess risk calculated from animal low-dose extrapolation is the excess above a risk of one for a human exposed population relative to an unexposed or general population.

$$\text{Predicted human relative risk} = 1 + \frac{P(d)_{UCL,\ 5\text{-stage model}}}{\text{Proportion of deaths due to specific cancer}}$$

Proportions of deaths calculated from 1980 mortality data.

$P(d)_{UCL}$ are described in EPA, 1984b.

b Personal exposure estimates from EPA, 1984b.

c Upper bound predicted human relative risks based on a $P(d)_{UCL,\ 5\text{-stage model}}$, where P(d) is estimated from the number of animals bearing squamous cell carcinomas.

d Upper bound predicted human relative risks based on $P(d)_{UCL,\ 5\text{-stage model}}$, where P(d) is estimated from the total number of animals bearing squamous cell carcinomas or polypoid adenomas.

exposure was around 0.64 ppm or greater. None of the studies could detect the predicted relative risks that were based on animals bearing only squamous cell carcinomas for brain, or for leukemia, or lymphopoietic, or colon, or lung neoplasia for the populations studied.

4.7.3 Conclusion

The EPA has examined 28 studies which related to formaldehyde. Three of these studies (Vaughan et al., 1986a,b; Blair et al., 1986, 1987; and Stayner et al., 1986) were designed to detect moderate elevations in human cancer risks; the remaining 25 studies had detection limits that exceeded corresponding expected excesses in site-specific neoplastic risks. Results from 9 studies (Vaughan et al., 1986a,b; Blair et al., 1986, 1987; Stayner et al., 1986; Olsen et al., 1984; Hardell et al., 1982; Hayes et al., 1986; Acheson et al., 1984a; Liebling et al., 1984; and Stayner et al., 1984) suggest that lung, nasopharyngeal, sinonasal, and oro-hypo-pharyngeal cancers are associated with formaldehyde exposure.

In each of the above 9 studies, the populations were also undoubtedly exposed to other agents and these exposures may have contributed to the observed increase in cancer risk. Five studies, however, addressed confounding. Vaughan et al. (1986a,b) controlled for smoking and alcohol consumption in their analyses. Hayes et al. (1986) and Olsen et al. (1984) controlled for wood-dust exposure; the detection limits in both studies exceeded corresponding expected excesses in sinonasal neoplastic

risk. Stayner et al. (1986) measured possible confounders such as phenol or particulate dusts in their study and thought the contribution of the confounders to the observed excesses in buccal cavity or pharyngeal mortality were minimal to none. Note, Stayner et al. could not measure the impact of smoking on their observed excesses in mortality. Blair et al. (1986), on the other hand, stated that the lack of a consistent elevation for tobacco-related causes of deaths suggested that their cohort's smoking habits did not differ substantially from those of the general population. Regarding diagnostic bias accounting for the observed brain cancer excesses, the brain cancer excesses remained when other like socioeconomic groups were used as the comparison. Socioeconomic status may be a confounder in the observed associations with upper respiratory cancers, but no data currently exist for evaluation. As identified earlier, smoking, sometimes associated with socio-economic status, either has been taken into account in analyses or was thought to be appreciably similar within the individual study comparison groups.

Based on the above human evidence, formaldehyde can be placed in the "limited evidence of carcinogenicity" category. This category is defined as "indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be addressed" (EPA, 1986).

Formaldehyde should not be placed in the categories "inadequate evidence" or "sufficient evidence of carcinogenicity." "Inadequate evidence" is defined as

"indicating that one or two conditions prevailed: (a) there were few pertinent data, or (b) the available studies, while showing evidence of an association, did not exclude chance, bias, or confounding." Placement into the "inadequate evidence" category would imply that the studies contained insufficient data to consider adjusting for alternative interpretations. The aforegoing discussion shows this is not the case. "Sufficient evidence of carcinogenicity" is defined as "indicates that there is a causal relationship between the agent and human cancer." A variety of plausible important exposures could have confounded these results, but no adjustment could be made for them. In addition, the association between mobile home residence and nasopharyngeal cancer was a first report; future epidemiological studies would be needed to confirm a causal association between the formaldehyde exposure in a mobile home and the incidence of nasopharyngeal cancer.

On this basis, EPA has concluded that the epidemiological evidence is "limited".

4.8. Weight-of-Evidence

4.8.1. Assessment of Human Evidence

EPA examined 28 epidemiologic studies relevant to HCHO. Three of these studies, two cohort (Blair et al., 1986; 1987 Stayner et al., 1986) and one case-control (Vaughan et al., (1986a,b), were well conducted and specifically designed to detect small to moderate increases in HCHO-associated human risks. Each of these three studies observed statistically significant associations between respiratory site-specific cancers and exposure to HCHO or HCHO-containing products. In each of the above three studies, the populations studied were also undoubtedly exposed to other chemicals and these exposures may have contributed to the observed increases in cancer risk. Only the study by Vaughan et al. (1986a,b) controlled for smoking and alcohol consumption.

The Blair et al. (1986; 1987) cohort study observed significant excesses in lung and nasopharyngeal cancers among U.S. workers occupationally exposed to HCHO at 10 industrial sites. Blair et al. (1987) conclude that formaldehyde and particulates appear to be a risk factor for nasopharyngeal cancer. Blair et al. (1986), however, argued that the lung cancer excesses provided little evidence of an association with HCHO exposure since the lung cancer risk did not increase consistently with either increasing intensity or cumulative HCHO exposure. EPA, after reviewing these data, has concluded that the significant excesses in total lung cancer mortality, in

analyses either with or without a latency period equal to or greater than 20 years, and together with nasopharyngeal cancer mortality among HCHO-exposed workers are meaningful despite the lack of significant trends with exposure.

The Stayner et al. (1986) cohort study reported statistically significant excesses in mortality from buccal cavity tumors among HCHO-exposed garment workers. The SMR was highest among workers with a long duration of employment (exposure) and follow-up period (latency).

Results from the case-control study by Vaughan et al. (1986a,b) showed a significant association between nasopharyngeal cancer and having lived 10 or more years in a "mobile home". Persons for whom this association was drawn had lived in mobile homes that were built in the 1950s to 1970s. This study also reported significant associations between sinonasal cancer and orohypopharyngeal cancer and exposure to resins, glues, and adhesives (SAIC, 1986). No significant trends were found in cancer incidence at any of these sites with respect to occupational HCHO exposure; however, the risk estimates for the highest exposure level and cancers of the orohypo-and naso-pharynx appeared elevated. However, this population, like the two previously discussed, was also undoubtedly exposed to other chemicals which may have contributed to the observed increases in cancer risk.

EPA reviewed 25 other epidemiologic studies. These studies had limited ability (lower power) to detect small to moderate

increases in HCHO-related risks due to (1) small sample sizes; (2) small numbers of observed site-specific deaths; and (3) insufficient follow-up. Even with these potential limitations, six of the 25 studies (Acheson et al., 1984a; Hardell et al., 1982; Hayes et al., 1985; Liebling et al., 1984; Olsen et al., 1984; Stayner et al., 1985) reported significant associations between excess site-specific respiratory (lung, buccal cavity, and pharyngeal) cancers and exposure to HCHO.

The Olsen et al. (1984), Hayes et al. (1986), and Hardell et al. (1982) studies reported significant excesses of sinonasal cancer in individuals who were exposed to both HCHO and wood-dust, or who were employed in particleboard manufacturing where HCHO is a component of the resins used to make particleboard. Only the Hayes et al. (1986) and Olsen et al. (1984) studies controlled for wood-dust exposure; the detection limits in both studies, however, exceeded corresponding expected excesses in the incidence of sinonasal tumors and, therefore, no significant excesses were likely to have been observed.

The Acheson et al. (1984a) study conducted in the United Kingdom supports the results of Blair et al. in that, when compared to mortality rates of the general population, significant excesses in mortality from lung cancer were observed in one of six HCHO resin producing plants in England. A trend of borderline significance with dose was observed for this one plant. Acheson et al. concluded that the increases in mortality from lung cancer were not related to HCHO exposure since the

elevation and trend were not statistically significant when compared with local lung cancer rates. EPA believes that the risks and trends from analyses using local lung cancer rates as the comparison risks appeared sufficiently increased for corroborative use.

The remaining two studies reported significant excesses of buccal cavity cancer among garment workers in 3 plants (Stayner et al., 1985) and excesses of buccal cavity and pharyngeal cancer among HCHO resin workers in 1 plant (Liebling et al., 1984). Portions of the Liebling et al. (1984) and Blair et al. (1986, 1987) studies overlapped as did portions of the two Stayner et al. (1985; 1986) studies. However, the non-overlapping portions and improved design of the more recent studies (i.e., Blair et al. 1986, 1987; Stayner et al. 1986) reinforce the conclusions of the earlier studies.

Analyses of the remaining 19 epidemiologic studies have indicated the possibility that observed leukemia and neoplasms of the brain and colon may be associated with HCHO exposure. The biological support for such postulates, however, has not yet been demonstrated.

Based on a review of these studies, EPA has concluded that under EPA's Guidelines for Carcinogenic Risk Assessment there is "limited" evidence to indicate that HCHO may be a carcinogen in humans. Nine studies reported statistically significant associations between site-specific respiratory neoplasms and exposure to HCHO or HCHO-containing products. This is of

interest since inhalation is the primary route of exposure in humans. Although the common exposure in all of these studies was HCHO, the epidemiologic evidence is categorized as "limited" primarily due to possible exposures to other agents which may have confounded the findings of excess 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 (Kerns et al., 1983), Albert et al. (1982) and Tobe et al. (1985). In the CIIT study, statistically significant numbers of squamous cell carcinomas of the nasal cavity of Fischer 344 male and female rats were seen. The CIIT 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. Benign tumors (i.e., polypoid adenomas) were seen in male rats in the CIIT study at all dose levels and in female rats exposed to 2 ppm of HCHO. Notably, the dose-response curve for the benign tumors in this study did not mirror the carcinoma response; the tumor incidence was highest at 2.0 ppm and decreased at higher doses.

Tobe et al. also observed a statistically significant increase in the numbers of squamous cell carcinomas in the same strain of male rats as was used in the CIIT study. Albert et al. reported a statistically significant elevation of the same malignant tumor type in male rats of a different strain. In both

the Tobe et al. and Albert et al. studies benign squamous cell papillomas were seen. This observation was in contrast to the CIIT study in which polypoid adenomas were the only benign tumors observed. Hamsters have been tested in long-term inhalation studies (Dalbey, 1982) but no increased incidence of tumors was seen in HCHO-treated animals. However, deficiencies in the study design and poor survival limit the interpretation of the results from these studies.

Additional support is provided by studies by Dalbey (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 these data seems to indicate little 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.

Another factor that bears on the possible carcinogenicity of HCHO, is the different responses seen in laboratory animals to HCHO. HCHO has 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. 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, but this finding is tempered by poor survival, limited pathology, and other factors. The study using monkeys (Rusch et al.) indicates that, at least for nonneoplastic lesions (squamous metaplasia), rats and monkeys respond similarly.

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 (by inhalation). In addition, other aldehydes such as glycidaldehyde and malondialdehyde have been shown to be carcinogenic.

Finally, HCHO's rapid metabolism and pharmacokinetic data, the protective action of the mucous layer, and respiratory response to sensory irritants have been discussed in the HCHO literature as factors that may bear on judgements of the mganitude of the potential human cancer risk posed by HCHO and will be discussed in sections 7 and 9.

In conclusion, based upon a review of the above data, EPA has concluded that there is "sufficient" evidence of carcinogenicity of HCHO in animals by the inhalation route. This finding is based on the induction by HCHO of an increased incidence of a rare type of malignant tumor (i.e., nasal squamous-cell carcinoma) in both sexes of rats, in multiple inhalation experiments, and in multiple species (i.e., rats and mice). In these long-term laboratory studies, tumors were not observed beyond the initial site of nasal contact nor have other mammalian in vivo tests shown conclusive effects at distant sites.

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 EPA's Guidelines for Cancer Risk Assessment (EPA, 1986),

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.

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 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	0-0.05
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. 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. In smog-

chamber tests human subjects tested could readily detect and react to HCHO at as low as 0.01 ppm. The irritant effects of HCHO seem to be accentuated when it is mixed with other gases.

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 and adnexal 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 higher levels, 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 lacrimation 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 occupationally exposed to 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.

In a study of workers exposed to phenolic resin fumes by Schoenberg and Mitchell (1975), there was evidence of chronic airway obstruction in workers exposed for more than five years. This was measured by lower FEV 1.0/FVC and MEF 50%/FVC ratios. However, as opposed to the high percentage of workers reporting acute respiratory symptoms, only small decreases in pulmonary function during the workday and workweek were found. In a similar study, it was found that workers exposed to a phenol-HCHO type resin, hexamethylenetetramine-resorcinal, experienced significant acute lung effects (lung function measured before and after shifts) as measured by decrements in tests measuring "small airways" effects. However, there was no difference in baseline lung function tests in the exposed and control populations (Gamble et al., 1976). Finally, workers exposed to HCHO from the manufacture of fiberglass batts and the fixation of tissues (histology technicians) had similar symptom profiles. Chest tightness, burning, shortness of breath, cough, and palpitations increased in frequency from unexposed to increasingly exposed groups. Significant reductions in baseline flow rates were noted for batt makers and were most likely due to chronic HCHO exposure and cigarette smoking. Deficits persisted so that they were seen in baseline studies done after a 20-day shutdown period (Kilburn et al., 1985a).

In contrast to the studies described above, studies by Main and Hogan (1983), Levine et al. (1984), and Day et al. (1984) reported no deficits in pulmonary function of workers in mobile

trailers, morticians, and residents of UFFI homes, respectively. However, Main and Hogan did find significantly increased symptoms of eye and throat irritation and headache and fatigue among the exposed group. The residents of UFFI homes experienced a high frequency of eye irritation and moderate rates of nasal congestion and tearing when exposed to 1.0 ppm HCHO for 90 minutes in a chamber (Day et al., 1984). No significant increase in respiratory disease was found in the morticians studied by Levine et al.

In reviewing a number of morbidity studies, including the Schoenberg et al. (1975) and Gamble et al. (1976) studies, the Epidemiology Panel of the Consensus Workshop (1984) concluded that:

> No important reductions in forced vital capacity were observed. Reductions in forced expiratory volume in one second and forced expiratory volume (expressed as a percentage of forced vital capacity) when observed were small. These were not detected when exposure to formaldehyde was solely as a vapor. There was either a weak or absent association of reduced pulmonary function tests with exposure in the few studies where this factor was analyzed. Workshift (acute) changes in pulmonary function tests (PFT) have been assessed only when other dust was present and/or the formaldehyde itself was a particulate or incorporated in particles. Acute PFT reductions were not consistently present, were small and showed no regular association with exposure. Although some symptoms were present, the changes in PFT were clinically insignificant, and there is no convincing evidence formaldehyde exposure results in restriction or obstruction at the doses studied. There is some suggestion that the symptoms are reversible and of minor import. However, because of the demonstated irritant potential of formaldehyde, selection bias may be occurring in the exposed populations so that these studies are likely to underestimate adverse effects of formaldehyde exposure.

Studies cited that were not available to the Panel do not materially affect their findings.

Pulmonary 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 and might be fatal in sensitive persons (NRC, 1981).

5.1.5. Asthma

In addition to its direct irritant effects on the respiratory system, HCHO has been shown to cause bronchial asthma-like symptoms in humans (Hendrick et al., 1982; Burge et al., 1985; and Nordman et al., 1985). Although asthmatic attacks may in some cases be due specifically to HCHO sensitization or allergy, the evidence for this is less than certain (Consensus Workshop, 1984). HCHO seems to act more commonly as a direct airway irritant in persons who have bronchial asthma from other causes (Burge et al., 1985 and Nordman et al., 1985). However, the HCHO concentrations required to elicit such attacks are relatively high, higher than would be expected in most nonoccupational environments. For example, no bronchoconstriction was observed in seven mild asthmatics who were exposed to 1 ppm HCHO for 10 minutes at rest and to 1 or 3 ppm during mild exercise (Sheppard et al., 1984). In a study of 21 asthmatics living in UFFI homes, no consistent bronchial effects were produced from three hour exposures to: Placebo, 0.54 ppm HCHO, UFFI particles 0.5/ml, and HCHO free UFFI off-

gases (Lees et al., 1985). Witek et al. (1985) reports no effects in healthy and asthmatic individuals exposed to 2.0 ppm HCHO with and without mild exercise, and in a group of laboratory workers routinely exposed to HCHO.

