California Environmental Protection Agency

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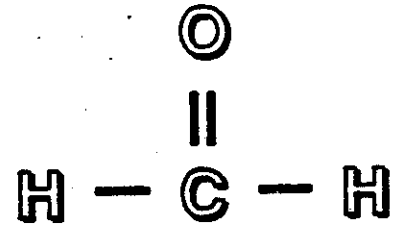
TECHNICAL SUPPORT DOCUMENT

Final Report on the Identification of FORMALDEHYDE



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Part B
Health Assessment

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CANCER RISK ASSESSMENT FOR AIRBORNE FORMALDEHYDE

Office of Environmental Health Hazard Assessment
Air Toxicology and Epidemiology Section

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SUMMARY

Formaldehyde is a volatile, reactive chemical used extensively in wood product manufacturing, mobile and conventional home construction, the garment industry, and the medical profession. These activities release substantial amounts of formaldehyde into the surrounding air. Other sources that contribute to environmental formaldehyde levels include automobile exhaust, cigarette smoke, and smog. Due to its widespread use, a substantial number of California residents are exposed to formaldehyde, both occupationally and in the home.

Formaldehyde occurs in important steps of normal mammalian metabolism. The primary pathway for the metabolism of formaldehyde leads to formic acid, a reaction catalyzed by formaldehyde dehydrogenase and glutathione. Additional metabolic pathways oxidize both formaldehyde and formic acid to carbon dioxide. Such metabolism detoxifies the formaldehyde. Clearance of formaldehyde from the plasma by both animals and humans is quite rapid, with the half-life of formaldehyde in plasma estimated at between 1 and 1.5 minutes. Toxic effects occurring after formaldehyde exposure appear to be attributable primarily to the parent molecule in the contact tissue.

A number of adverse health effects in humans have been associated with formaldehyde exposure. These include ocular, nasal, and dermal irritation, nausea, headaches, allergic sensitization, and possible exacerbation of bronchial asthma. Humans vary substantially in their sensitivity to formaldehyde. For most individuals these effects typically occur at exposure levels between 0.1 and 3 ppm. The lowest levels causing effects in most of the studies, which have dealt with normal populations, have ranged from 0.037 to 3.0 ppm (EPA, 1987a). Sensitive individuals may experience acute symptoms related to irritation at lower concentrations.

Exposure of experimental animals to formaldehyde does not appear to result in any significant teratogenic or reproductive effects. No adverse reproductive effects were reported following oral administration of formaldehyde even at doses high enough to result in substantial maternal mortality. It has been suggested that the very short biological half-life of formaldehyde in the dam greatly limits the exposure to the embryo. There is no evidence in humans that clearly demonstrates that formaldehyde exposure has caused adverse reproductive outcomes, and the Consensus Workshop on Formaldehyde (EPA 1984) stated that formaldehyde should pose little, if any, risk as a potential human teratogen.

Formaldehyde has been shown to cause a number of genotoxic effects in a variety of cell culture and *in vitro* assays, including DNA-protein crosslinks, sister chromatid exchanges, gene mutations, single strand breaks, and chromosomal aberrations (Consensus Workshop on Formaldehyde, 1984; IARC, 1987). Many of the *in vivo* studies have yielded negative or equivocal results, which led Ma and Harris (1988) to suggest in their extensive review that the formaldehyde reacts with the first site of contact and does not necessarily penetrate to and therefore react with deeper cells. Because of the genotoxic effects of formaldehyde observed in many studies, including observation of DNA-protein crosslinks *in vivo* by

Casanova et al. (1989, 1991), OEHHA staff conclude that formaldehyde is genotoxic and mutagenic.

Formaldehyde is carcinogenic in rodents, producing squamous cell carcinomas in the nasal passages of male and female rats and male mice. Several different types of potentially precancerous abnormalities, including polypoid adenomas and squamous cell papillomas, have also been observed. The epidemiological evidence, while suggestive of a risk of human cancer due to formaldehyde exposure, is insufficient for risk assessment purposes on its own. Both the International Agency for Research on Cancer and the U. S. Environmental Protection Agency have classified formaldehyde as a probable human carcinogen, based on sufficient evidence for carcinogenicity in animals and limited evidence in humans. The staff of OEHHA agree with this classification. In a comprehensive rule making on occupational exposure to formaldehyde, the U.S. Occupational Safety and Health Administration (OSHA 1987) has summarized its position by concluding that, based on animal and human studies, "formaldehyde should be regarded as an occupational carcinogen."

Exposure to formaldehyde leads to formation of DNA-protein crosslinks in the nasal passages of rats, which can serve as a measure of the tissue dose (Casanova et al., 1984, 1987, 1989, 1991). The U.S. EPA (1987) relied on the administered dose to calculate carcinogenic risk from formaldehyde exposure, stating that the molecular dosimetry available at that time did not provide an adequate basis for a risk assessment. However, the recently published data on DNA crosslinks appear to be reliable enough to use as an indicator of tissue dose. So the staff of OEHHA have included that approach in this risk assessment, as did the U.S. EPA in their draft document (1991). The rationale is that, because the naturally-occurring defense mechanisms saturate as the concentration of inhaled formaldehyde increases, the amount of formaldehyde reaching the DNA increases disproportionately. Thus, using the molecular dosimetry data yields a more accurate dose and in turn provides a more accurate risk assessment.

In developing a spectrum of predictions of cancer risk to humans, the present assessment applies a pharmacokinetic interpolation of the molecular dosimetry data to the cancer bioassay data of Kerns et al. (1983). The analysis uses two different kinds of models to predict the risk to the rats at environmental levels of exposure. One kind is the linearized multistage model, as implemented on computer by GLOBAL86. The other kind, developed by Moolgavkar and others, is a model which takes into account the proliferation of premalignant cells due to the formaldehyde exposure. Both kinds of model derive upper confidence limits (UCL) for excess cancer risk. Following predictions of rodent risk to environmental levels of formaldehyde, the analysis extrapolates the risk to humans by means of three different scaling factors. Two scaling factors take into account the contact mechanism of carcinogenesis. However they do so in different ways. One uses only a generic calculation in terms of body mass. The other takes specific account of comparative data on DNA binding data in rats and monkeys to adjust the metabolic rate for humans; it assumes humans respond as do monkeys and uses the data of Casanova et al. (1989, 1991). The third scaling factor follows the default option of the California carcinogen guidelines, which calculates the adjustment for rat exposures to obtain the

equivalent human exposure on the basis of intake rate divided by body surface area.

For the best value of UCL on unit risk for a lifetime of exposure, the OEHHA staff have selected 7 x 10^{-3} ppm^{-1} (9.0 x 10^{-6} $(\mu g/m^3)^{-1}$), based on molecular dosimetry data in a three-stage model and using the standard surface-area scaling factor, 1.2. The range of calculated values of UCL on unit risks is 0.3 x 10^{-3} ppm^{-1} to 40 x 10^{-3} ppm^{-1} (0.25 x 10^{-6} to 33 x 10^{-6} $(\mu g/m^3)^{-1}$), based on the two different kinds of models and the three different scaling factors. This range is defined by the results of calculations from 10 different risk models, including multistage models that use two different measures of exposure to inhaled formaldehyde, applied and molecular dosimetry, and seven different cell proliferation models that all use the molecular dosimetry data. For comparison the U.S. EPA (1987) calculated a UCL for lifetime unit risk of 15 x 10^{-3} ppm^{-1} (13 x 10^{-6} $(\mu g/m^3)^{-1}$), based on the administered dose (exposure) in a five-stage model with no scaling factor. That value is about twice the best value selected by OEHHA staff and falls within the present range of calculations. More recently the U.S. EPA (1991) has proposed two different values for UCL on unit risk, both within the lower portion of the present range and both using a two-stage model with tissue dosimetry: 2.8 x 10^{-3} ppm^{-1}, based on the rat data, and 0.33 x 10^{-3} ppm^{-1}, based on rat data adjusted using the monkey data (Casanova et al. 1991).

All these values represent upper bounds in the sense that it is unlikely, based on the information considered, that the risk would be exceeded. We note that in calculating upper confidence limits for this assessment many key sources of uncertainty were not addressed quantitatively. For example, the uncertainties involved in excluding benign tumors at low concentrations and the uncertainties of the proliferation model and its parameters, as well as the dosimetric model and its parameters, could lead to lower or higher estimates. Thus, even though the values here are reported as upper confidence limits, higher plausible estimates could be derived from the data.

A review of epidemiological studies for workers exposed to formaldehyde leads to selection of the study by Blair et al. (1986) as the most reliable for quantitative comparisons. That study, the largest and best documented study available, evaluated mortality in a cohort of more than 26,000 workers. The observed risk of death by lung cancer in exposed workers was 15 x 10^{-3} over their career. Based on extrapolation of rat predictions to humans for a 40-hour work week for 20 years and an exposure level of 1.0 ppm, the prediction of 95% upper confidence limits on respiratory tract cancer was 32 x 10^{-3} for the three-stage tissue-dose model with generic contact scaling factor. Thus, the upper portion of the range of human predictions from the rat data is consistent with the worker observation.

Consistent with the conclusion reached by both the U.S. EPA (1987a) and the Consensus Workshop on Formaldehyde (EPA 1984), OEHHA staff have found that the evidence against a carcinogenic threshold outweighs the evidence for such a threshold for formaldehyde. There is substantial evidence of genotoxic activity of formaldehyde. Also, using molecular dosimetry to calculate the quantity of formaldehyde reaching the site of action provides

a non-threshold explanation of the shape of the observed curve for incidence versus exposure describing the cancer bioassay in rats.

Based on the findings of formaldehyde-induced carcinogenicity and the results of the risk assessment, OEHHA staff find that formaldehyde is an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

SPECIAL NOTE:

The use of a cell proliferation model in the risk assessment of formaldehyde is not to be construed as a general policy of the Office of Environmental Health Hazard Assessment for all compounds. Staff concluded that formaldehyde constituted a special case in which incorporation of cell proliferation data into the risk assessment was justified. Consideration of cell proliferation data in the risk assessment of other compounds should be made on a case-by-case basis, however, staff have at present not identified any other compounds for which cell proliferation data should be used in the risk assessment.

FORMALDEHYDE EVALUATION HIGHLIGHTS

I. National and International Evaluation (Other Agencies' Evaluations).

A. U.S. Environmental Protection Agency (EPA, 1987)

1. Short-term tests: Mutagenic in numerous test systems and causes cell transformation.

2. Animal carcinogenicity assays: Sufficient evidence of animal carcinogenicity by inhalation.

3. Human evidence: Limited evidence of human carcinogenicity.

4. Conclusion: Formaldehyde is considered a probable human carcinogen, ranked in group B1.

B. International Agency For Research on Cancer (IARC, 1987)

1. Short-term tests: Produces mutations and genetic abnormalities in human cells in vitro and transforms rodent cells in vitro. There is also evidence of genetic damage in test systems in vivo.