In a study of 230 persons who had been exposed to HCHO and suffered asthma-like symptoms, 218 did not respond when challenged with 2.0 ppm HCHO, including 71 subjects with demonstrated bronchial hyperactivity (histamine or methacholine challenge test). The 12 individuals that did respond were diagnosed as "true HCHO asthmatics" and all had been exposed occupationally (Nordman et al., 1985). Finally, in a study of 15 workers occupationally exposed to HCHO who were exposed to approximately 4.0 ppm HCHO under controlled conditions, six workers developed immediate asthmatic reactions, which were most likely due to its irritation properties, while three workers developed what was diagnosed as HCHO-caused hypersensitivity (Burge et al., 1985).

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. A paper by Brooks et al. (1985) reports two cases in which asthma-like symptoms may have been caused by a single exposure to high levels of an irritating agent. Symptoms persisted for at least four years and were accompanied by early inflammatory responses in the lung. No

documented preexisting respiratory illness was found. The authors have termed the illness observed reactive airways dysfunction syndrome (RADS). Because many occupations have the potential for episodic, high level HCHO exposure, RADS should be considered as a possibility.

Diagnosis of immune sensitization has been based upon knowledge that individuals were exposed to HCHO before the onset of symptoms, reported complaints and symptoms, and spirometric pattern on obstructive 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 be produced in response to HCHO exposure. However, a study by Patterson et al. (1986) has demonstrated the presence of IgE antibodies against HCHO-human serum albumin conjugates and human serum albumin (HSA). The authors believe the immunologic response is HCHO related because of a similar pattern in dogs immunized with HCHO or HCHO-dog albumin and the fact that anti-HSA antibodies have not been identified in patients reactive to other hapten-HSA compounds. Respiratory sensitization with HCHO has not been demonstrated with animals (Lee et al., 1984). In some human studies in which patients complained of respiratory illness, they did not respond positively to bronchial challenge testing with HCHO gas, but it does appear from the work of Hendrick et al. (1982), Burge et al.

(1985), and Nordman et al. (1985) that HCHO can induce hypersensitivity by the inhalation route. However, the data indicate that this may be a rare event. In addition, no data are available describing induction concentrations, but it appears that challenge concentrations as low as 1.0 ppm can elicit a response (Nordman et al., 1985).

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 (Consensus Workshop, 1984). 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 can precipitate an acute asthmatic attack, sometimes at concentrations below 5 ppm. Although conclusive evidence is not available, it appears that HCHO is capable of inducing respiratory tract allergy, but data are lacking on induction concentrations. 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. Finally, a dose-response analysis of the human data appears in section 8.

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. 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. 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 are 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 allergic contact dermatitis in garment workers for instance are lacking.

Table 5-2.
DELAYED TYPE HYPERSENSITIVITY (HUMAN SKIN) 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 (clinical)	30 ppm	4/8 (50%)
	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.).

However, a study by Patterson et al. (1986) has demonstrated the presence of IgG, IgM, IgA, and IgE antibodies against HCHO human serum albumin (HSA), but no correlations could be drawn between the antibodies against HCHO-HSA and symptoms or complication in patients using dialysis equipment sterlized with HCHO.

5.3. Cellular Changes

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

In the Kerns 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 F-344 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 Kerns 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, other than squamous metaplasia, 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. Data submitted 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	0.2	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). Out of a total of 156 observations per group.

The effect of HCHO on nasal mucociliary function in the rat has been studied by Morgan et al. (1986) (see Section 4.4.3.2.). Male Fischer 344 rats were exposed for 6 hours per day for 1, 2, 4, 9 or 14 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.

The affects of HCHO on the human nasal system has been studied by a number of authors. Anderson and Molhave (1983) reported decreases in nasal mucus flow rates at air concentrations as low as 0.38 ppm. In a study of five employees of a sporting goods store in which pressed wood panels were used in the basement, Solomons and Cochrane (1984) report finding nasal turbinate swelling in all five employees that persistent at least four months beyond the point measures were taken to reduce exposure to the point that no irritation symptoms remained. Unfortunately, actual HCHO concentrations were not measured. However, the lack of eye irritation may indicate that HCHO concentration had been reduced to below about 1.0 ppm or may indicate tolerance to HCHO. Initial concentrations may have been much higher (>3 ppm) because the employees could not stay in the basement for more than a few minutes due to intolerable eye and upper respiratory tract irritation, choking, and marked

dyspnea. Lacroix et al. (1985) report on the clinical assessment of 76 children who had been exposed to UFFI. Among the many symptoms observed were abnormal nasal mucosa and nasal secretions. Finally, in a study of workers processing particleboard by Edling et al. (1985), it was found that the group exposed (20 men) had a significantly higher nasal mucosa histological score (points were assigned to eight factors describing histological characteristics, e.g. loss of cilia, keratosis, etc.) than a referent group of 25 men. HCHO exposure levels were in the range of 0.1-1.1 ppm. Average exposure time for the men was seven years. Five of the exposed group (25%) had swollen or dry changes, or both, of the nasal mucosa. This was characterized histologically as loss of cilia and goblet cells, squamous metaplasia, and, in some instances, mild dysplasia.

In summary, it is clear that observable cellular changes begin to occur above 1 ppm HCHO in animals, 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. The human data indicate that mucocillary clearance system effects may be occurring in humans at concentrations as low as 0.1 ppm, but data in this regard are sparse. Consideration of the animal data indicates that the rat model is a reasonable predictor of human effects, even though a rat is obliged to breathe through its nose, whereas a human is not.

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, 1974; Widdicombe, 1977). Reports suggesting that inhibition of the clearance system may predispose certain children to respiratory infections were reviewed by the Consensus Workshop (1984). Their conclusion was that better designed studies are needed to characterize this effect. In a study by Tuthill (1984) of respiratory disease in children and woodstove use, it was found that the strongest relationship of all study variables was that of HCHO exposure. Excess acute respiratory illness was significantly related to HCHO exposure. However, HCHO concentration was estimated using parameters such as remodeling, UFFI in walls, and mobile homes. Thus the results of this study must be tempered by this and certain design limitations.

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 (CNS) responses to HCHO have been tested in a variety of ways, including 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). However, in general, how HCHO affects the CNS is not clearly defined (Consensus Workshop, 1984).

5.4.1. Neurochemical Changes

Studies using radiolabeled HCHO have shown radioactivity in the brains of rats after inhalation exposures. However, the chemical identity of the radioactive material has not been determined. It is unlikely to be HCHO because of its rapid metabolism. Some kind of condensation product or labeled amino acid from one-carbon metabolism may be present.

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 because of the testing protocol.

HCHO (at high concentrations) has been reported to cause cerebral acid proteinase activity in rats in one study and decrease in cerebral RNA concentration, together with decreases in the succinate dehydrogenase and acid proteinase activities, in another (Consensus Workshop, 1984). In a study by Boja et al. (1985) in which rats were exposed to 5.0 ppm HCHO, for 3 hours on 2 consecutive days, levels of 5-hydroxyindoleacetic acid,

3,4-dihydroxyphenylacetic acid, and dopamine were increased in the hypothalamus. The toxicological significance of these neurochemical changes is unclear.

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

Several 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). More recent studies by Kilburn et al. (1985a, 1985b) of histology technicians showed disturbances of memory, mood, equilibrium and sleep that occurred simultaneously with headache and indigestion in 76 women technicians, while male technicians were not appreciably different than a male comparison group. 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 secondary 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 for 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 such as, increased duration of gestation and body weight of offspring, microscopic changes in the liver, kidneys, and other organs of fetuses from exposed

dams, and decreased levels of nucleic in the testes of exposed males.

A dermal study by Overman (1985), reported that applications of formalin to the backs of pregnant hamsters for 2 hours per day on day 8, 9, 10 or 11 of gestation increased resorptions but did not cause birth defects. The author speculated that the increased incidence of resorptions may have been stress related because of evidence that rats and mice subject to stress experience increased resorptions, but no teratogenic effects in the survivors (see Kimmel et al., 1976).

A study by Marks et al. (1980) was reviewed by the Consensus Workshop (1984) which concluded that it was the only adequate study (at that time) 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 in vivo, a number of investigators exposed animals to hexamethylene-tetramine 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.

Glycerol formal (GF), a possible slow HCHO-releasing agent, has been reported to be teratogenic in the rat. However, Asby et al. (1986) studied the hydrolysis of GF and its effects in a mouse bone marrow micronucleus assay, which is known to be sensitive to certain slow HCHO-releasing agents. No hydrolysis was observed and the micronucleus assay was negative. Consequently, the teratogenic activity of GF is unlikely to be due to HCHO (Asby et al., 1986).

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.

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 causal 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 and 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. Consequently, it is uncertain whether the effects reported are due to HCHO itself, to another chemical agent, or to the interaction of numerous chemicals.

The Consensus Workshop (1984) reviewed three studies related to the potential of HCHO to cause germ-cell mutations. A study by Fonlignie-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 Epstein 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.

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 and Ulsamer (1984) summarizes the association between exposure to HCHO and effects on 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).

Gibson (1984), in reply to Beall and Ulsamer (1984), notes the absence of any hepatic changes attributed to HCHO in the Kerns et al. (1983) (CIIT study) study. Also, other than effects in the respiratory systems of rats and mice, HCHO has not been shown to cause toxic effects at other sites. In the Tobe et al. (1985) study, where rats were exposed to 15 ppm HCHO for 28 months, no changes other than in the respiratory system could be attributed to HCHO exposure. A decrease in liver weight was noted, but this was assumed to be caused by a decrease in food intake, not by a direct toxic effect.

Addressing the issue of systemic effects, the Consensus Workshop (1984) stated that "There is no convincing evidence in experimental animals that inhalation exposure causes significant primary toxicologic effects in organs other than the upper respiratory tract."

6. EXPOSURE ASSESSMENT

6.1. Introduction

The sources of HCHO can be grouped into two major categories: 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 production of HCHO during incomplete combustion of hydrocarbons in fossil fuels and refuse, and certain natural processes.

The 1984 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, 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 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 the May 1985 draft risk assessment.

Subsequent to the draft risk assessment, the Agency commissioned additional contractor studies to assess garment worker (PEI, 1985) and residential (Versar, 1986a,b,c) exposure to HCHO in more depth. The exposure estimates from these reports were used as the primary basis for this risk assessment. The conclusions of these contractor reports are summarized in this document; more detailed information regarding exposure can be obtained by referring to the contractor reports.

6.3. Populations at Risk

The two populations at risk examined here are certain home residents and garment workers.

6.3.1. Home Residents

Based on a projection of manufactured housing starts by Schweer (1987), it is estimated that 7,800,000 persons may occupy new manufactured homes during the next ten years. This figure assumes 295,000 starts per year and 2.64 persons per home.

Similarly, an estimated 214,000 new conventional homes containing significant quantities of pressed wood products as construction materials will be started each year for the next ten

years with an occupancy rate of 2.95 persons for a total of 6,310,000 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. Assuming that the number of potentially exposed garment workers remains steady at 777,000, then a total of almost 15,000,000 persons over the next ten years may have the potential to be exposed to elevated levels of HCHO.

Table 6-1.
POPULATIONS AT RISK

Category	Population Estimates	
	per yr	10 yrs
Manufactured homes	779,000	7,790,000
Conventional homes	631,000	6,310,000

* Schweer (1987)

6.4. Sources of HCHO in Population Categories of Concern

The principal sources of HCHO in the two population 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 Containing Pressed-Wood Products

6.4.1.1. Pressed-wood product descriptions

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 of total production capacity). 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 was used for construction, including decking in manufactured home manufacture and flooring underlayment in conventional housing.

Recent data indicate that particleboard is used in home construction at a rate of 0.16 square feet (ft^2) ($\cong$ 0.5 m^2) per 1 cubic foot (ft^3) of indoor air volume in mobile homes. The

loading rate (ft^2/ft^3) in conventional homes is lower on average, approximately 0.05 ft^2/ft^3 ($\cong$ 0.17 m^2/m^3) (see Table 6-2). However, loading rates in conventional homes may vary considerably from homes that contain only particleboard as a cabinet material to homes whose floors are constructed with particleboard underlayment.

MDF is also a composition board. It is comprised of wood fibers and 8 to 14 percent UF resin solids by weight. Approximately 95 percent of MDF production (over 600 million square feet in 1983) was used to manufacture furniture, doors, fixtures, and cabinetry. No data are available on the precise extent of MDF's use in either mobile or conventional homes.

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 4.3 billion square feet consumed in 1983, 55 percent was used for indoor paneling, 30 percent for furniture and cabinets, and 15 percent for doors and laminated flooring.

Table 6-2. Use of Pressed-Wood Products in Home Construction

Category	Type of home[f]			
	SFD	TH	MF	MH
New Homes (U.S.)[a,b]				
Percent units containing				
Hardwood plywood paneling	7.6	9.3	8.5	most
Particleboard underlayment	30.5	9.2	1.7	most
Average loading rates,[c] (m^2/m^3)				
Hardwood plywood paneling	0.066	0.059	0.049	1.0
Particleboard underlayment	0.118	0.092	0.033	-
Particleboard shelving	0.010	0.016	0.020	-
Particleboard kitchen cabinets	0.039	0.052	0.059	-
Total particleboard	0.167	0.160	0.112	0.5
New Homes (Canada)[d]				
Percent units containing				
Particleboard	100	100	100	100
Average loading rates (m^2/m^3)				
Total particleboard	0.145	0.100	0.079	0.479
Existing Homes (U.S.)[e]				
Percent units containing				
Hardwood plywood paneling	35.5	--	--	most
Particleboard	90.3	--	--	most
Average loading rate (m^2/m^3)				
Hardwood plywood paneling	0.098	--	--	1.0
Particleboard	0.058	--	--	0.5

Note

Data reflect only interior uses of UF pressed wood products. Loading rates are for those homes containing these products.

[a]Source: NPA (1984) and HPMA (1984) for conventional homes - Based on interpretation of the results of a survey of 900 home builders (103 responses) regarding the extent of use of particleboard and hardwood plywood paneling in new homes containing these products (NAHB 1984).

[b]Source: Meyer and Hermanns (1984a), NAHB (1984), MHI (1984) for mobile homes.

(Footnotes continued on next page)

Table 6-2. Footnotes (continued)

[c] m^2 of produce surface area/m^3 of indoor air volume.

[d] Source: InterArt (1983) - based on in-home surveys at 9 SFD, 1 TH, 1 MF and 1 MH. Total loading includes underlayment, shelving and cabinets. SFD loadings ranged from 0.028 to 0.491 m^2/m^3.

[e] Source: Schutte (1981) - Based on in-home surveys at 31 SFD. Average loadings based on homes containing these products.

[f] SFD = Single family dwelling
TH = Townhouse
MF = Multifamily dwelling
MH = Mobile home

6.4.1.2. HCHO release from pressed-wood products

Each of the pressed-wood products described above contain UF resins which release HCHO over time. The release is attributable to two basic sources (Podall, 1984):

1. Free (unreacted) HCHO present as a result of incomplete crosslinking during resin cure.
2. Decomposition of unstable UF resin or resin-wood chemical species as a result of their intrinsic instability and/or due to hydrolysis.

Free HCHO, which is present in cured resin at low levels (<1 percent) is the most significant source of HCHO release from pressed-wood products in the initial period after they are manufactured (Podall, 1984). The specific time period in which free HCHO dominates releases is not known.

The second source, decomposition and hydrolysis, pertains to the large proportion of HCHO-bearing species like methylene ureas, urea methylene ethers, and cellulose-crosslinked species that may release HCHO for a much longer period of time (Podall, 1984). These species differ in their susceptibility to hydrolytic attack and decomposition, and their relative rates and durations of release can only be hypothesized at this time.

Release of HCHO from UF-resin containing pressed-wood products is complex, with numerous interrelated aspects. The pressed-wood product manufacturing process, and other factors, affect the amount of each HCHO-releasing species present in the finished product. The resin formulation has a direct effect on

release; resins with a low HCHO:urea ratio have, when cured, a lower level of free HCHO but may be less stable and more susceptible to hydrolysis (Myers, 1984). Other additives to the resin, such as acid catalysts, change the resin chemistry and influence the release profiles. The conditions under which the resin is cured affect bond strength, determining to some extent the stability of the resin components. The character of the wood itself also affects HCHO release; the more acidic the wood, the greater the tendency for acid hydrolysis and HCHO release (Podall, 1984).

Under normal use conditions, the release of HCHO decreases with time, as discussed previously. Emission reductions linked to product aging relate to a decrease over time in both the HCHO present in the board as a residual from manufacturing and the latent HCHO present in the board in hydrolytically labile resin and wood components. The emission rate decay curve for a board is apparently exponential with time; the residual HCHO is emitted at relatively high rates followed by a slow release of latent HCHO. Although the short-term emission rate behavior of boards has been reported in numerous studies, little quantitative information is available on the long-term emission rates, particularly for newer products made with low HCHO-urea ratio resins or treated with scavengers.