2. Animal carcinogenicity assays: Sufficient evidence of animal carcinogenicity by inhalation.

3. Human evidence: Limited evidence of human carcinogenicity.

4. Conclusion: Formaldehyde is a probable human carcinogen, category 2A.

C. Conclusions: Both EPA and IARC concluded that there is sufficient evidence that formaldehyde is carcinogenic in animals (rats and mice) by inhalation and that it is genotoxic. Many occupational studies with formaldehyde exposure have found elevated relative risks, with nasal and nasopharyngeal cancers offering the strongest evidence. Although lung cancers were elevated, they did not display clear patterns of increasing risk with various measures of exposure.

II. Carcinogenic Threshold

A. Shape of the dose-response curve

1. Animal: The carcinogenic dose-response curve for nasal squamous cell carcinoma in rats is consistent with the multistage model. The dose-response curve was derived from four data points, a control group, and three exposure concentrations.

2. Human: Data are not sufficient to describe.

B. Animal pharmacokinetic information: Moderate to good. No evidence for the presence of a carcinogenic threshold at low exposures. The detoxification pathway appears to have a component which is active at low exposures but which saturates at high exposures.

C. Human pharmacokinetic information: Very limited. At low doses humans are likely to have qualitatively similar characteristics to rats and monkeys.

D. Conclusions: The positive short-term genetic activity tests, the observed animal carcinogenic dose-response curve, and the trend of metabolic inactivation at low doses lead the staff of DHS to conclude that formaldehyde is genotoxic and should not be considered to have a carcinogenic threshold.

III. Exposure Sources

A. Air levels

1. Ambient levels measured in the Los Angeles basin area: 0.005 to 0.030 ppm.

2. Ambient levels measured in "hot spots": unknown.

3. Indoor air: Concentrations are variable depending on the size of the room, ventilation, quantity released, and time since release. Measured formaldehyde concentrations in conventional housing average about 0.050 ppm. In mobile homes average exposure was 0.069 ppm in California.

4. Overall exposure: The only available estimate for overall California exposure is 0.053 ppm.

B. Reported levels in water

1. National Data

a. Ambient waters: unknown.

b. Drinking water: unknown.

2. California drinking water: unknown.

C. Reported levels in food: unknown.

D. Other exposures

Fluid from kidney dialysis machines disinfected with formaldehyde has been reported to have an average of 6.7 ppm in solution.

IV. Quantitative Risk Assessment

A. Range of 95% upper confidence level (UCL) on unit risk estimates for lifetime excess cancer cases

1. Per $\mu g/m^3$: 0.25×10^{-6} to 33×10^{-6}

2. Per ppm: 0.3×10^{-3} to 40×10^{-3}

3. Per ppb: 0.3×10^{-6} to 40×10^{-6}

The range of risk from a single animal bioassay includes the results of using 3 scaling factors and 10 risk models, seven of which include cell proliferation effects.

B. Range of extrapolation: Ratio of positive animal test to average human exposure: 80.

C. Pharmacokinetic adjustments

1. Use of a dosimetric or tissue basis in the calculation of formaldehyde risk reduces the number of stages needed to fit the cancer data in the multistage model from five to three. The three-stage tissue-based (metabolic) model with a rat-to-human scaling factor of 1.2 provides the present best value of UCL on unit risk, 7.0×10^{-3} ppm^{-1} (5.0×10^{-6} $(\mu g/m^3)^{-1}$). The EPA (1987a) used a five-stage exposure-based model, without tissue-based data and without a scaling factor, obtaining 1.5×10^{-2} ppm^{-1} (1.3×10^{-5} $(\mu g/m^3)^{-1}$ for UCL on unit risk.

D. Comparison with potencies of other carcinogenic compounds:

1. Based on the present best value of upper confidence limit for unit risk, 7×10^{-3} ppm^{-1} or 5×10^{-6} $(\mu g/m^3)^{-1}$, formaldehyde is in the fourth quartile of 59 carcinogens for which EPA has calculated potencies.

2. The eight volatile organic compounds which the State of California has declared to be Toxic Air Contaminants range in carcinogenic potency from 1×10^{-6} $(\mu g/m^3)^{-1}$ (methylene chloride) to 8.8×10^{-5} $(\mu g/m^3)^{-1}$ (ethylene oxide). Based on the present best value of unit risk, 5×10^{-6} $(\mu g/m^3)^{-1}$, formaldehyde is between those compounds in potency as just expressed.

Allometric: Allometry is the study of the change in proportion of various parts of an organism as a consequence of growth.[1] Here, the study includes interspecies comparisons. Thus, "allometric" factors refer to proportional differences in physiological attributes among species, expressed as powers of the ratio of body masses of the respective species.

Best value of unit risk: The "unit" in "unit risk" refers to the units used in measuring the concentration of a pollutant in air. Generally, the units are usually either parts per billion (ppb) or micrograms per cubic meter ($\mu g/m^3$ or ug/m^3). Ppb and $\mu g/m^3$ are not the same. At 1 ppb, the pollutant accounts for one billionth of the air's volume. At 1 $\mu g/m^3$, there is 1 μg of the pollutant in each m^3 of air. "Unit risk" is the cancer risk thought to be associated with lifetime exposure to 1 concentration unit of the pollutant (either 1 ppb or 1 $\mu g/m^3$). The "best value" of unit risk is the unit risk estimate most appropriate for use in risk assessment. Multiplying the measured air concentration of a pollutant by its unit risk gives an estimate of the cancer risk faced by exposed people.