6.4.1.3. 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
  - 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.

The Consumer Product Safety Commission (CPSC) in 1982 prohibited the installation of UFFI in residential buildings and schools. Although it was later overturned by a Federal court, the CPSC ban on UFFI caused the virtual elimination of the UFFI industry (Formaldehyde Institute, 1984). There is considerable debate among the regulatory agencies and the UFFI industry as to the extent of long-term HCHO emissions from UFFI presently in place (Hawthorne et al., 1983). UFFI is not discussed in detail in this section; refer to Versar (1986c) for further information and references.

Though no residential sources of HCHO have been as well-studied as urea-HCHO foam insulation and pressed-wood products made from UF resins, there are fairly complete data on the

importance of pressed-wood products with PF resins, on fabrics treated with UF resins for permanent press, on fueled appliances, and on cigarette smoke as sources of residential levels.

Common applications of PF resin pressed-wood products include roof and wall sheathing, subflooring, and siding. Small amounts are used for shelving, cabinets, indoor paneling, and fixtures (APA, 1984). Phenol-HCHO resins are inherently more stable than are UF resins, and pressed-wood products made of PF resin emit HCHO at much lower rates than do products made with UF resins. The small amount of HCHO that is emitted from the panel products is the result of residual HCHO that remains in the resin (APA, 1984).

There are several published studies on HCHO emissions from PF pressed-wood panel products. Myers and Nagaoka (1981) found that HCHO levels in chamber tests rarely exceeded 0.1 ppm in the presence of PF particleboard at 25°C. Matthews et al. (1983, reports X-XV) tested PF hardboard and softwood plywood and obtained similar results. Myers (1983) measured higher levels (0.3 ppm) initially in tests of waferboard and particleboard made with PF resins, but levels declined rapidly. The American Plywood Association (APA, 1984) has submitted data (reviewed by Versar, 1986c) indicating that PF-resin pressed wood products emit little HCHO.

Other generic product lines containing PF that are used in construction applications are fibrous glass insulation and

ceiling tiles. In 1983, as a result of a study on HCHO release from consumer products (Pickrell et al., 1982), CPSC decided to further evaluate HCHO emissions from fibrous glass insulation and ceiling tiles. These products, when compared with other products tested, were among the highest group of emitters tested by Pickrell et al. (1982). Concern about these test results arose because of the high loading rates of these products in homes. Under normal use conditions (in attics), insulation would be subjected to temperatures much higher than normal room temperatures, thereby increasing potential HCHO emissions.

Further evaluation by Matthews et al. (1983) and Matthews and Westley (1983) (under contract to CPSC) indicated that a predicted increase of no more than 0.022 ppm in indoor HCHO level would result from use of new ceiling tiles or new insulation. As the products age, the HCHO emission rates and resulting indoor concentrations would be expected to decline significantly.

Available data on treated fabrics (Pickrell et al., 1982, 1984) indicate that, with emission rates only as high as 115 $ug/m^2/hr$, these can be relatively important sources in homes only with large surface areas of furnishings like draperies (at least when new). The data on combustion appliances show that HCHO release is a function of whether the appliance is tuned and functioning properly. Gas stoves may emit less than 2 to nearly 30 mg HCHO per hour of use; gas heaters can emit less than 5 to over 60 mg/hr, depending on the efficiency of burning; and new kerosene heaters emit up to of 3.9 mg/hr of HCHO (Traynor et al.,

1982; Girman et al., 1983; Fortmann et al., 1984; Traynor et al., 1983; Caceres et al, 1983).

The emissions data on sidestream cigarette smoke range from 20 ug per cigarette (Bardana, 1984) to nearly 1.5 mg/cigarette (reported by Matthews et al., 1984). Several studies, however, concur on an emission rate of 1.0 to 1.2 mg/cigarette. The importance of this source is obviously related to use patterns. Studies where numerous persons chain-smoked in a poorly ventilated room (Timm and Smith, 1979) did indeed show that HCHO levels were elevated after a short period of time, but other studies (Traynor and Nitschke, 1984) in the homes of smokers indicated that, at a smoking rate of 10 cigarettes per day, HCHO levels were not elevated over controls with similar loading rates of other sources.

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 carbamate 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. HCHO Levels in Homes

Table 6-3 briefly summarizes the residential HCHO monitoring studies reviewed by Versar (1986a, c). However, because of the changing nature of pressed-wood products with UF resins and the constant evolution and improvement in monitoring techniques, this residential monitoring data base is not the most appropriate for describing current HCHO exposure in homes. Many data sets are based on investigation of homes from which complaints of HCHO symptoms have been filed; these data sets may not be representative of average exposure because of bias toward high concentrations. Homes studied before 1980 were built with

Table 6-3. Summary of Residential Formaldehyde Monitoring

Study/sampling date(s) (reference)	Number of homes	Number of samples	Mean (ppm) or range of means	Range (ppm)	Comments
CONVENTIONAL HOMES					
Fleming & Associates New York Study (Traynor & Nitschke 1984)	30	--	0.040	0.007-0.151	Non-complaint homes.
Univ. Washington (1982-1983) (Breysse 1984)	59	113	--	<0.1 to > 1.0	Primarily complaint homes. Only 4 of 113 measurements >0.5 ppm.
LBL (1979-present) (Girman et al. 1983)	24 (EE) 16 (W)	--	--	<0.005 to 0.214 <0.005 to 0.079	Includes energy-efficient (EE) and older, weatherized (W) non-complaint homes around the U.S.
Geomet (1978) (Moschandreas et al. 1978)	11	~114	0.02 to 0.16 0.05 (overall)	<0.01 to 0.50	Includes conventional, "experimental", and apartment homes around U.S. Non complaint homes. Assuming 60% of total aldehydes is formaldehyde.
Canadian UFFI/ICC (1981) (UFFI/ICC 1981)	378	--	0.034	<0.01 to ≤ 0.20	Study of UFFI and non-UFFI homes; mean is for non-UFFI homes. (Mean w/UFFI = 0.054 ppm for 1,897 homes).
ORNL/CPSC 40 Tennessee home Study (1982) (Hawthorne et al. 1984)	29	--	0.060	<0.025 to > 0.25	Study of UFFI and non-UFFI homes; mean is for non-UFFI homes. (Mean w/UFFI = 0.011 ppm for 11 homes).
Private Washington labs (1983) (Breysse 1984)	25 specified conventional	76	--	<0.05 to >0.5	None exceeded 1.0 ppm. 45 of 76 between 0.05 and 0.09 ppm.
UK study (~1980-1982) (Everett 1983)	50	--	0.041	--	Study was of UFFI and non-UFFI homes; mean is for non-UFFI homes. (Mean w/UFFI = 0.093 ppm).

Table 6-3. (continued)

Study/sampling date(s) (reference)	Number of homes	Number of samples	Mean (ppm) or range of means	Range (ppm)	Comments
Dutch study (1977-1980) (Van der Wal 1982)	36	--	--	0.032 to 1.444 (range of maximums)	Prior to control implementation. Largely complaint homes.
	5	--	--	0.048 to 0.602	After panel coating.
Houston, Texas study (1980) (Stock and Mendez 1985)	38 conventional	38	0.04	<0.008 to 0.14	Non-complaint homes; no UFFI.
	7 energy-efficient conventional	7	0.07	0.04 to 0.11	
	19 apartments	19	0.08	0.02 to 0.27	
	11 condominiums	11	0.09	<0.008 to 0.29	
	3 energy-efficient condominiums	3	0.18	0.15 to 0.20	
Sacramento, California (1982) (Wagner 1982)	12	17	0.106	0.078 to 0.163	All homes less than 5 yrs old. All homes with air exhange rates less than 0.5 per hour.
San Francisco, California (1984) (Sexton et al. 1985b)	51	51	0.038	0.013 to 0.085	Only 2 homes less than 6 yrs old. 39 homes more than 10 yrs old. Non-complaint homes.
Iowa study (1980) (Schutte et al. 1982)	31	372	0.063	0.013 to 0.34	Non-complaint homes.
SAI California survey (1984) (SAI 1984)	6	--	0.084	0.046 to 0.153	New, non-complaint homes.
	64	--	0.050	0.018 to 0.120	Older, non-complaint homes.
Indiana Board of Health study (1979-1983) (Konopinski 1983)	120	120	0.09	ND to 1.35	Study of UFFI and non-UFFI homes; mean is for non-UFFI homes; includes some complaint homes. (Mean w/UFFI = 0.05 ppm for 119 homes).

Table 6-3. (continued)

Study/sampling date(s) (reference)	Number of homes	Number of samples	Mean (ppm) or range of means	Range (ppm)	Comments
Godish (1983)	29	—	0.05	0.03 to 0.07	Study of UFFI and non-UFFI homes; mean is for non-UFFI homes containing no particleboard flooring, cabinetry or paneling. (Mean w/UFFI = 0.07 ppm for 28 homes).
Cohn (1981)	103	—	0.027	—	
Swiss homes (1983) (Kuhn and Wanner 1984)	46	--	—	~0.1 to 0.7	Highest level prior to occupancy.
Netherlands study (1981-1982) (Cornet 1983 - Holland study)	52	—	0.048 to 0.055	—	Homes without particleboard, as measured by the chromotropic acid method.
Swedish homes (1975-1977) (Sundin 1978)	319	--	0.58	0.1 to 2.0	Few details available.
Danish homes (1973) (Andersen et al. 1975)	23	—	1.44	0.07 to 1.87	Homes known to have particleboard construction materials.
MOBILE HOMES					
Geomet (1978) (Moschandreas et al. 1978)	2	84	0.21	0.07 to 0.46	Assuming 60% of total aldehydes is formaldehyde. Non-complaint homes.
Univ. Washington (1982-1983) (Breysse 1984)	430	822	—	<0.1 to >1.0	37 of 822 measurements >1.0 ppm. Complaint homes.
MHI (1984) (Conners 1984)	1	15	0.34	0.24 to 0.46	3-month old home built specifically for test
Clayton (1980-1981) (Singh et al. 1982a)	259	--	0.62 (adjusted)	0.02 to 2.9 (adjusted)	Non-complaint, occupied and nonoccupied. Concentration by home age evaluated.

Table 6-3. (continued)

Study/sampling date(s) (reference)	Number of homes	Number of samples	Mean (ppm) or range of means	Range (ppm)	Comments
Wisconsin (1980) (Anderson et al. 1983)	137	920	0.38	0.02 to 2.26	Non-complaint, occupied homes. Concentration by home age evaluated.
Minnesota (1980-1981) (Stone et al. 1981)	109	—	0.61	--	Average home age <2 yrs. Complaint homes.
Tennessee (1982-1983) (Hodges 1984)	77	--	0.30	0.02 to 1.43	Complaint homes; no age data.
	55	--	0.23	0.02 to 1.92	Complaint homes, see Table 27 for data by home age.
Kentucky (1979-1980) (Conyers 1984)	103	--	0.43	0.01 to 1.99	Complaint homes, see Table 28 for data by home age.
Texas study (1982-1983) (Univ. Texas 1983)	121	--	0.18	0.04 to 0.35	Non-complaint homes. Excludes results from one county (El Paso) where evaporative coolers were in use.
SAI California survey (1984) (SAI 1984)	3	--	0.114	0.068 to 0.144	Passive LBL sampler; one week; non complaint
California State survey (1984) (Sexton et al. 1985a, 1985b)	663	663	0.091	<0.010 to 0.464	Passive AQR monitor; one week during summer; non-complaint.

- Insufficient data in reviewed literature to report value.

ND = Not Detectable, or Below Detection Limit.

with products made of high HCHO:urea ratio resins that are no longer on the market; they cannot be considered as baseline exposures for that reason. The most appropriate data for describing current exposures in mobile and conventional homes are, therefore, those generated by random sampling of noncomplaint homes after 1980, preferably after 1982 (when manufacturers began using resins with mole ratios of 1.5 (F:U) or less). These restrictions on the "appropriate" data base still leave a considerable volume of monitoring data on levels in homes. Table 6-4 summarizes the noncomplaint (random) data on HCHO levels in conventional and mobile homes.

6.5.2. Manufactured Homes

HUD has recently promulgated changes in its Manufactured Home Construction and Safety Standards (24 CFR 3280). The changes, published in the FEDERAL REGISTER of August 9, 1984 (47 FR 31996), set product emission standards for particleboard (0.3 ppm) and plywood (0.2 ppm). HUD believes that if the product standards are met and no other major emitters of HCHO are present (e.g., medium density fiberboard), ambient levels will not exceed 0.4 ppm (EPA estimate of 0.15 ppm as a 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.

Table 6-4. Summary of Residential Monitoring Data from Randomly-Sampled Homes

Number of homes	Mean (ppm)	Range (ppm)	Investigator, date (date of monitoring)
Conventional			
30	0.040	0.007 - 0.151	Traynor 1984
40	—	<0.005 - 0.214	Girman 1983 (1979-83)
17	0.05	<0.01 - 0.50	Moschandreas 1978 (1978)
29	0.060	<0.025 - >0.25	Hawthorne 1984 (1982)
31	0.063	0.013 - 0.34	Schutte 1982 (1980)
6	0.084	0.046 - 0.153	SAI 1984 (1984)
120	0.09	—	Konopinski 1984 (1979-1983)
29	0.05	0.03 - 0.07	Godish 1983
103	0.027	—	Cohn 1981
78	0.07	<0.008 - 0.29	Stock and Mendez 1985 (1980) (includes apartments and condominiums)
51	0.038	0.013 - 0.085	Sexton et al. 1985b (1984)
Mobile			
2	0.21	0.07 - 0.46	Moschandreas 1978 (1978)
259	0.62	0.02 - 2.9	Singh 1982 (1980-1981)
137	0.38	0.02 - 2.26	Anderson 1983 (1980)
121	0.18	0.04 - 0.35	University of Texas 1983 (1982)
3	0.114	0.068 - 0.144	SAI 1984 (1984)
663	0.091	<0.01 - 0.48	Sexton et al. 1985b (1984)

EPA estimates a ten-year average ambient HCHO level of 0.10 ppm for new manufactured homes. EPA has used this estimate and the estimated 10-year average for new homes that just meets the HUD target level of 0.4 ppm (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.

The average HCHO level in mobile homes appears to have declined in recent years due to the use of lower-emitting pressed wood products in mobile home construction and to the natural decay of HCHO emissions from products in existing mobile homes. Average levels in the existing stock of mobile homes are now around 0.2 to 0.5 ppm, with mean levels in individual homes (including complaint homes) ranging from less than 0.1 to over 1.0 ppm.

This apparent decline is shown graphically in Figure 6-1. The Conyers (1984) study of complaint mobile homes, initiated in 1980, showed mean HCHO levels of 0.85 ppm in new homes. An

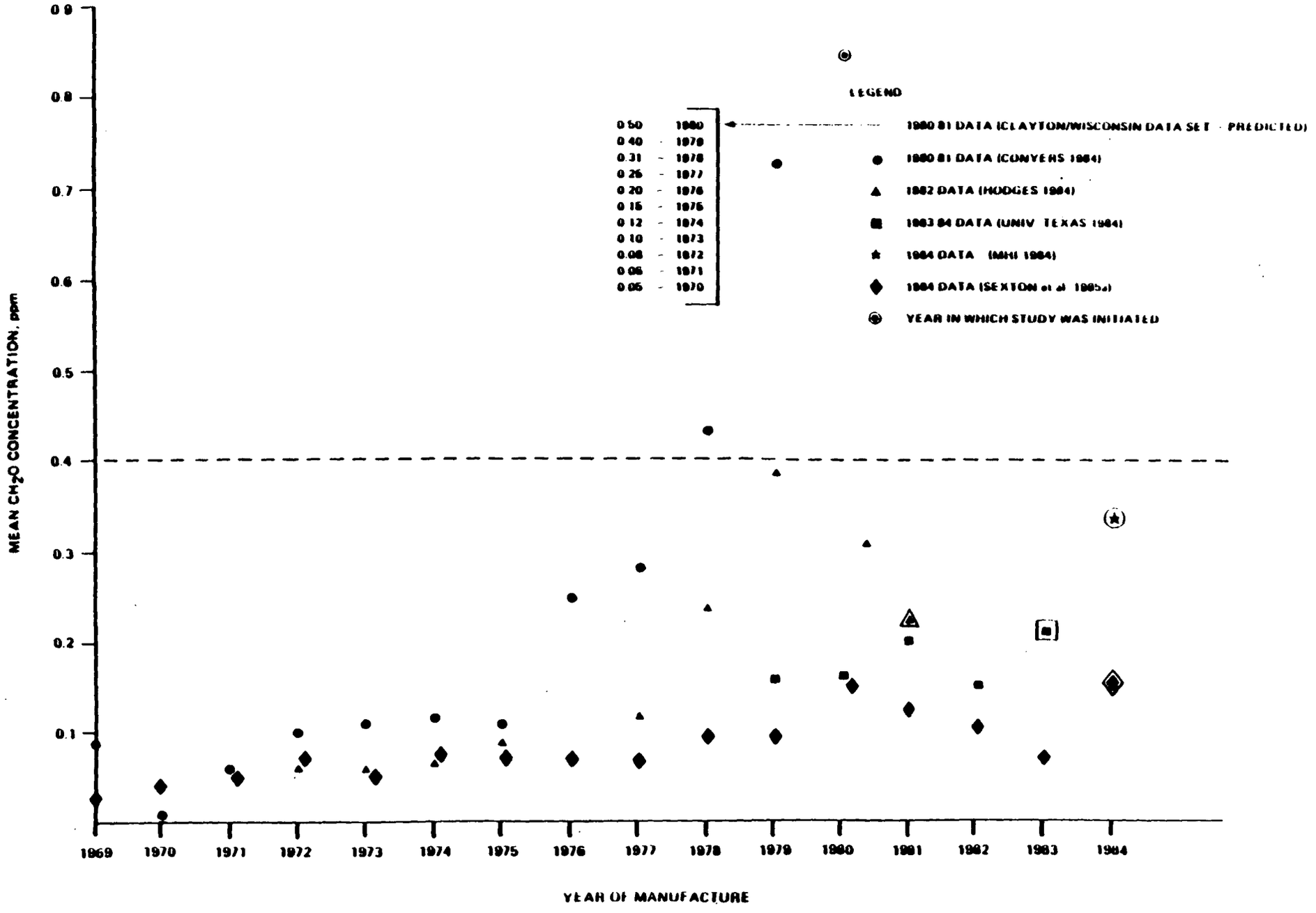


Figure 6-1. LEVELS IN MOBILE HOMES CORRESPONDING TO YEAR OF MANUFACTURE

exponential function describing the relationship between HCHO level and home age (r^2=0.35) for the combined Singh (1982) and Anderson (1983) data (i.e. the Clayton/Wisconsin data set) (1200 data points) predicts an average level of 0.5 ppm in new 1970 to 1980 vintage mobile homes (noncomplaint). Results of studies begun in more recent years (University of Texas, 1984; MHI, 1984; Sexton et al., 1985; Groah et al., 1985) indicate that initial HCHO levels in new homes on average fall within the range of 0.2 to 0.3 ppm.

Using the exponential function describing the Clayton/ Wisconsin data to estimate decay of HCHO emissions over time, 10 year average concentrations can be estimated. For initial concentrations in new homes of 0.5 ppm (i.e., Clayton/Wisconsin data set), 0.4 ppm (i.e., the HUD target level), and 0.25 ppm (i.e., midpoint of range of recent study of new home levels), the 10-year average concentration estimates are 0.19 ppm, 0.15 ppm, and 0.10 ppm, respectively.

The fraction of homes with elevated levels of HCHO also appears to have declined in recent years. Figure 6-2 shows that the majority of homes less than 215 days old in the Clayton/ Wisconsin data set had HCHO concentrations above 0.4 ppm. More recent studies indicate that this fraction is decreasing. The California survey of 663 mobile homes (Sexton et al., 1985) reported levels exceeding 0.4 ppm only in two and three-year old homes. The Texas study (University of Texas, 1984) reported that

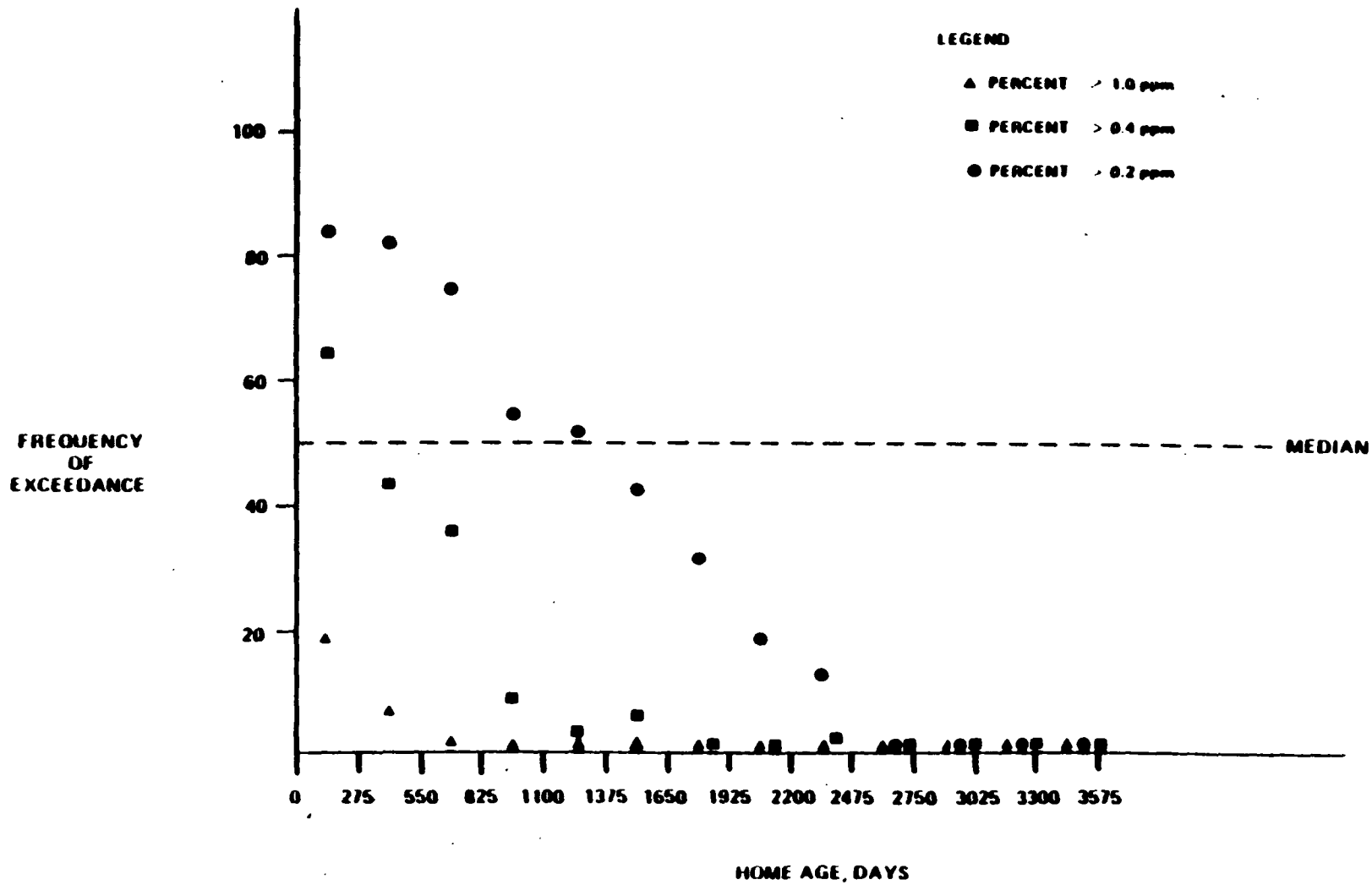


Figure 6-2. FREQUENCY OF FORMALDEHYDE LEVELS, BY HOME AGE, EXCEEDING 1.0, 0.4, AND 0.2 ppm IN CLAYTON AND WISCONSIN DATA COMBINED

the highest mean in any group of homes was 0.35 ppm (ten homes in one county less than one year old); it is likely that one or more of these had levels above 0.4 ppm, but not approaching 1.0 ppm.

Levels measured at any one temperature and humidity can, however, be misleading. Table 6-5 which illustrates the effect of temperature and humidity changes on a 0.4 ppm reading at 25°C and 50 percent relative humidity (the HUD target) shows that under more extreme conditions (30°C/70 percent RH), the predicted level could rise to 0.92 ppm. Because changes in temperature and humidity occur over the course of a day and with 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, 1986b).

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 level 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 6-6 and 6-7, and Figure 6-1) they could be expected to occur in a substantial fraction of new manufactured homes.

Table 6-5. 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 6-6.
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. Three measurements were typically taken in each single-wide home and four measurements were taken in each double-wide home. The data in the Table reflect the average concentration measured in each home.

Source: Versar (1986a) statistical analysis of data supplied by Singh et al. (1982).

Table 6-7.
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 (1986a) statistical analysis of data supplied by Wisconsin Division of Health (1984).

6.5.3. Conventional Homes

The average HCHO levels reported in several monitoring studies of conventional homes range from less than 0.03 to 0.09 ppm (see Table 6-4). Newer homes and energy efficient homes with low air exchange rates tend to have higher HCHO levels (often exceeding 0.1 ppm) than older homes (Versar, 1986c). Results of recent studies indicate that initial HCHO levels in new conventional homes generally fall within the range of 0.05 to 0.2 ppm; few measurements exceeded 0.3 ppm (Stock and Mendez, 1985; Hawthorne et al., 1984; SAI, 1984; Wagner, 1982). Computer modeling to estimate initial HCHO levels in conventional homes built using significant amounts of pressed wood (i.e., either underlayment, paneling or both) yields values ranging from 0.1 to 0.2 ppm (Versar, 1986). Using the exponential decay function described in Section 6.5.2, the 10 year average concentration for a home with an initial concentration of 0.15 ppm (i.e., approximate midpoint of range of new home levels) is estimated to be 0.07 ppm. Summaries of some of the major HCHO monitoring studies are presented below.

The Lawrence Berkeley Laboratory (LBL) has summarized HCHO concentrations in 40 residential 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 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 1981 Canadian study (UFFI/ICC, 1981) also studied non-UFFI homes. Table 6-8 summarizes these data, showing that levels in none of the 378 homes exceeded 0.2 ppm.

Table 6-8. 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 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. Neither the age of the homes nor the age of the UFFI installations was reported.

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 6-9 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 6-9. 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) HCHO levels were found to fluctuate significantly both during the day 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 6-10. A total of 6 of the 189 samples (3.1 percent) were over 0.5 ppm and 56 samples (26.5 percent) were over 0.1 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.

Table 6-10. 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 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.
- 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.

Stock and Mendez (1985) measured HCHO concentrations inside 78 homes in the Houston, Texas area during the summer of 1980. No mobile homes, UFFI homes, or complaint homes were sampled. Indoor concentrations ranged from less than 0.008 ppm to 0.29 ppm with an average value of 0.07 ppm for detectable concentrations (Number of samples, N=75). Three energy efficient condominiums had, as a housing category, the highest mean level (0.18 ppm). Condominiums (N=11), apartments (N=19), and energy-efficient houses (N=7) represented the mid-range with mean levels of 0.09, 0.08, and 0.07 ppm, respectively; the mean of 38 conventional houses was 0.04 ppm.

Wagner (1982) measured HCHO levels in 12 California homes that fall into a prescribed "worst-case" category of building and occupancy characteristics (i.e., low infiltration and ventilation rates, new construction, presence of gas stoves). Weekly average

concentrations ranged from 0.078 to 0.163 ppm with a mean of 0.106 ppm.

Sexton et al. (1985) measured HCHO levels in 51 home dwellings. Weekly average concentrations ranged from 0.013 to 0.085 ppm with a geometric mean of 0.035 ppm and an arithmetic mean of 0.038 ppm. Seventy-six percent of the homes were more than 10 years old and only two were less than six years old.

A downward tend in HCHO levels in conventional homes is seen in Figure 6-3. The relative proportion of low HCHO levels in homes that have been monitored has increased over the past six years, and the proportion of high levels have decreased. These data are limited and caution in interpretation is recommended (Versar, 1986a).

6.5.4. Garment Worker Exposure

HCHO levels in apparel manufacturing facilities were generally below 3 ppm prior to 1980 (see Table 6-11). OSHA had established a 3 ppm TWA (time-weighed average) in 1967. However, OSHA is presently considering establishing a new level (see 50 FR 50412; December 10, 1985). The ACGIH (American Conference of Government Industrial Hygienists) recommended level is 1 ppm TWA. In recent years, HCHO levels observed were generally below 1 ppm (see Table 6-12). The data in Tables 6-11 and 6-12 must be viewed with caution because in 1983, the National Institute for Occupational Safety and Health (NIOSH) discovered that the commercially prepared inpregnated charcoal tubes which had been used in previous personal monitoring studies were unstable.

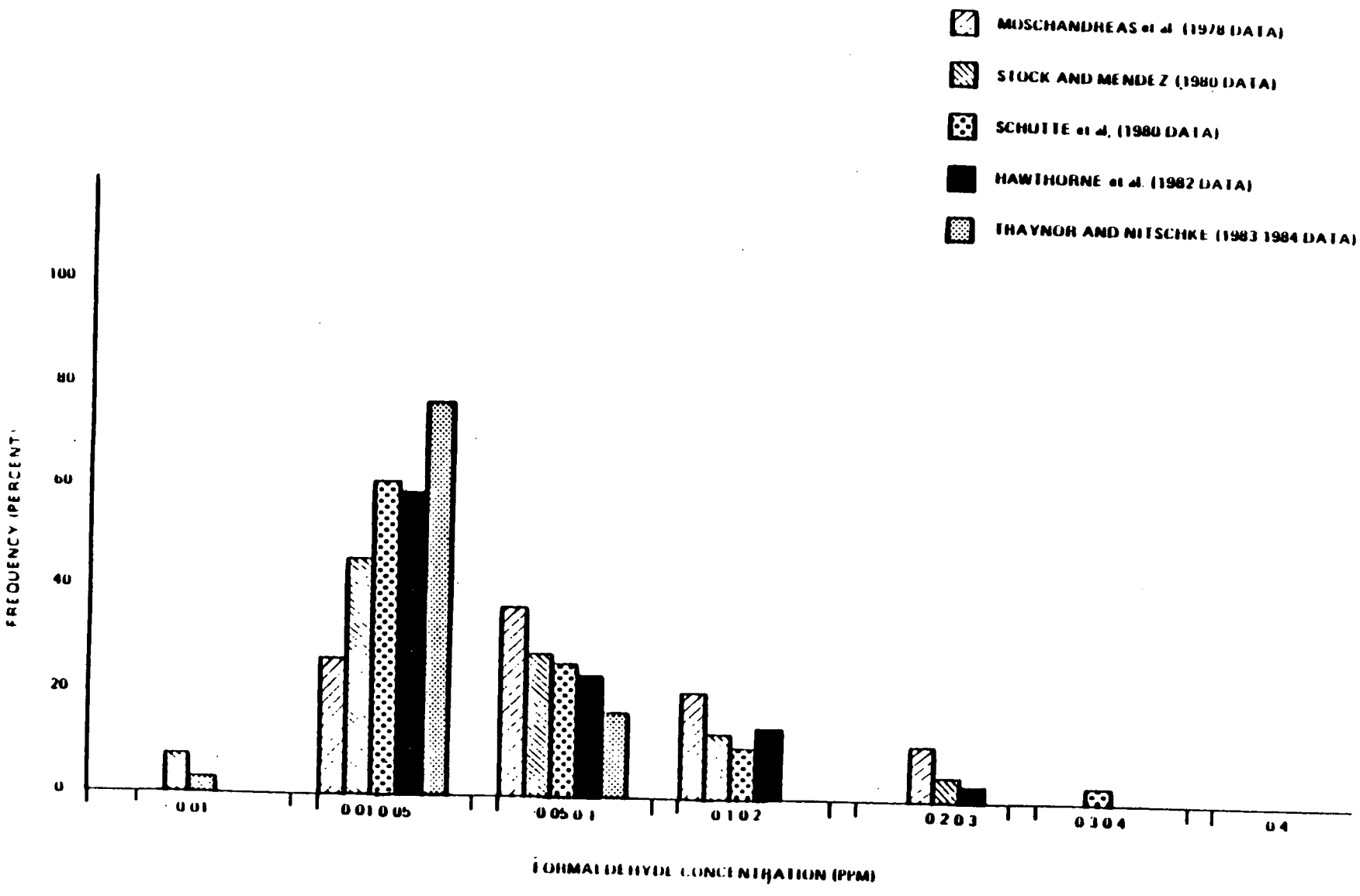


Figure 6-3. Frequency Distribution of Levels in Conventional Homes

Table 6-11. 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.	1 - 11 (1955)[d]	NS	NS
Garment manufacture	NS; formaldehyde-containing resins.	0.3 - 2.7 (TWA-area, 1966)	32	1
	Permanent press	<0.1 - 1.4 (TWA, 1979)[e]	30	1
	Permanent press	0.15 - 0.38 (TWA, 1966)[e]	9	1
	Permanent press	0.9 - 2.7 (TWA-area, 1966)	NS	2
	Permanent press	0.000-0.968 (TWA-personal, 1975)	40	1,2
	NS	2.000 - 3.840 (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. Dreager 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 6-12. RECENT MONITORING DATA FOR FORMALDEHYDE IN THE GARMENT MANUFACTURING INDUSTRY