Cell proliferation: an increase in the number of cells (in a living tissue or an experimental culture). To measure this increase, investigators add a labeling substance (tritiated thymidine) to cell cultures. Growing cells incorporate the "label" into their genetic material. Using the label, the investigators can track the cell's genetic material as it is divided into offspring cells, and the offspring cells can be counted.

DNA-protein crosslinks (DPX): DNA is the primary genetic material of cells. It is usually found in two strands that are loosely bound together, like two very weak magnets. If a protein molecule bonds tightly to both strands of DNA, it acts like glue and forms a "crosslink." To use DNA, a cell must be able to separate the two strands, so a crosslink can be fatal to a cell or seriously disrupt its function. Ordinarily, protein molecules do not bind to DNA. Some substances can "activate" protein molecules, however, allowing them to bind.

Dosimetric contact scaling factor: See "generic contact scaling factor," below. A "dosimetric" scaling factor incorporates information relevant to the handling of a given dose (of carcinogen) within the exposed animals. Here, the information is the animals' metabolic rates.

Generic contact scaling factor: See "scaling factor," below. A "contact" scaling factor assumes that cancer is caused where a carcinogenic substance first comes into contact with the body; it reflects the relative surface areas of the animals (or contacted organs) in question. The word "generic" simply means "general," or that no particular type of contact scaling factor is implied.

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[1] *The American Heritage Dictionary*, 2nd coll. ed. Boston: Houghton Mifflin Company, 1982.

Genotoxic: A substance is genotoxic if it can damage genetic material (e.g., the DNA in chromosomes).

Lifetime equivalent exposure: the exposure level that, if maintained over a lifetime, would result in the same cumulative dose as did an actual (varying or discontinuous) experimental exposure regimen.

Likelihood function: a function constructed from a statistical model and a set of observed data, which gives the probability of the observed data for various values of the unknown model parameters. The parameter values that maximize the probability are the maximum likelihood estimates of the parameters.[2]

Molecular dosimetry data: information regarding the concentration of toxicant molecules in a tissue of concern.

Monte Carlo simulation (study, trial): Complex relationships that are difficult to solve by mathematical analysis are sometimes studied by computer experiments that simulate and analyze a sequence of events, using random numbers. Such experiments are called Monte Carlo trials, or studies, in recognition of Monte Carlo as one of the gambling capitals of the world.[3] Here, a Monte Carlo study uses simulated data obtained using a Poisson-distributed random variable for cancer incidence at each exposure level. The means (and variances, since with Poisson distributions they are equal) of the random variables are set using the maximum likelihood estimate of parameters estimated using the actual incidence data.

Scaling factor: "Scaling factors" are used with study results from one species (or size) of animal to estimate a health risk in another species (or size) of animal, usually humans. They are also commonly used to "scale" doses across species (or animals), that is, to estimate what dose of a toxic substance will have a health effect in a second species (or animal) equivalent to the effect caused by a given dose in a first species (or animal). For example, scaling factors are used in charts that estimate driving ability (or legality) based on alcohol intake and body weight. Scaling factors are numerical variables, generally ratios of body weight or surface area. Here, the effect of concern is the incidence rate of cancer.

Surface area scaling factor: See "scaling factor," above. A default scaling factor designed to adjust dose across species based on intake

Three-stage tissue-dose model: A "tissue-dose" model for cancer risk assessment uses tissue dose (see below) as the measure of exposure. A "three-stage" model assumes that there are three stages involved in carcinogenesis on which the carcinogen may act. Here, the software "GLOBAL86" is used to fit a three-stage tissue-dose model to the data.

Tissue dose: the amount of a toxicant in a body tissue.

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[2] *A Dictionary of Epidemiology*, 2nd ed., John M. Last, ed. New York: Oxford University Press, 1988.
[3] *Ibid.*

Upper confidence limit (UCL): Many experiments are designed to estimate numerical parameters, such as the cancer risk posed to an animal by a certain exposure to an air pollutant. An experiment's data can be combined with statistical assumptions to derive an "upper confidence limit" on the true value of a parameter. It is thought that if an experiment were repeated many times (gathering new data each time, and disregarding the old data), the upper confidence limit derived from the experiment's data would equal or exceed the true value of the parameter a certain proportion of those times. That proportion is the "confidence level" of the UCL (it is usually 95%). When researchers report a 95% UCL, they are 95% confident that, if the assumptions embodied in their calculations are correct, they have given good guidance regarding the true value of the parameter (i.e., "it's at or below the UCL"). Without acknowledging the assumptions, one should not state that there is a 95% probability that the true value of a parameter lies at or below a 95% UCL. Nonetheless, 95% UCLs may be used as "upper bounds" on parameters in risk assessment.

CANCER RISK ASSESSMENT FOR AIRBORNE FORMALDEHYDE

Introduction

The Air Toxicology and Epidemiology Section of the Office of Environmental Health Hazard Assessment (OEHHA) has developed this assessment of cancer risk due to inhalation of ambient formaldehyde at the request of the California Air Resources Board (ARB). The OEHHA staff have based their assessment upon a document published by the U. S. Environmental Protection Agency (EPA, 1987a), Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde, April 1987. The present risk assessment brings the EPA assessment up to date and concludes with an application to ambient atmospheric conditions in California. Closely related rulemaking documents by the U.S. Occupational Safety and Health Administration (OSHA) contain extensive discussion of the issues (1985 and 1987a), and that information has furnished further background for the present assessment. Furthermore, recent developments in formaldehyde risk assessment at EPA have been followed and considered in preparing this update.