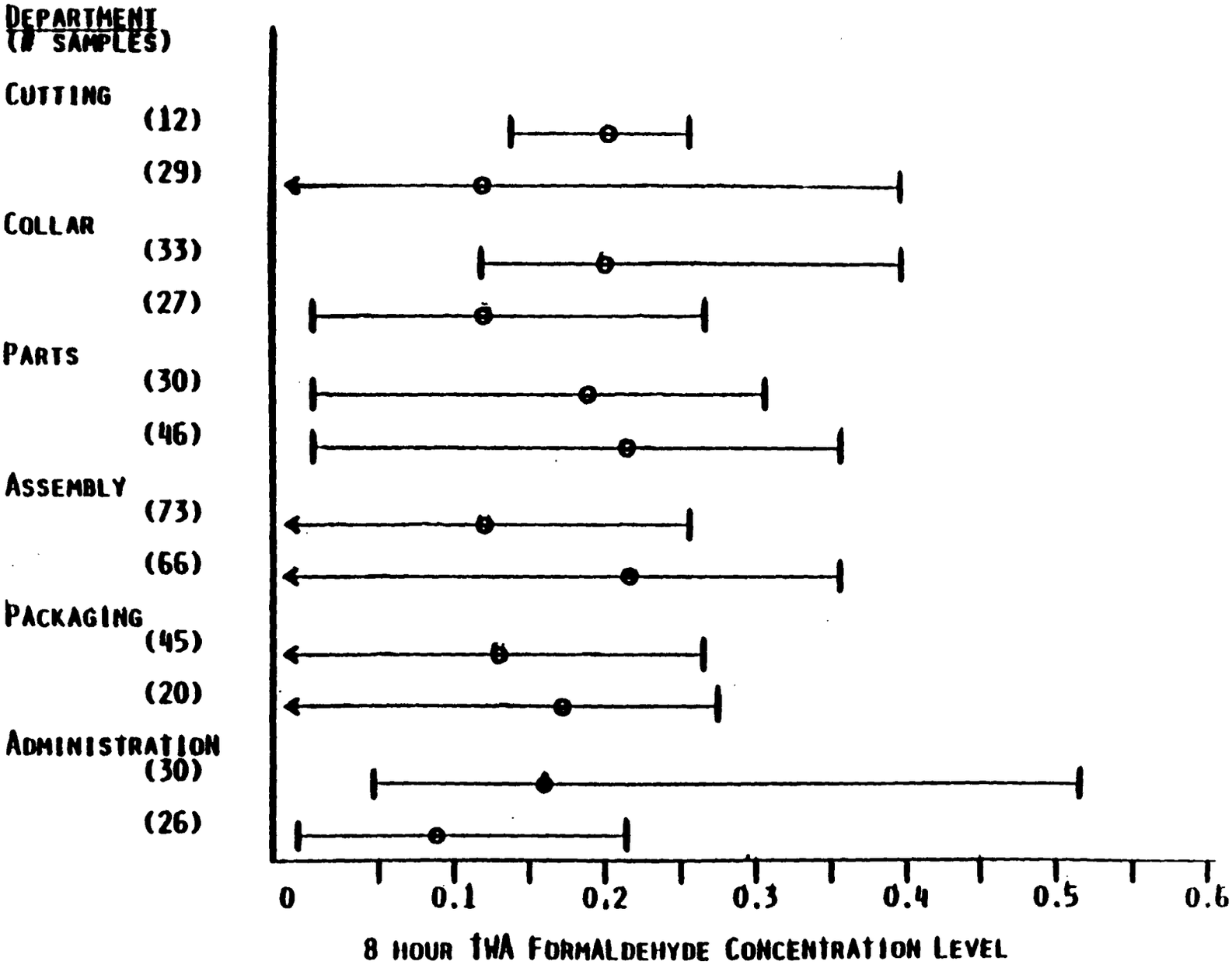
SIC code[a]	Company	Fabric type/treatment	Measured formaldehyde concentrations, ppm	Number of measurements	Sampling method[b]
2253	Manchester Knitted Fashions, Inc., Concord, NH	NS[c]	0.070-0.100 (TWA-personal, 1984)	2	NS
2311	Coastal Industries, Birmingham, AL	NS	2.0 (screen, 1982)	1	NS
	Arrow Shirt Co. Lewistown, PA	Polyesters, polyester-cotton blends, nylon blends; DMDMEU[d]	0.13-0.57 (TWA-area, 1980) 0.14 (TWA-personal, 1980)	9 1	1 1
2321	Woolrich Woolen 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.[e] Americus, GA	Cotton and polyester; formaldehyde-based resin, precured	0.050-0.40 (TWA-personal, 1983) 0.34-0.37 (TWA-area, 1983) 0.27-0.44 (Grab, 1983)	12 2 14	4 4 5
	C. F. Hathaway Co. Bauer-Foxcraft, NC	NS; formaldehyde-based resin precured	<0.12-0.22 (TWA-breathing zone, 1981)[f] 0.08-0.17 (TWA-area, 1981) 0.13-0.21 (TWA-area, 1981) 0.32 (Peak, 1981)	20 22 NA[g] NA	4 1,4 5 5
	C. F. Hathaway Co. Waterville, ME	NS; formaldehyde-based resin precured	<0.12-<0.27 (TWA-breathing zone, 1981)[f] 0.08-0.30 (TWA-area, 1981) 0.10-0.08 (TWA-area, 1981) 0.94 (Peak, 1981)	20 24 NA NA	4 1,4 5 5
	Kingston Shirt Co.[h] Kingston, NC	NS; formaldehyde-based resin precured	<0.060-3.57 (TWA-personal, 1982) 0.15-0.47 (TWA-area, 1982)	12 2	4 4
	Arrow Shirt Co. Atlanta, GA	NS; formaldehyde-based resin precured, pre-cut	1.02-2.23 (TWA-breathing zone, 1980) 0.87-2.07 (TWA-area, 1980) 0.1-1.0 (Grab, 1980)	19 10 10	4 1,4 5
		NS; DMDMEU, precured, pre-cut	0.034-0.794 (TWA-personal, 1981) 0.00-0.48 (TWA-area, 1981)	101 17	4 5
	Arrow Shirt Co. Lewistown, PA	NS; formaldehyde-based resin pre-cured, pre-cut	0.15-0.30 (TWA-personal, 1981) 0.11-0.48 (TWA-area, 1981) 0.34-0.58 (TWA-area, 1981) 0.71 (Peak, 1981)	10 22 NA NA	4 1,4 5 5
2328	Lee County Mfg. Co.	NS	0.440 (Ceiling-area, 1982)	1	NS
	Bellcraft Mfg. Co. Atlanta, GA	NS	0.160 (TWA-personal, 1980) 0.320 (Peak, 1980) 3.000 (Screen, 1980)	2 2 1	NS NS NS
	Lee Co. Inc. Birmingham, AL	NS	0.000 (Screen, date unknown)	1	NS

Table 6-12. **(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	0.02-0.54 (TWA-personal, 1982) 0.58 (TWA-area, 1982)	36 2	1,2,? 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., NJ	NS	0.000 (Screen, 1980)	1	NS
2352	Harber 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. Dreager Brand indicator tubes
7. P & CAM 350.
[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.

Table 6-13. NIOSH Monitoring Data--Ranges by Department



Thus, the monitoring data above may be suspect since the loss of HCHO from the tubes was 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 in-depth 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 6-13 and 6-14. These tables show that all levels of exposure were less than 0.51 ppm TWA. Also, as Table 6-13 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 very narrow and compares well within the overall combined mean exposure level of 0.17 ppm, which was used for the quantitative cancer risk assessment. In addition, the average exposure levels used in EPA's section 4(f) determination (EPA, 1984), 0.23 ppm (area) and 0.64 ppm (personal) (Versar, 1982), were also used for this cancer risk assessment.

Table 6-14.

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 affect variation in HCHO levels in these plants include variation in ambient temperature, humidity, type of fabric 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 narrow. 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 new HUD Standard homes of 0.15 ppm or less. 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 conventional homes, although reported mean levels are lower, 0.03 to 0.09 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. The ten-year average HCHO concentration for a new home built with significant amounts of pressed wood is estimated to be 0.07 ppm.

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

In principal, data from studies of humans are preferred for making numerical risk estimates. However, as is often the case, the available epidemiologic data on HCHO were not suitable for low dose quantitative cancer risk estimation, mainly because of a lack of adequate exposure information in the studies. Accordingly, results from studies in animals were used to estimate low-dose human cancer risk. This is done by fitting mathematical models to the observed animal data. In addition, even though the epidemiologic studies were not suitable for quantifying a dose-response curve, those studies with observed statistically elevated cancer risks provided some support for the animal-based predicted upper bound risk. This comparison, while yielding valuable information to the assessment, should be viewed with caution since exposure levels in these epidemiologic studies were subject to some variation.

7.1. Risk Estimates Based on Squamous Cell Carcinoma Data

Data from three different studies were considered for their appropriateness to this risk assessment, studies by Kerns et al. (1983) (the CIIT study), Albert et al. (1982) (the NYU study), and Tobe et al. (1985). Dose-response modeling was applied to the CIIT data for Fischer 344 rats using squamous cell carcinomas of the nasal turbinates as an endpoint. See Table 7-1 for the statistical significance of the response in the CIIT and Tobe studies. The NYU study provides corroborating evidence of a similar response in another strain of rats (Sprague-Dawley).

Table 7-1

Carcinoma tumor incidence in Fischer 344 rats and male B6C3F1 mice

Fisher Exact Test Results

Species	Dose (ppm)			
	Control	2.0	5.6	14.3
Fischer 344 Rats of the CIIT Study (males and females combined)	0/156 (0)	0/159 (0) [a]	2/153 (.01) p_f=0.24 [b]	94/140 (.67) p_f<0.01
	Control	2.0	5.6	14.3
B6C3F1 Mice of the CIIT Study (Males)	0/109 (0)	0/100 (0)	0/106 (0)	2/106 (.02) p_f=0.24
	Control	0.3	2.0	15.0
Fischer 344 Rats of the Tobe Study	0/32 (0)	0/32 (0)	0/32 (0)	14/32 (.44) p_f<0.01

a/- Numbers in parentheses are proportions responding.

b/- Fisher Exact Test p-value. Small values indicate that the response in dosed animals may be significantly different from the response in the control animals. This p-value should be compared to 0.017 for significance at the 0.05 level. This is a multiple comparison, which uses a critical value of α/k for k (in this case k=3) comparisons with the same control group.

Table 7-1

Neoplastic polypoid adenoma incidence in Fischer 344 rats.

Fisher Exact Test Results

Species	Dose (ppm)	
	Control	2.0
Polypoid Adenomas in Fischer 344 Rats of the CIIT Study.	1/156 (1)	7/159 (.04) p_f=0.04

That study, however, was considered less appropriate for risk estimation since it contains only one nonzero exposure concentration, and, based on the CIIT data, one would expect the true dose-response curve in the experimental range to be highly nonlinear. The Tobe study was not relied on for primary risk estimation because a tumor response was seen only at the highest dose group and the number of animals per group was relatively small (32). However, risk estimates based on the Tobe data are discussed in sections 7.3 and 7.4. 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 and responses at those 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 were 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 respective 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. These numbers were for the significance tests in Table 7-1.

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.

Administered dose expressed as ambient air concentration was used directly as the measure of dose in this assessment. 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 of the uncertainty associated with this approach (as discussed previously). However, use of these data reduces the maximum likelihood estimate of risk approximately by a factor of 50 and reduces the upper bound estimate of risk by a factor of 3.

Since risk at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models and procedures have been developed to extrapolate from high to low doses. Different extrapolation methods may give a reasonable fit to the observed data but may lead to large differences in the projected risks at low doses. In keeping with EPA's Guidelines for Carcinogen Risk Assessment and the OSTP Principle Number 26, the choice of low dose extrapolation method is based on consistency with current understanding of the mechanisms of carcinogenesis and not solely on goodness of fit to the observed tumor data. When data and information are limited, and when uncertainty exists regarding the mechanisms of carcinogenic action, the OSTP principles suggest that models or procedures which incorporate low-dose linearity are preferred when compatible with the limited information available. EPA's Guidelines recommend that the linearized multistage procedure be employed in the absence of

adequate information to the contrary and specify the possible presentation of various other models for comparative purposes. This presentation is given in Appendix 3. In addition, see Cohn (1984), Siegel et al. (1983), Brown (1984), Sielken (1983) and Clement Associates (1982) for discussions concerning quantitative methods/models for quantifying the potential risks to humans from HCHO based on the Kerns et al. (1983) study.

The behavior of eleven models used to extrapolate risks was examined in Appendix 3. These were all dichotomous models ("tumor-no tumor" models). These models along with their parameter estimates, standard errors, log-likelihoods, and χ^2 goodness-of-fit test statistics and p-values are presented for the CIIT Fischer 344 rat data on squamous cell carcinomas. Those interested in the underlying assumptions of these models and their mathematical form are referred to Appendix 4.

Each of the eleven models listed in Appendix 3 was used to extrapolate risks from the CIIT rat study. They were the additive and independent forms of the probit, logistic regression, Weibull, and gamma-multihit models and the one, three and five stage multistage models.

The multistage model without restrictions on the order of the polynomial in dose is the model of choice. As discussed above, the Guidelines specify that unless another model can be justified, the linearized multistage procedure will be employed (EPA, 1986). In the case of HCHO, we know that it is mutagenic, can react with nuclear material and processes, is structurally

related to other carcinogens, is cytotoxic, and is clearly carcinogenic in the rat. All reasons that taken together justify use of the linearized multistage procedure.

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 bounds in the dose ranges of interest. The latter corresponds to the number from a linearized multistage model procedure.

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 Workshop on Formaldehyde (1984). In addition, although much data have been developed to elucidate the possible mechanism for the nonlinear carcinogenic response observed in the CIIT rat study, at this time low dose linearity cannot be ruled out.

The likelihood of response was 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 = 1.5, 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 unit risk and estimated individual and population risks to humans for various exposure categories are presented in Table 7-2.

Table 7-2.
ESTIMATED RISKS BASED ON 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	Upper Bound Estimate of Risk
Mobile Home Residents	7,800,000*			
1. Based on current monitoring data		0.10 ppm (112 hrs/wk for 10 yrs)	2×10^{-10} [B1] (<1)	1.5×10^{-4} [B1]** (1,170)
2. Based on HUD target level		0.15 ppm (112 hrs/wk for 10 yrs)	1×10^{-9} [B1] (<1)	2×10^{-4} [B1] (1,560)
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	6,310,000*	0.07 ppm (112 hrs/wk for 10 yrs)	6×10^{-11} [B1] (<1)	1×10^{-4} [B1] (630)
Unit Risk		1 ug/m^3-- 0.00082 ppm (for 70 yrs)		1.3×10^{-5} [B1]

*Population estimates are based on anticipated additions to the housing stock over the next 10 years as estimated by Schweer (1987).

**Classification under EPA's Guidelines for Carcinogen Risk Assessment--
[B1]=Probable Human Carcinogen.

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 for analysis pruposes.

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. Other explanations are also possible as discussed in section 7.4.1.

Risk estimates using polypoid adenomas appear in Table 7-3. 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 7-3.
RISK EXTIMATES USING POLYPOID ADENOMA DATA

Category	Dose	Maximum Likelihood Estimate of Risk	95 Upper Confidence Limit on Risk
Mobile Home Residents Based on HUD Target Level	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}
Unit Risk	1 ug/m^3-- 0.00082 ppm (for 70 yrs)		1.7×10^{-4}

7.3. Uncertainty in Risk Estimates

Model-derived risk estimates should be viewed in the proper context. The upper bound estimate should not be viewed as a point estimate of risk. As the Guidelines state (EPA, 1986): "the linearized multistage procedure leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may be as low as zero." Other factors are also important.

As Table 7-2 illustrates, there is a wide range between the MLE and upper bound estimates, 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 Kerns 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

Ten perturbations of the squamous cell carcinoma data for the Fischer 344 rats were selected by slight alteration in one of the dose-response proportions or the elimination of a dose level from the study in an attempt to show sensitivity to these perturbations was examined by modeling. These estimates appear in Appendix 5. It was found that, in general, slight perturbations of the data do not significantly disturb the predictive power of the model for upper bound estimates. This is not the case for MLEs. Only extreme perturbations significantly affect upper bound risk estimates. Consequently, when modeling data that are very non-linear, one should not place great certainty on MLE estimates. In addition, model choice can lead to uncertainty. As Appendix 3 illustrates, there is a wide divergence in risk estimates obtained using the CIIT rat data. Independent background, tolerance distribution models such as, the probit, logit, and Weibull, produce estimates indicating virtually zero risk (probit predicts zero risk). The independent and additive background gamma-multihit models produce similar results. However, when additive background models are used risk estimates are much higher, with the multistage model giving the highest risks. As discussed in section 7.1, the linearized multistage procedure was used for primary risk estimation.

As discussed above, the major contributor to the uncertainty seen in the risk estimates using the multistage model is the steep dose-response seen in the Kerns 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. Even so, the marked nonlinearity of the response introduces considerable uncertainty into any discussion of the possible mechanism of HCHO induced carcinogenicity at exposures below the experimental range.

The different responses seen in the animals tested also leads to a degree of uncertainty. Although rats, mice, and hamsters have been tested in long-term bioassays, only in rats have statistically significant numbers of neoplasms been observed. Only two carcinomas were seen in mice at the highest dose in the CIIT study, but the nature of this response is complicated by the fact that mice are able to reduce their breathing rate to a greater extent than rats. If this effect is accounted for, the "dose" mice received at 14.3 ppm is approximately that which the rats received at 5.6 ppm, where two carcinomas were observed. Consequently, on a "dose" received basis, rats and mice may be equally sensitive to HCHO. Although no neoplasms were seen in the hamster study, a number of factors may be responsible. First, there was poor survival. About 40% of the 88 hamster died before eighty weeks, and only 20 hamsters survived ninety weeks or more. If a response comparable to that of the CIIT study were expected, 25% or five of the hamsters surviving ninety weeks or more would have had tumors. However, the duration of the study may not have permitted them to be grossly visible. Second, the limited pathology protocol may not have been able to detect small tumors. And third, the dosing

regimen and physiologic factors (changes in breathing rate) may have been factors (see section 4.1).

Although the foregoing helps explain some of the species differences observed, there remains the possibility that other, unknown, factors may be important. However, in any event, no data have been developed to show that humans would respond differently to HCHO than rats and data exist showing that rats and monkeys respond similarly to HCHO when nasal irritation and squamous metaplasia are used an endpoints.

It is often useful to compare lifetime excess risks estimated from the epidemiologic studies to those risks estimated from animal data. Tables 7-4 and 7-5 and Figure 7-1 present such a comparison. Estimated lifetime excess risk can be determined for either occupational or domestic exposure to HCHO. This comparison assumes that exposure to HCHO is associated with an increase in neoplasms at one site only and that the site-specific excess risk observed in the epidemiological study is the excess above a risk of one for the study population relative to the U.S. population (Margosches and Springer, 1983). Hence, lifetime excess risks based on the epidemiological studies are calculated by multiplying the excess risk observed in the epidemiologic study by the site-specific mortality ratio. 1980 mortality data are used in this calculation.

The estimated lifetime excess risks were based on significant associations observed in the Blair et al. (1986), Vaughan et al. (1986a,b), Hayes et al. (1986), Stroup, Harrington and Oakes (1982), and Harrington

Table 7-4.
Upper Bound Risk Estimates Based on
the CIIT Data for Given Exposures to HCHO

Exposure	Level (ppm)	Animal Based Upper Bound[a]
Resin Worker	0.24	5×10^{-4}
	1.4	3×10^{-3}
Furniture Worker	0.1	1×10^{-4}
	1.3	2×10^{-3}
Pathologists	3.2	6×10^{-3}
Mobile Home Residents (10 years)	0.19	3×10^{-4}

a Based on the linearized multistage model and the rat data from Kerns et al. (1983).

Table 7-5

Estimated Lifetime Excess Risks
Calculated from the Epidemiologic Studies

Exposure	Author	Site	Risk Ratio	Estimated Lifetime Excess Risk[a]
Resins	Blair et al.	Lung	1.32[b]	2×10^{-2}
		Nasopharynx	2.0[c]	8×10^{-4}
Resin, Glue	Vaughan et al.	Nasal Cavity & Sinuses	3.8	7×10^{-4}
HCHO & Wood	Hayes et al.	Nasal Cavity & Sinuses	1.9[c]	2×10^{-3}
Pathologists	Harrington & Shannon	Leukemia	2.0	2×10^{-2}
	Harrington & Oakes	Brain	3.31	1×10^{-2}
Anatomists	Stroup	Brain	2.7	8×10^{-3}

[a] Estimated lifetime excess risk = $(RR-1) * \left[\frac{\text{\# of site-specific deaths}}{\text{proprotion of site specific deaths}}\right]$

Mortality proportion based on 1980 deaths.

[b] Analysis of white male wage workers with greater than 20 years latency and HCHO exposure above 0ppm-year.

[c] Analysis of white male wage worker with HCHO exposure greater than 0ppm-year.

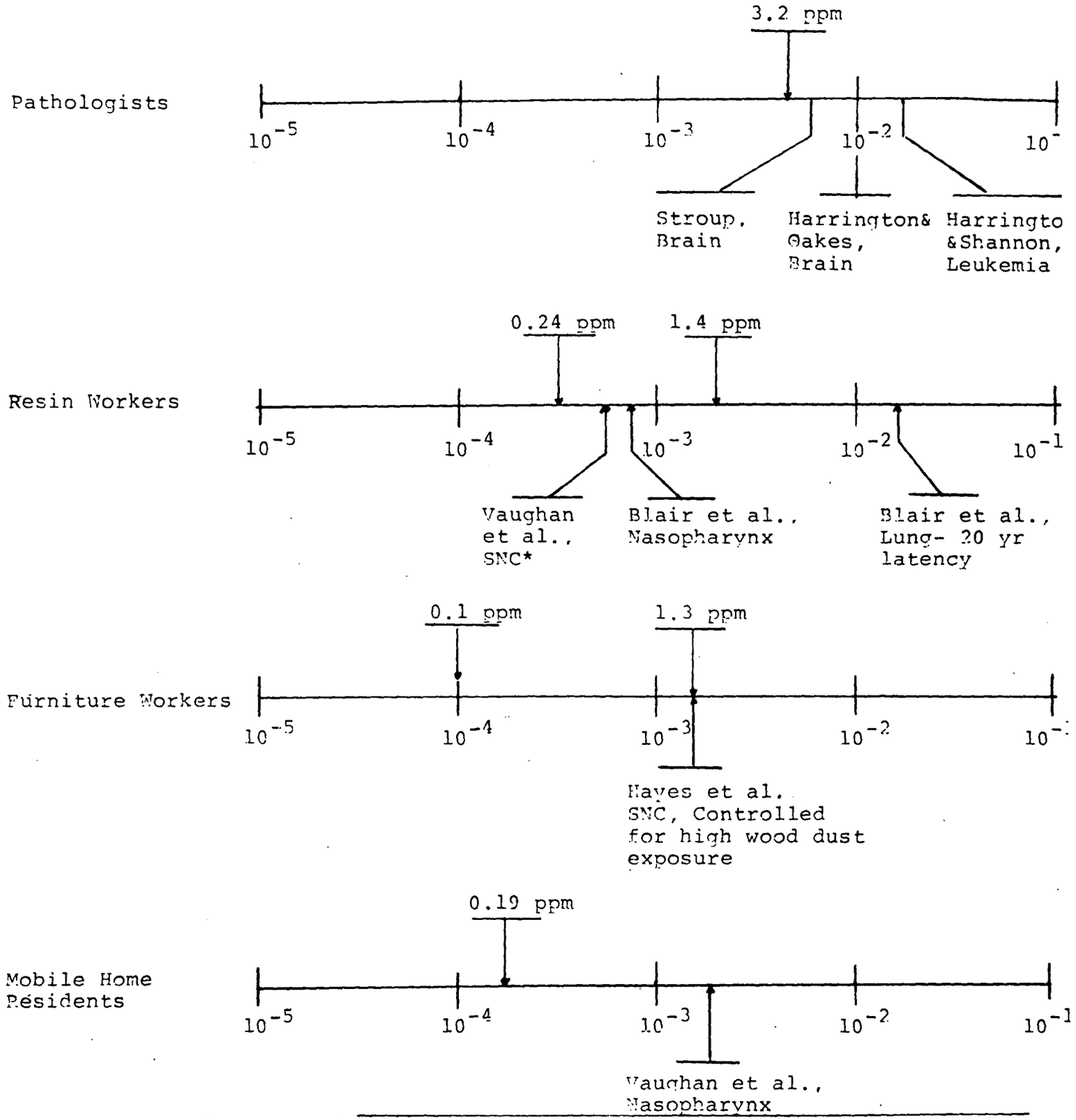


Figure 7-1. Comparison of the upper bound risks based on the animal data to estimated lifetime excess risks based on the epidemiological studies. Animal-based upper bound risks for the identified exposure level to HCHO are above the line. The estimated excess lifetime risks based on the observed excesses in site-specific neoplasms are below the line.

* Nasal sinus and cavity neoplasms.

and Shannon (1975) studies. For example, when one examines lifetime risks from exposure to resins, the estimated lifetime excess risk associated with the 35% increase in lung cancer among white males with a greater than 20 years latency reported by Blair et al. (1986) would be 2×10^{-2} and the estimated lifetime excess risk associated with their reported 200% increase in nasopharyngeal cancers would be 8×10^{-4}. The 280% increase observed by Vaughan et al., (as reported in SAIC, 1986) for nasal sinus and cavity neoplasms in conjunction with exposure greater than 10,000 hours to resins, glues, and adhesives gives an estimated lifetime excess risk of 7×10^{-4}. The upper bound risk for an exposure of 0.24 ppm HCHO based on the animal data is 5×10^{-4}, and for an exposure of 1.4 ppm HCHO, would be 3×10^{-3}.

Comparing the results reported by Hayes et al. (1986) is more complicated since Hayes et al. do not delineate the exposed population. However, if one chooses an exposure group, such as furniture workers who may be exposed to both wood dust and HCHO, one can make some observations. The reported exposure for furniture workers ranges from 0.1 ppm to 1.3 ppm HCHO as an 8-hour, time-weighted-average. Upper bound risks based on the animal data associated with these exposures are 1×10^{-4} and 2×10^{-3}, respectively. Using the 90% increase in nasal cavity and sinus risk observed in analyses which controlled for high wood dust exposure, the estimated lifetime excess risk based on the Hayes et al. study would be 2×10^{-3}.

Thus, when individual tumor types are examined, one can see that the upper bounds are not indicating larger excesses than

seen in certain studies given uncertainties about exposure. Although HCHO's potential carcinogenic effects are not expected to be limited to one site in humans because humans do not necessarily breathe through their noses as rats do, the analysis described above provides a 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-upper bound). 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. Mobile 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, three positions can be taken concerning the presentation of the risk estimates. One is to calculate risk estimates separately for squamous cell carinomas and polypoid adenomas. The second is to add the risk estimates for an overall estimate of carcinogenic risk, and the third is to assume some conversion rate for the benign tumors and then add the risk estimates as in the second position. These are discussed below.

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

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

The squamous carcinomas observed in the Kerns 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 Kerns et al. (1983) study. However, because of the nonlinearity of the dose-response relationship, there is a wide divergence between the upper bound and maximum likelihood estimates (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. Although apparently causally related to HCHO exposure, 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. Several possible explanations for these observations follow in roughly increasing order of likelihood (SAB, 1985):

- lack of a causal relationship,
- tumor modulating factors in the rat, which are induced or enhanced by HCHO exposure,
- chance (random) fluctuations in the data,
- target size decreases with loss of cell type of origin,

- o differences in time to tumor,
- o differences in diagnostic efficiency between the two kinds of tumors, and
- o competition with the simultaneously occurring carcinomas at higher doses.

Thus, it is difficult to adequately 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 Kerns 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 Kerns 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 or of the initiating agent. 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 from the squamous cell carcinoma data is dwarfed by the estimated adenoma response. For instance, the upper bound estimate of risk to garment workers exposed to 0.64 ppm of HCHO is 1×10^{-3} using squamous cell carcinoma data. The risk estimate based on benign tumors at the same concentration is 2×10^{-2}. Adding the two estimates gives 2.1×10^{-2}. Following the Guidelines (EPA, 1986) 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 Kerns study) suggests otherwise (see section 4.2.1).

It may not be correct to assume that the majority of tumors estimated for the human population from the Kerns study 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 discussed in section 4.2.1., the nature and progression of benign tumors in the nasal cavity of rats is poorly understood. The polypoid adenomas observed in the Kerns 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.

The common types of benign lesions seen in the nasal cavity of humans are nasal polyps, squamous papillomas, and transitional type papillomas.

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, squamous and transitional type papillomas are true neoplasms. Squamous papilloma of the vestibule is the most common tumor of the nasal cavity, representing approximately one-third of all benign tumors found. Malignant change is considered a rare event (Friedmann and Osborn, 1982). Transitional type papillomas have an incidence that is reported to vary from 0.4 to 19 percent of all nasal and sinus neoplasms of the mucosa (Bosley, 1984; Friedmann and Osborn, 1982; Hyams, 1971; Sellars, 1982; Lampertico et al., 1963; Seydell, 1933). Their clinical appearance 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), and are variously described as inverted squamous papilloma, cylindrical or transitional cell papilloma, and inverting papilloma (Friedmann and Osborn, 1982). The reported associated frequency of squamous cell carcinoma with transitional papilloma is between 1.5 to 50

percent (Bosley, 1984; Friedmann and Osborn, 1982; Hyams, 1971; Snyder et al. 1972; Ridolfi et al., 1977; Lasser et al., 1976; Vrabec, 1975; Osborn, 1970; Yamaguchi et al., 1979; Brown, 1964).

The most common benign mucosal gland tumor is the microcystic papillary adenoma, which is the human counterpart of the rat polypoid adenoma (Kerns, 1985). In humans, these tumors represent 1.6 percent of all tumors of the nose and sinuses and 2.4 percent of all tumors in the nasal cavity region. In addition, malignant transformation has never been encountered (Friedmann and Osborn, 1982)

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 great 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. Calculate Risks Separately But Add the Risk After Assuming a Conversion Rate for the Benign Tumors

This option is the same as the option described in section 7.4.2 except that the risk estimates generated from the benign tumor data would be adjusted to reflect the potential to progress to malignancies. This method may provide a more realistic estimate of carcinogenic risk, but it still suffers from the problem of adding estimates derived from different extrapolation procedures.

However, if one were to assume certain conversion rates based on the bioassay and human data, overall estimates of cancer risk can be presented.

In the Kerns study, 15 polypoid adenomas were observed in the exposed groups (see Table 4-1) versus one adenocarcinoma (possible malignant counterpart), which is a 1:15 ratio. For the most common human benign tumor of the nasal mucosa, transitional type papilloma, Friedmann and Osborn (1982) have documented 12 possible conversions related to between 700 and 800 papillomas, a ratio of 1:50. In contrast, the human counterpart of the rat polypoid adenoma is the microcystic papillary adenoma (Swenberg and Boreiko, 1985) which has never been reported to convert to malignancy (Friedmann and Osborn, 1982). In addition, multistage carcinogenesic protocols on mouse skin and in rat liver produce malignant to benign ratios of 1:20 to 1:100 (Swenberg and Boreiko, 1985). As discussed above, the conversion rates range from 0 to about 7 percent. Since there is uncertainty in any of the ratios discussed, assuming a 1:10 ratio, or a 10 percent conversion rate, appears reasonable. If the estimates in Tables 7-2 and 7-3 are combined using a 10 percent conversion rate, then risk estimates would be about a factor or 2.5 higher than those based on the malignant tumor data.

7.4.4. Other Considerations-Squamous Papillomas

In contrast to the Kerns study, the studies by Tobe and Albert found significant numbers of squamous papillomas instead of polypoid adenomas. Because these tumors are of the same cell type as the squamous cell carcinomas, these lesions are thought to represent the benign counterpart of the carcinomas (Consensus Workshop on Formaldehyde, 1984). However, Takano et al. (1982)

have questioned the importance of papillomas in relation to carcinoma development. In any event, papillomas were seen in two HCHO studies suggesting that both types of benign tumors should be evaluated.