Quantitative predictions of cancer rates due to fomaldehyde exposure have relied primarily on data obtained from rodent cancer bioassays. In the principal cancer study a large percentage, 67%, of rats at risk in the highest exposure level, 14.3 ppm, developed squamous cell carcinomas of the nasal passages, compared to a 0% incidence for control animals (Kerns et al., 1983; EPA, 1987a). Other rodent studies (Albert et al., 1982; Tobe et al., 1985) have supported this finding.

Human exposures to formaldehyde are common due to industrial processes, to construction materials, to consumer products, to automobile exhaust, to waste disposal sites, and to other intentional and accidental releases. Such exposures occur at lower concentrations than in the rodent cancer bioassays; therefore, an acceptable mathematical modelling approach is needed to predict cancer risks at the lower concentrations to which humans are ordinarily exposed. Risks of respiratory tract cancers, estimated from epidemiological data on workers who experienced an intermediate exposure, are consistent with the higher portion of the range of the present predictions based on rodents.

In calculations of risk the present assessment departs from the EPA (1987a) assessment in three substantial ways. Two have to do with the method of characterizing the dose rate for input into the multistage model. The third takes into account of the effect of proliferation of premalignant cells in a two-stage model.

(1) The present approach uses the rate of binding of formaldehyde to DNA in the nasal lining of the rat, in order to characterize the dose rate. The rate of binding to DNA in the nasal tissue is related to exposure in a steepening manner in a pharmacokinetic model; thus a ten-fold increase in dose yields a greater than ten-fold increase in binding. The EPA (1987a) decided to use administered dose (inhalation exposure) rather than estimated tissue dose for risk estimation purposes because their reviewers did not consider the tissue data then available for their assessment to be adequate. The

EPA did otherwise endorse the idea of using the pharmacokinetic model. OSHA (1987) likewise rejected the use of tissue dose at that time. Recently, better data have become available, and in their draft update of 1991, the EPA used the nasal tissue binding data as a measure of dose in a manner somewhat similar to that of the present assessment. The staff of OEHHA conclude that the pharmacokinetic model is now an appropriate choice to evaluate the carcinogenic risks associated with formaldehyde.

(2) The present approach uses three different scaling factors to extrapolate the equivalent dose rate from rats to humans. One scaling follows the default option in the carcinogen guidelines, developed by the California Department of Health Services (DHS), of intake rate per body surface area (DHS 1985), and at 1.2, is very close to the EPA value of unity. Two other scalings take into account the contact mechanism of formaldehyde carcinogenesis in a manner that otherwise follows the default principle, one giving the higher value of 5.0, the other giving the lower value of 0.28. EPA (1987a) did not specifically discuss the issue of scaling to extrapolate from rodents to humans for formaldehyde. OSHA (1985, 1987) presented an extensive discussion, but did not find any of the suggested approaches to be convincing and thus decided against using a scaling factor.

(3) The present approach includes a set of mathematical models that take into account the effect of proliferation of cells that can lead to cancer. The EPA draft update (1991) discusses some of the difficulties of proceeding with this analysis due to lack of relevant data. Commenters on the January, 1991, draft of this document urged the use of cell proliferation models. The results of the present work show that relative to the multistage-model results, the cell proliferation models that fit the cancer bioassay data well increase the estimate of unit risk by 30 to 50%, while a model which produces only a marginal fit decreases the unit risk 5.3-fold.

The selection of the default scaling with the use of a tissue dose (metabolic exposure) in the multistage model gives a best value for upper confidence limit (UCL) on the unit risk which is half that obtained by EPA (1987a).

Role in Normal Metabolism

Formaldehyde is an important intermediate in the biosynthesis of several essential cellular molecules, including amino acids, lipids, and nucleotides. It also serves as an alkylating agent for nucleic acids and proteins. Because of its chemical reactivity, free formaldehyde is not typically found intracellularly, or else is found only at very low levels. Instead, the little formaldehyde needed by cells is in a storage form bound to tetrahydrofolate. In this manner the formyl group is chemically bound, yet available to act as a formylating agent for specific reactions. The primary source of endogenous intracellular formaldehyde is from the degradation of serine and other amino acids. See extensive discussions by EPA (1987) and OSHA (1985).

Toxicity and Carcinogenicity of Formaldehyde

Formaldehyde has exhibited a number of toxic effects, as discussed in the EPA (1987a) document and in the OSHA (1985, 1987) documents. Acute effects include irritation of the skin, eyes and mucous membranes, as well as nausea, headaches, and possible exacerbation of bronchial asthma. Formaldehyde can also induce long-term allergic sensitization. For most individuals the lowest observed level of effects is in the range 0.1 to 3 ppm. For sensitive individuals the effects may occur in the range 0.03 to 0.07 ppm. The most critical effect of chronic exposure is cancer. Nelson et al. (1986) provided a review of the technical issues. Samet et al. (1986) provided a review of the epidemiology. Heck et al. (1989) reviewed several issues of formaldehyde toxicity in some depth. The present assessment focuses on the potential human carcinogenic effects associated with exposures to formaldehyde.