The relationship between the papilloma/carcinoma response in the Tobe and Albert studies is quite constant. In the Tobe study, 5 of 19 tumors observed or 26 percent were papillomas. A similar result was seen in the Albert study were 34 of 110 tumors or 24 percent were papillomas. The papilloma response is clearly HCHO related and appeared in two strains of rats (Fischer 344 and Sprague-Dawley rat). It is not clear why no papillomas were observed in the Kerns study. However, the behavior of papillomas seen in the human population should also be evaluated since there is no reason to assume that the polypoid adenoma response in the CIIT study is more important in determining human risk than the papilloma response.

To determine the contribution benign tumors would make to risk estimates derived from the Tobe study, three data sets were used to derive risk estimates. (These estimates were not used as primary estimators of risk because there was no response at the lower dose levels which consequently leads to higher estimates of risk than those derived from the CIIT data.) One consisted of the benign tumors (5 per 32 rats), the second was the carcinoma response (14 per 32 rats), and finally combined malignant/benign (19 per 32 rats). The results from the exercise appear in Table 7-6.

Table 7-6.
RISK ESTIMATES BASED ON TOBE STUDY

	Response at 15.0 ppm (32 rats)	Risk Estimate (upper bound)	Added Risk Estimates
Papilloma	5	2.3×10^{-3}	5.1×10^{-3}
Carcinoma	14	2.8×10^{-3}	
Pooled carcinoma/ papilloma	19	2.8×10^{-3}	

As Table 7-6 illustrates, the benign tumors do not have any impact on the risk estimate derived from the pooled data. If one were to simply add the separate benign and malignant risk estimates, the resulting estimate would be about two times higher than that derived from the pooled data. Discounting the benign estimate by 90 percent (assumes 10 percent will progress) and then adding it to the malignant estimate gives a combined number that is only slightly higher (3.0×10^{-3}) than that derived from the pooled data (2.8×10^{-3}). This illustrates some of the uncertainty one encounters when using different methods of risk estimation and, in this case, shows that if pooled or a conversion rate is used, the benign tumors contribute little to the risk estimates.

7.4.5. Conclusion

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 unadjusted risk estimates (for progression) derived from them not be added to estimates derived from squamous cell carcinomas. It is recommended that risk estimates derived from squamous cell carcinomas be used to estimate human risk because of the frank expression of carcinogenicity in the rat, evidenced by a statistically significant, positive dose-response relationship. Little weight should be accorded risk estimates derived from adding adjusted benign risks to carcinoma risks because of the uncertainties (1) inherent in adding risk estimates derived from different mathematical procedures, (2) the nature of the benign tumor response, and (3) uncertainties surrounding the rate of benign to malignant conversion.

7.5. Summary

Although a number of factors that represent more or lesser degrees of uncertainty have been discussed above in relation to the quantitative estimates of human cancer risk, no factor alone or in combination with others indicates that the estimates of risk are not reasonable as upper bounds. The true risk could certainly be lower, but no data or modeling procedure is available to determine the true risk. Consequently, it is recommended that the risk estimates derived from the CIIT rat squamous carcinoma data be used as the estimates of potential human cancer risk from exposure to HCHO with due consideration given to the strengths and weaknesses of the data base.

8. ESTIMATES OF NONCANCER RISKS

8.1. Introduction

Although some of HCHO's noncarcinogenic effects are well characterized, the problem of determining the dose-reponse characteristics in populations for these effects remains. This section focuses on human data to determine if dose-response relationships can be drawn. Six cross-sectional and three controlled human studies were selected for review. These studies were identified by Battelle Columbus (1985) from review articles by Ulsamer et al. (1984) and the NRC (1982). From this group, six studies were extensively analyzed for presence of dose-response relationships. Additional searching identified six studies which were thought to have shown a possible dose-relationship; these were also analyzed. For a study to be selected for review, the exposure level and the prevalence or incidence of a health effect must have been identified.

Generally, an increase in the prevalence or incidence of eye, nose, or throat irritant effects with increasing HCHO exposure was observed across the studies. Since exposures are identified as ranges in seven of the studies, reductions in the prevalence or incidence of the irritant endpoints from small changes in HCHO levels are difficult to quantify.

One study of randomly selected mobile home residents (Hanrahan et al., 1984) reports a dose-response relationship between the reporting of eye irritation and HCHO level. Three clinical studies of volunteers (Kulle, 1985, Andersen and Molhave, 1984, and Bender et al., 1983) report irritant responses over several exposure

levels and EPA analyzed these data in a similiar manner as that of Hanrahan et al. (1984). The predicted response curve of Andersen and Molhave and Bender et al. are similiar to that of Hanrahan et al., but the response curve for Kulle predictes lower percentage response.

None of the twelve studies provides adequate data to quantify population risks for the irritant effects of HCHO. The studies, at best, provide a qualitative estimate of population response over a wide exposure range and quantitative estimates of responses for very selected groups.

8.2. Studies Reviewed

Studies examining ocular or nasal effects are reviewed since studies of these endpoints comprise the majority of literature which reports both exposure level and magnitude of the effect. 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 for dose-response relationships. The reviewed studies are of two designs: cross-sectional and controlled clinical experiments. A search of the literature did not reveal any case-control designed study. The cross-sectional studies were of mobile home residents and of occupationally exposed workers. In the clinical studies, small groups of healthy volunteers, fewer than 30, were exposed to varying concentrations of HCHO and their responses were recorded.

8.3. Limitations of Studies

Even though response trends are identified for individuals under study, 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 random or nonrandom sampling frames were 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 attributable 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 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 three controlled human studies identified did not utilize a randomization scheme. Study participants were self-selected and may not be representative of the general population.

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

**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.

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 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 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 to evaluate the intensity of the disease endpoint.

8.4 Results

The principal acute effects of HCHO, reported by all studies which were extensively examined, are those of irritations to eyes, nose, throat, upper respiratory tract, and skin. Tables 8-1 and 8-2 list, by study design, the prevalence or incidence of each effect and the associated HCHO level.

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

TABLE 8-1 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 Air Quality Study	Study of mobile homes.
	Headaches	females (5-15 yrs)	4.64[c]		
	Sneezing	females (>16 yrs)	1.91[c]		
	Any nasal abnormality	males & females (>11 yrs)	1.73[c]		
	Seborrhea	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 resorcinol workers in a tire manufacturing plant	10%	Gamble et al.	HR exposed workers had significant reductions in expiratory flow at low lung volumes, indicating increased resistance in small airways when compared to a group of workers from the entire plant.
	Itch		23%		
	Rash		17%		
	Shortness of breath		17%		
	Chest sputnum		20%		
	Burning sensation in heart region		11%		

a Battelle Columbus (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 8-1 (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 sputnum		23%		
	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 8-1 (Continued)

EXPOSURE LEVEL (ppm)	SYMPTOMS	SUBJECT OF STUDY	ESTIMATED PREVALENCE	STUDY	COMMENTS
<0.10-2.84	Burning eyes	Residents of	25%	Anderson	Study of mobile homes.
	Watering eyes	mobile homes	20%	et al.	
	Dry throat		24%		
	Swollen glands		6%		
	Diarrhea		10%		
	Running nose		35%		
	Sneezing		45%		
	Phlegm		25%		
	Wheezing		17%		
	Cough		44%		
	Headache		29%		
	Rash		11%		
0.1-0.8	Runny nose	Residents of	34%	Hanrahan et al.	Study of mobile homes.
	Dry/Sore throat	Mobile homes	33%		
	Coughing		28%		
0.1-3.0	Ear, nose, throat	Adults	79%	Garry 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	19%		
		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 8-1 (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 workers. No significant differences ($p>.05$) among any of the groups in either FVC or $FEV_{1.0}$. The group, present line more than 5 years or more, had a lower $FEV_{1.0}/FVC$ ratio; and significantly lower ($p<0.05$) MEF_{50}/FVC than the never-on-line group.
		>5 yrs	33%		
		1-5 yrs	30%		
		<1 yr	40%		
		Previous on line	12.5%		
		Never on line	6.7%		
	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%		

[e] Exposure levels are for present-on-line-workers only.

TABLE 8-2 (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%)	Andersen and Mølhave
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.

TABLE 8-2 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 8-2 (Continued)

Level of Exposure (ppm)	Symptom	Study Subject	Response	Author
0.0	Eye/Nose/Throat Irritation	Healthy Volunteers	3[d] (14%)	Kulle
	Eye Irritation		1 (4%)	
	Nose/Throat Irritation		3 (14%)	
0.5	Eye/Nose/Throat Irritation		1[e] (10%)	
	Eye Irritation		0 (0%)	
	Nose/Throat Irritation		1 (10%)	
1.0	Eye/Nose/Throat Irritation		6[d] (27%)	
	Eye Irritation		4 (18%)	
	Nose/Throat Irritation		2 (9%)	
2.0	Eye/Nose/Throat Irritation		12[d] (55%)	
	Eye Irritation		10 (46%)	
	Nose/Throat Irritation		7 (32%)	
3.0	Eye/Nose/Throat Irritation		9[f] (100%)	
	Eye Irritation		9 (100%)	
	Nose/Throat Irritation		2 (22%)	

[d]A total of 22 subjects were exposed.
[e]A total of 10 subjects were exposed.
[f]A total of 9 subjects were exposed.

Table 8-2 (continued)

Level of Exposure (ppm)	Symptom	Study Subject	Response	Author
0	Eye irritation	Research Staff	-	Bender et al.
0.35	Eye irritation		41.7%[gh]	
0.56	Eye irritation		53.8%[i]	
0.7	Eye irritation		57.1%[j]	
0.9	Eye irritation		60.0%[k]	
1.0	Eye irritation		74.1%[l]	

[g] Subjects with HCHO response time less than clean air response time.

[h] Total of 12 subjects were exposed.

[i] Total of 26 subjects were exposed.

[j] Total of 7 subjects were exposed.

[k] Total of 5 subjects were exposed.

[l] Total of 27 subjects were exposed.

Five of the studies (e.g., Texas Air Quality, 1983, Anderson et al., 1983, Garry et al., 1980, Olsen and Dossing, 1982 and Hanrahan et al., 1984) were of occupants of mobile homes. Among these 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 (Texas Air Quality, 1983). Three studies (Texas Air Quality, 1983; Anderson et al., 1983; Hanrahan, 1984) report significant ($p<0.05$) dose-response relationships between certain acute effects and HCHO level. The Texas Air Quality (1983) 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. Anderson et al. (1983) reported in occupants of a random sample of 100 mobile homes that burning of the eye was significantly associated with the level of HCHO in the home. Not only did the prevalence of burning eyes increase significantly with increasing mean HCHO level, but also the proportion of individuals who believed their burning eyes were related to household conditions went from 50 percent to 87 percent. Hanrahan et al. (1984) reported a significant dose-response relationship between burning eyes/eye irritation and HCHO among study volunteers who lived in mobile homes. This observation had been adjusted for age.

When studies of mobile home residents are evaluated, it must be noted that not only ambient conditions within the home, but also seasonal temperature/humidity fluctuations can affect the rates of off-gassing (Anderson and Lundquist, 1985). 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. Hanrahan et al. (1984), however, stated that these factors did not influence HCHO levels in their study.

In three studies of workers in occupational settings, statistically significant increases in the number of 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 -- all were significantly increased in a group of rubber workers exposed to a HCHO-resin when compared to non-HCHO exposed workers (Gamble et al., 1976). Assessment of lung function in these workers showed significant reductions in expiratory flow rates, with the greatest reductions being shown by smokers. Area sampling of formaldehyde showed a mean concentration of 0.06 mg/m^3 for those workers who were in the exposed group. In another study of acrylic-wool filter manufacturing workers exposed to phenol-formaldehyde resin, Schoenberg and Mitchell (1975) observed significant increases in the prevalence of cough and cough-plus-phlegm symptoms when compared to never-on-line and previous-line

workers. Workers exposed for 5 or more years had lower lung function parameters (FEV_1/FVC ratio) than a group of workers who had smoked more but who had never been consistently exposed to resin fumes. Breathing zone measurements of HCHO ranged 0.40 - 0.80 ppm in this study, with higher levels (8.48 - 13.04 ppm) observed when cross-current fans were not operational. Kerfoot and Mooney (1975) 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 complained of upper respiratory irritation. For all three studies, other chemical exposures were present and it is not known to what degree the observed effects were due to possible interactions.

Four studies were of volunteers in controlled clinical experiments. Findings from these studies are similar to those of mobile home and occupational populations. Rader (1975), in testing six student volunteers in an anatomy laboratory, 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 dose groups over 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.

*The complaint score was a sum of the number of complaints times the severity of the response.

In a study by Bender et al. (1983), varying size groups of volunteers preselected by responding positively to HCHO at 1.3 and 2.2 ppm HCHO, were exposed to HCHO or clean air for six minutes (0, 0.35, 0.56, 0.7, 0.9, or 1.0 ppm). Eye irritation was measured as response time which was the length of time from initial exposure of the subject's eyes to the gas until eye irritation was noticed. Subjects were also asked to rate the severity of the response using a 0-3 scale (0=none, 1=slight, 2=moderate, 3=severe).

Although only the response at 1.0 ppm was statistically different than clean air, there was a trend toward earlier response to HCHO with increasing concentration. If the exposure groups for 0.7 and 0.9 ppm had been larger (5 and 7 subjects, respectively), the response might have been statistically different than clean air.

Severity of response was rated slightly to moderately irritating only at 1.0 ppm. The rating was less than slightly irritative for 0.35 to 0.9 ppm. In addition, severity was rated lower at the end of the six minute exposure indicating dimunition of response. This effect has been noted by Weber-Tschopp et al. (1977) and Kane et al. (1977) (Bender et al.).

Andersen and Molhave (1984) assessed the human health effects associated with prolonged exposure to HCHO under controlled thermal and atmospheric conditions. They observed an increasing trend in eye and nose irritation between exposure levels of 0.3 to 2.0 mg/m^3 HCHO. Among 16 subjects, 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, and several lung function parameters.

Finally, Kulle (1985), of the University of Maryland, examined irritant symptomology among volunteers who were exposed randomly to HCHO concentrations of 0.5, 1.0, 2.0, and 3.0 ppm. Odor and irritation determinations were made before exposure and at 180 minutes after exposure completion. Statistically significant increases in the number of eye and eye/nose/throat combined symptoms were observed for exposures over 2.0 ppm. The number of subjects detecting HCHO odor was statistically increased at HCHO levels of 0.5 ppm and above. Kulle notes that for subjects exposed to 1.0, 2.0, and 3.0 ppm HCHO, a significant linear trend with dose was observed for both odor and eye irritation and for all eye/nose/throat irritation.

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 using data from mobile home residents in Wisconsin, Minnesota, and Washington 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 (for example, dermatitis of the face or conjunctivitis). The HUD document 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 the 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 support a dose-response relationship between sensory effects and HCHO levels in mobile homes. Data presented do support a qualitative relationship. It is also important to note, however, that HUD's review does not address the question of concentration levels of HCHO in the mobile home and the magnitude of the possible 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. One must assume, however, that odor recognition coincides 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 of HCHO level and any corresponding eye, nose, and throat irritation.

In summary HUD's and OSHA's approaches provide some qualitative measure of acute effects from HCHO exposure. These techniques, however, can not identify a true dose-response relationship. The individual reviewed studies can only be used in the same manner; for qualitative estimates of population-based risks.

All but two of the reviewed studies estimate the prevalence of irritant effects for a given exposure level. Table 8-3 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.

Only the studies by Bender et al. (1983), Andersen and Molhave (1984), Hanrahan et al. (1984), and Kulle (1985) presented response data over a range of doses so as to allow estimation of irritation prevalence for a particular exposure

*Olfactory receptors can become saturated when breathing HCHO for a period of time and, when this occurs, people become refractory to the odor perception. Also, when saturation occurs, it would be extremely difficult to link odor perception to the manifestation of symptoms such as irritation.

Table 8-3. EXPOSURE RANGES FOR SELECTED ENDPOINTS

Acute Effect	Exposure Level	Prevalence	Author
Nose Irritation	0.04-0.09	23%	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%	Olsen and Dossing
	0.10-0.09	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

level. The data of Andersen and Molhave (1984) and Kulle (1985) have been analyzed by EPA using logistic regression analyses for comparability. Hanrahan et al. (1984) presented in their paper results of logistic regression analyses of their data. The Hanrahan et al. (1984) results were controlled for age, gender, and smoking. Figures 8-1 - 8-4 show the percent response predicted at selected exposures for eye irritation (Hanrahan et al., 1984) and eye, nose, and throat irritation (Andersen and Molhave, 1984 and Kulle, 1985). The trends for all three curves are statistically significant. The predicted response curves for Hanrahan et al., (1984) who studied randomly sampled mobile home residents, and for Andersen and Molhave (1984) and Bender et al. (1983), who clinically studied volunteers, are very similiar. The response curve for Kulle (1985), on the other hand, predicts a lower percentage response than the three above studies for a given exposure level. Likewise, for exposure levels above 0.5 ppm, the upper 95% confidence intervals for predicted response from Kulle's data are lower than the 95% confidence bounds of the Andersen and Molhave and the Hanrahan et al. predicted response curves.