Several studies have shown that chronic exposure to formaldehyde produces cancer in male mice and several strains of rats of both sexes. A study sponsored by the Chemical Industry Institute for Toxicology (CIIT) has provided the most quantitatively useful evidence for the carcinogenicity of formaldehyde (Swenberg et al., 1980; Kerns et al., 1983). This study used 120 male and 120 female Fischer-344 rats in each dose group, including a group in clean air. The adjusted tumor incidences (adjusted for competing causes of death, including scheduled interim sacrifices) for squamous cell carcinomas in the nasal passages of males and females combined, when exposed to 0, 2.0, 5.6, or 14.3 ppm formaldehyde for 6 hours/day, 5 days/week for up to 24 months, were 0/156, 0/159, 2/153 and 94/140 (EPA, 1987a). In an analogous study on mice, two mice in the high dose group (14.3 ppm) developed squamous cell carcinomas, a finding that was not statistically significant but was thought to be biologically significant due to the absence of this tumor in control animals and to concurrence with rat studies. Kerns et al. (1983) also reported benign tumors, including polypoid adenomas and squamous cell papillomas. Swenberg et al. (1980) described a number of additional lesions in the nasal turbinates of rats exposed to formaldehyde for 18 months, including rhinitis, epithelial dysplasia and hyperplasia, squamous hyperplasia, and cellular atypia that occurred in a dose-related manner. Other inhalation studies (Albert et al., 1982; Tobe et al., 1985) have provided positive evidence for the carcinogenicity of formaldehyde. These findings and other findings on carcinogenicity in animals have been discussed in depth in Chapter 4 of the EPA (1987) document. More recent studies are summarized in Appendix B of the present document.

Recent investigations of chronic toxicity have shown formaldehyde administered orally for 24 months to be carcinogenic in Sprague-Dawley rats but not in Wistar rats. Soffritti et al. (1989), using six exposure groups each of 50 male and 50 female Sprague-Dawley rats, with drinking water concentration of 10 to 1500 mg/l formaldehyde, reported increases in the percent of animals bearing leukemias and gastro-intestinal neoplasia at the higher exposures. Til et al. (1989), using three exposure groups, each of 70 male and 70 female Wistar rats, with drinking water concentrations of 20 to 1900 mg/l, reported numerous pathological charges at the highest exposure level, but no evidence of carcinogenicity at any level. Tobe et al. (1989), using three exposure groups, each of 20 male and 20 female

Wistar rats, with drinking water concentrations of 200 to 5000 mg/l, also reported pathological changes at the highest exposures level but no significant increases in the incidence of any tumor in these small treatment groups. In a letter to the editor, Feron et al. (1990) questioned the conclusions and some methods of Soffritti et al (1989).

Other types of exposures have produced a spectrum of results. Watanabe et al. (1954) presented a brief preliminary report of experimentally inducing sarcomas by repeated injections of an aqueous solution of formaldehyde in rats. Mueller et al. (1978) induced a preneoplastic lesion of the oral mucosa by repeated exposure to formalin solution in rabbits. Homma et al. (1986) found that a formalin solution repeatedly administered in transplated rat bladders did not promote formation of tumors. Takahashi et al. (1986) found that formalin solution in diet did promote stomach tumors in Wistar rats. Iverson et al. (1988) found that topical skin application of formaldehyde solution in mice did not promote the formation of skin tumors.

Epidemiological studies have shown formaldehyde exposure to be significiantly associated with cancer at sites in the respiratory tract in workers and in the general population. Studies of embalmers, who have used formaldehyde, have shown increased rates of brain cancer and of leukemia. See Appendix C for summaries and data on epidemiology studies.

Many studies in the epidemiological literature support a link between formaldehyde and elevated risk of cancers of the upper respiratory tract. Among the industrial cohort studies, Stayner (1988) reported a relative risk of 3.4 (90% CI: 1.2-7.9) for buccal cancer, and Blair et al. (1986) reported a relative risk of 3.00 (90% CI: 1.30-5.92) for nasopharyngeal cancer. Among industrial proportional mortality studies, Liebling et al. (1984) reported a relative risk of 8.70 (90% CI: 1.50-27.33) for buccal/pharyngeal cancer and Stayner et al. (1985) reported a relative risk of 7.5 (90% CI: 2.0-19) for buccal cancer In all of these studies the elevated risk was statistically significant. The population-based case control studies reported statistically significant relationships between formaldehyde exposure and upper respiratory cancers in three studies (Vaughan et al., 1986 a,b; Hayes et al., 1986; Olsen et al., 1984), although these cancers can appear in any of several sites.

In a subsequent report Blair et al. (1987) presented a summary of a further analysis resulting in a significant association between nasopharyngeal cancer and simultaneous exposure to formaldehyde and to particulate, indicating that such exposure may be a risk factor. Collins et al. (1988) have critiqued this finding and have added data.

The three largest -- and therefore potentially most sensitive -- industrial cohort studies reported elevated rates of lung cancer. The largest, Blair et al. (1986) with 26,561 U.S. workers, reported a statistically elevated death rate due to lung cancer, equivalent to 35% above the national average. The other two studies reporting elevated death rates due to lung cancer were Acheson et al. (1984a, 1984b) with 7680 British males workers, mostly young, and Stayner et al. (1988) with 11,030 U.S. workers, predominantly female. Some of the categories in the Acheson study showed statistically significant increases of lung cancer. The Stayner study

found lung cancer to be elevated 14% overall, which was not statistically significant, but the exposures were well below those of the other two studies.

In the Blair et al. (1986) study the investigators concluded that a causal relationship between formaldehyde exposure and lung cancer was unlikely because of a lack of dose gradient for those tumors. In order to assess the criticism that a "healthy-worker effect" may have distorted the interpretation of Blair et al. (1986), Robins et al. (1988) performed a complex reanalysis that found no exposure effect on the lung cancer mortality. Sterling and Weinkam (1988) also performed a reanalysis on the basis that Blair et al. (1986) failed to account for a "healthy-worker" effect in the original report. Because of computational errors affecting their results Sterling and Weinkam (1989a,b) published corrections. These corrected results showed that lung cancer was related to formaldehyde exposure in a dose-dependent manner, which was statistically significant. In a subsequent analysis of the same workers Blair et al. (1990) explored the source of the elevated rate of lung cancer, eventually concluding that exposure to phenol, melamine, urea, and wood dust and other substances might account for some or all of the excess observed. More recently Marsh et al. (1992) performed an independent reanalysis of the same data. These investigators did not confirm Sterling and Weinkam's finding of a statistically significant trend of lung cancer with cumulative exposure. However, they did find that the risk ratio estimates for lung cancer were elevated for the higher categories of cumulative formaldehyde exposure relative to the baseline category.

Recent epidemiological studies contribute to the conclusions only marginally. Gerin et al. (1989) presented the results of a large case control study with 3726 cancer patients. The odds ratio for the highest exposure group with adenocarcinoma of the lung was nearly significant at the 95% confidence level, and there was an apparent trend of incidence of this cancer with exposure. Nevertheless, the authors concluded that there was no persuasive evidence of an increased risk of any type of cancer among men exposed to these levels of formaldehyde. The study did not consider cancers of the nasal cavity, of the brain, or of leukemia. Bertazzi et al. (1989) presented an extension of a previous study (Bertazzi, 1986) which had detected elevated lung cancer among 1332 workers in a resin manufacturing plant subject to formaldehyde exposure. In the extended study with more accurate estimates of exposure, the lung cancer rate was not elevated above expected for those exposed to formaldehyde (Bertazzi, 1989). Linos et al. (1990) reported elevated rates of follicular non-Hodgkin's lyphoma and of acute myeloid leukemia among embalmers and funeral directors in a population-based case control study. The investigators did not attribute these tumors to formaldehyde exposure. Malker et al. (1990) found significantly elevated rates of incidence of nasopharyngeal cancer among workers in fiberboard plants and among book binders, both being subject to formaldehyde exposure.

Four recent occupational studies have investigated the relationship of formaldehyde exposure to histological changes, some of which are potentially precancerous lesions, in the nasal mucosa. Holstrom et al. (1989) found that workers exposed to well defined levels of formaldehyde developed significant changes in the middle turbinate, while those exposed

to both formaldehyde and wood dust did not. Boysen et al. (1990) found in nasal biopses that workers exposed to formaldehyde showed a significantly higher degree of metaplastic alterations. Edling (1988) found significant histological differences in the nasal mucosa of formaldehyde workers compared to unexposed workers but found no histological differences between those exposed to formaldehyde and those exposed to formaldehyde and wood dust. Berke (1987) found no statistical relationship between exfoliated nasal cells in formaldehyde-exposed workers and control groups. The results of these four studies are varied, the studies all use small numbers of subjects and the study designs are not sufficiently definitive. Thus, these studies, even taken together, do not establish a relationship, but they do provide some indication of possible histologic change due to formaldehyde exposure in humans, consistent with results in animals.

Several groups of investigators have produced reviews on the issue of carcinogenicity of formaldehyde (IARC, 1987; Nelson et al. 1986; Universities Associated for Research and Education in Pathology Inc., 1988; Council on Environmental Affairs, American Medical Association, 1989; Purchase and Paddle, 1989; Blair et al., 1990). The leading group, International Agency for Research on Cancer (1987), has reviewed the evidence for carcinogenicity and in their official publication found it to be limited in humans and sufficient in animals.

Considering both the determination of sufficient evidence that formaldehyde is an animal carcinogen and the determination of limited human evidence, EPA has classified formaldehyde in Group B-1, a probable human carcinogen (1987a, page xiii). OSHA has concluded that "formaldehyde should be regarded as an occupational carcinogen," based upon animal and human studies (1987, page 46173). Considering these previous determinations, along with the evidence of carcinogenicity summarized above, OEHHA staff conclude that formaldehyde is a probable human carcinogen and meets the definition of a "toxic air contaminant": an air pollutant which may cause or contribute to an increase in mortality or an increase in serious illness, or which may pose a present or potential hazard to human health.

Possible Mechanisms of Formaldehyde Carcinogenesis

The mechanism by which formaldehyde causes cancer in experimental animals has not been fully elucidated. Formaldehyde has been shown to interact with DNA in a number of short-term genotoxicity assays, suggesting that a somatic mutation may be at least partially responsible for the observed carcinogenic effects. A summary of the genotoxic effects seen after formaldehyde exposure include gene mutations, single strand DNA breaks, DNA-protein crosslinks, sister chromatid exchanges (SCE), and chromosomal aberrations (Consensus Workshop on Formaldehyde, EPA 1984; IARC, 1987, Ma and Harris 1988). Mutagenic activity resulting from formaldehyde exposure has been observed in *Escherichia coli*, *Pseudomonas fluorescens*, *Salmonella typhimurium*, and different strains of viruses, yeast, fungi, *Drosophila*, grasshoppers, and mammalian cells (Ulsamer et al., 1984). *In vitro*, formaldehyde has been shown to transform BALB/c3T3 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 (Consensus Workshop on Formaldehyde, 1984). The mutagenicity and genotoxicity associated with formaldehyde have been compiled by IARC (1987) and are

discussed in more detail in the EPA document (1987a) and in the OSHA documents (1985, 1987) and by Ma and Harris (1988). More recently Crosby et al. (1988) have studied the molecular nature of formaldehyde-induced mutations and identified different mechanisms of mutation under different conditions.