Figure 8-1. Predicted irritative response over a range of HCHO levels (Data from Hanrahan, et al. 1984).

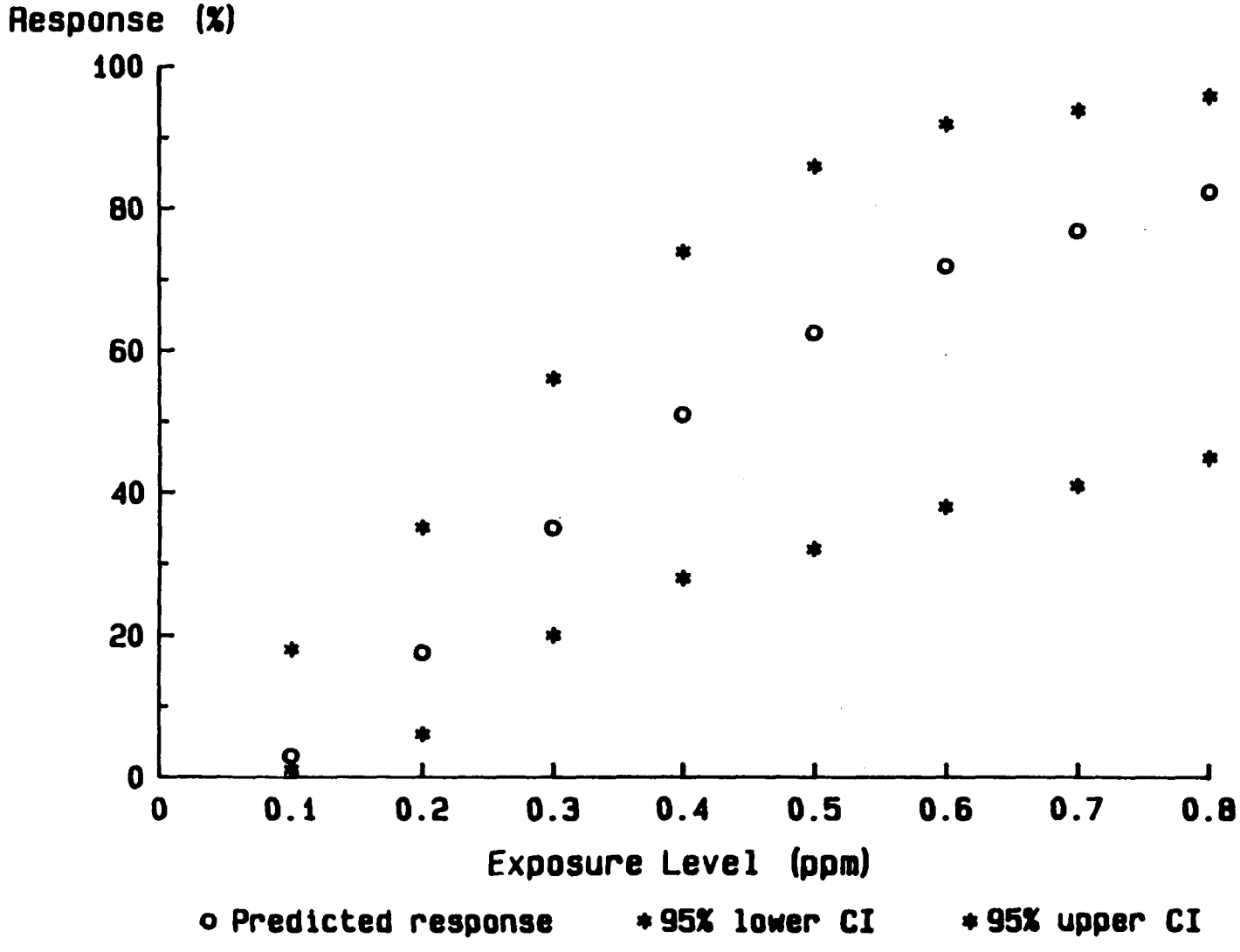


Figure 8-2. Predicted irritative response over a range of HCHO levels (Data from Andersen and Molhave 1984).

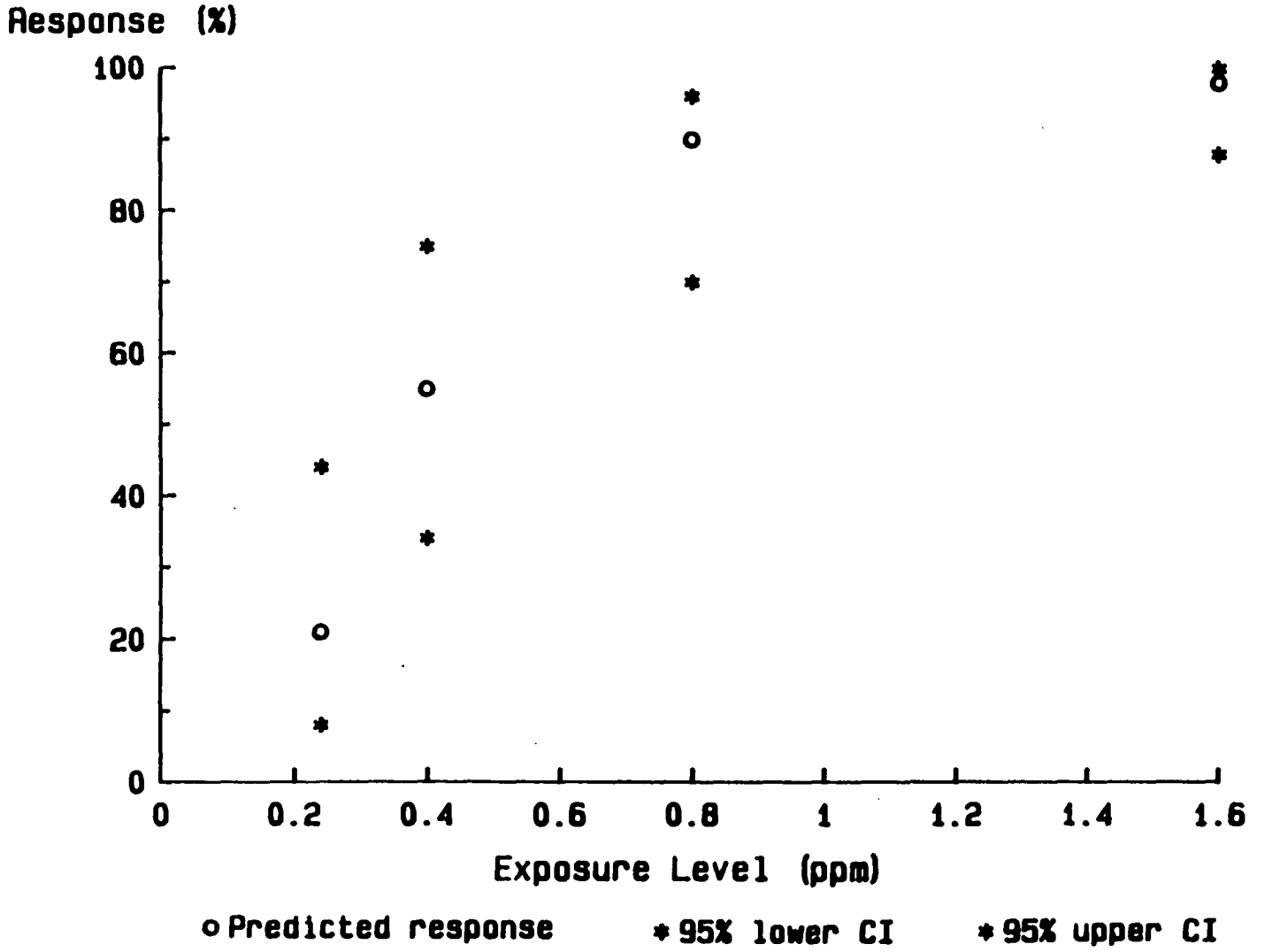


Figure 8-3. Predicted irritative response over a range of HCHO levels (Data from Kulle 1985).

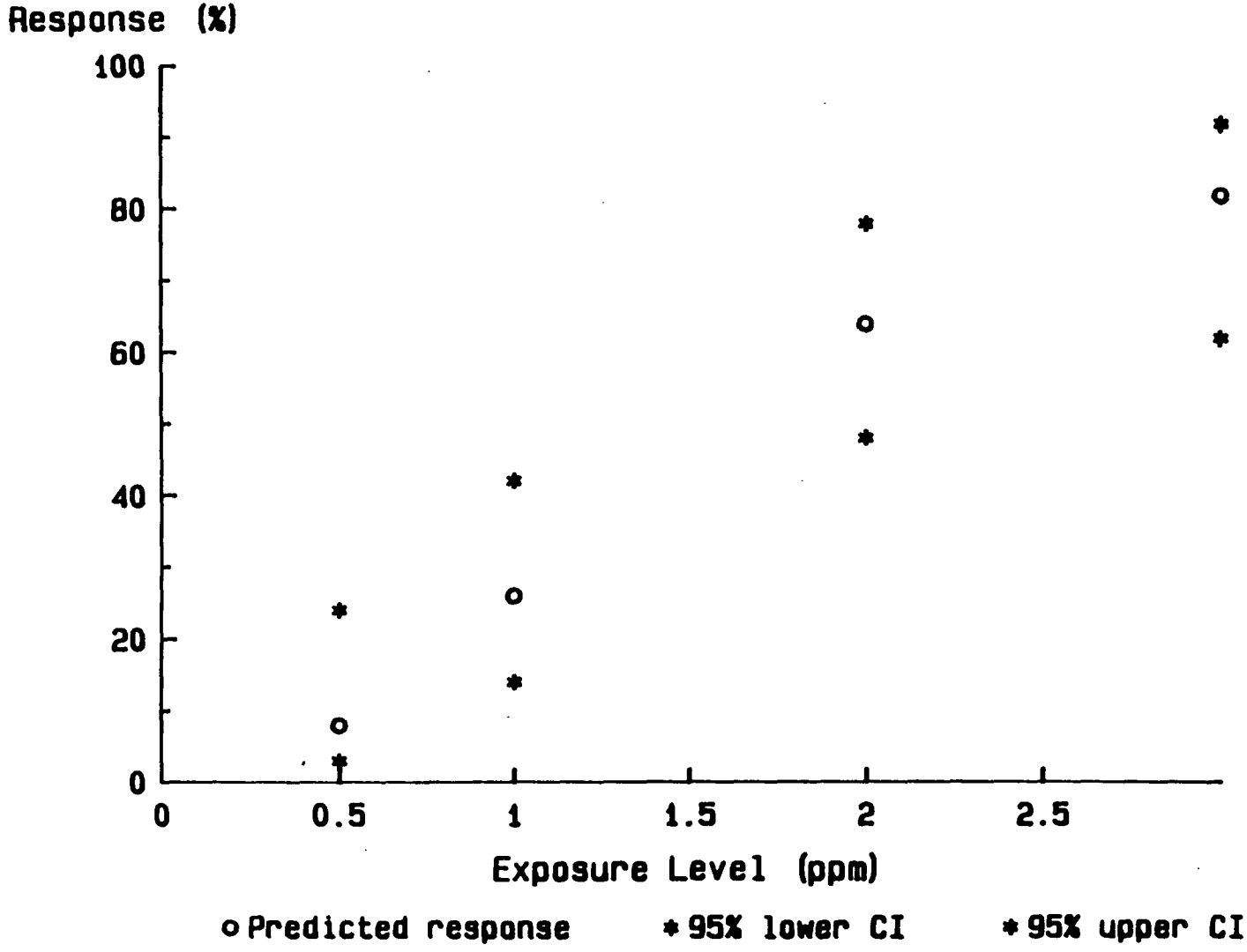
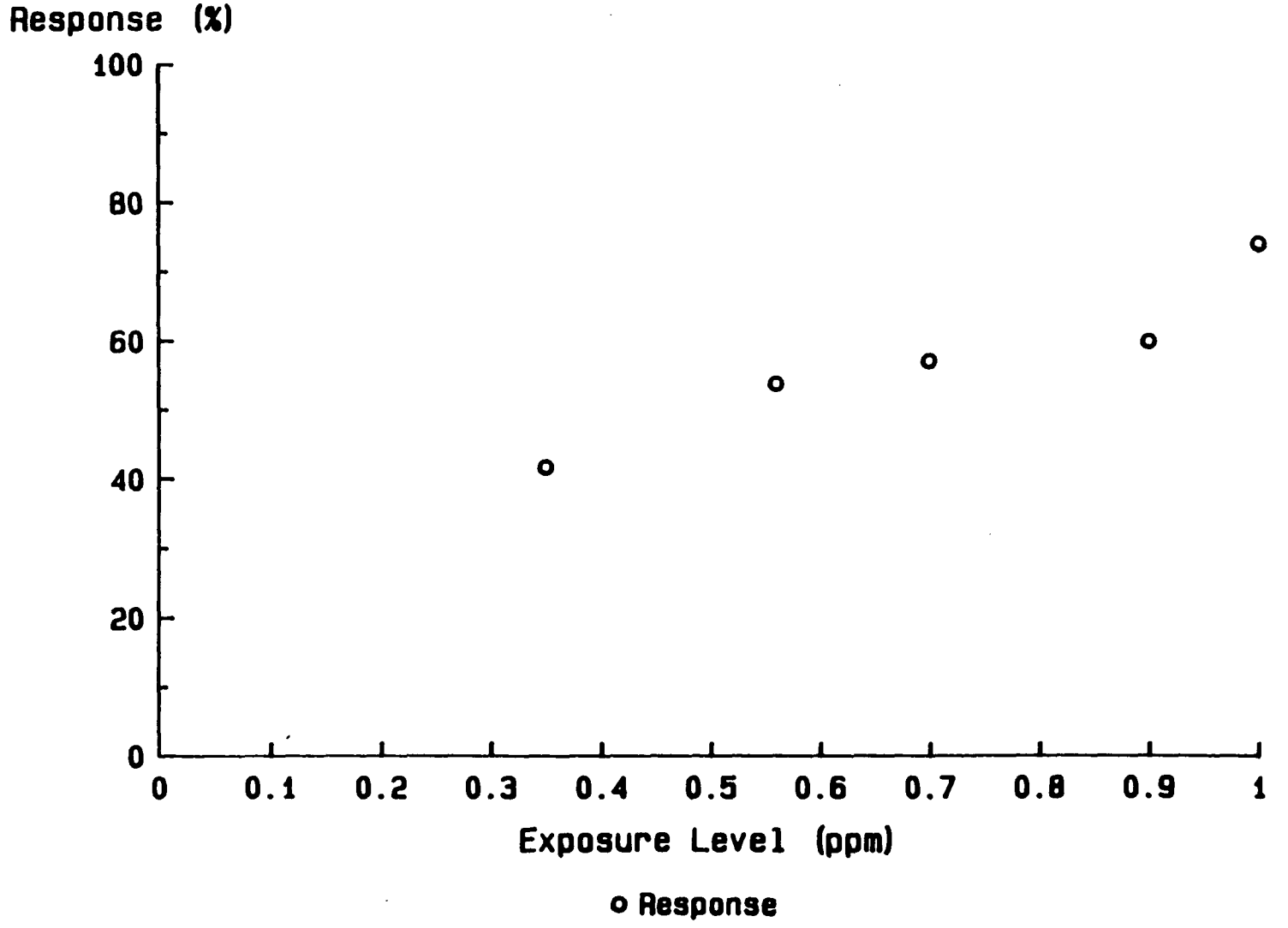


Figure 8-4. Eye irritation response over a range of HCHO levels (Data from Bender, et al.).



Care must be taken in inferring from the results in Figures 8-1 to 8-4 to the general population. First, three of the studies are based on study subjects who are volunteers and selection bias may be present. The one study whose population was randomly selected is of a cross-sectional design, making causation difficult to infer. Second, all studies had small numbers of subjects, 16 in Andersen and Molhave, 28 in Bender et al., 61 in Hanrahan et al., and 22 in Kulle. Larger studies of randomly selected subjects are needed to estimate general population risks.

In conclusion, none of the reviewed studies provide adequate data to quantify general 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 and quantitative estimates of responses for very select populations. 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.

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