Cellular Responses to Formaldehyde

Mammals have defense systems to counteract and detoxify formaldehyde. These systems are important in regulating the actual levels to which cells are exposed. Exogenous formaldehyde exposure may disrupt these defense mechanisms and allow a greater interaction between formaldehyde and the cells.

Formaldehyde exposure may have deleterious effects on the mucociliary clearance apparatus that normally clears the airways. At formaldehyde concentrations of less than 1-2 ppm, the mucous layer can trap and remove a large proportion of the inhaled formaldehyde, thus preventing it from reaching the underlying epithelial layer. At higher formaldehyde concentrations (15 ppm) mucostasis and ciliastasis were observed at a number of anatomic sites in the rat nasal cavity (Morgan et al., 1983). A later study by Morgan et al. (1986) showed a dose-dependent decrease in mucociliary activity, with slight effects observed at both 2 and 6 ppm, and a more pronounced inhibitory effect at 15 ppm. Bogdanffy et al. (1987) showed that formaldehyde can bind to specific soluble protein fractions in both rat and human mucus, potentially altering mucus viscoelasticity and other physical characteristics of mucus. Because the mucus layer serves a protective barrier role for the delicate epithelial cells underneath it, inhibition of the normal function of both mucus and cilia may have a deleterious effect on these cells.

Several studies have shown that formaldehyde can have marked effects on the rates of cell turnover and, therefore, cell proliferation in the nasal passages of exposed animals. A labelling index for tritiated thymidine incorporated into the nucleus has shown marked increases in cell turnover rates in the nasal passages of both rats and mice exposed to formaldehyde (Chang et al. 1983; Swenberg et al. 1983b, 1986; Wilmer et al. 1987, 1989; Zwart et al. 1988; Monticello et al. 1989b 1990a; Reuzel et al. 1990; Wouterson et al. 1987; Appleman et al., 1988; Holstrom et al, 1989b) and also of monkeys (Monticello et al., 1989a,c). Cell proliferation rates in the rat are dependent on the concentration, the dose, and the length of the exposure period, as well as the specific location within the nasal cavity (Swenberg et al., 1986). Although the relationship between cell proliferation and tumor response is uncertain, an increase in the rate of cell proliferation would increase the opportunity for formaldehyde to interact with DNA, in turn increasing the likelihood of formaldehyde-induced mutation and formaldehyde-initiated cells.

Another defense mechanism against formaldehyde involves enzymatic detoxification with formaldehyde dehydrogenase. This reaction uses glutathione in converting formaldehyde to formic acid, which is subject to further metabolism. As the exposure concentration increases, the enzyme complex becomes saturated, leading to elevated intracellular levels of free

and glutathione-bound formaldehyde and increasing the opportunity for interaction with DNA.

Physiological Response to Formaldehyde

Another defense mechanism is the response in rodents, and especially mice, to decrease substantially their respiration rate when exposed to sensory irritants. For formaldehyde Chang et al. (1981) estimated the RD_{50}, which is the exposure level needed to reduce the respiratory rate by 50%, to be 4.9 ppm for mice and 31.7 ppm for rats, implying a reduced respiratory rate in mice compared to rats at the same exposure. This finding might well have important ramifications for the analysis of bioassay data. Reduction in respiratory rate would lower the administered dose at the same exposure, providing an explanation for the much lower incidence of tumors in mice compared to rats with the same exposure to formaldehyde.

Molecular Dosimetry

Characterization of dose acting at the target tissue for each administered dose or exposure permits improvements in the quantitative description of the toxic effect. The tissues in humans and rodents that have been found to be most susceptible to carcinogenesis are those lining the respiratory tract. Therefore, measures of effects on DNA in those tissues are useful in the risk assessment.

Investigators at the Chemical Industry Institute of Technology (CIIT) have presented a series of studies offering evidence that acute administration of airborne radiolabelled formaldehyde to rodents and primates leads to the formation of cross links between protein and DNA in nasal respiratory mucosa (Casanova-Schmitz et al. 1984; Casanova and Heck, 1987; Casanova et al. 1989). The tissue sections with the greatest amount of bound radiolabel are found at the same anatomical site where the highest incidence of squamous cell carcinomas occurs (Chang et al., 1983). Because the formation of DNA-protein crosslinks caused by formaldehyde can lead to a number of genotoxic effects, including mutations (Goldmacher and Thilly, 1983), cell transformations (Ragan and Boreiko, 1981), deletions (Beyajati et al., 1983), and chromosomal aberrations (Natarajan et al., 1983), the DNA-protein crosslink formation may play an important role in the induction of nasal cancer. For purposes of relating risk to exposure, the rate of binding of formaldehyde to DNA provides a useful measure of dose to the target tissue.

The initial labelling experiments suggested that the covalent binding of protein to rat nasal DNA occurred only at exposure concentrations of 2 ppm or greater (Casanova-Schmitz et al., 1984); however, new techniques offer better reliability and have demonstrated DNA-protein crosslink formation at concentrations at 0.3 ppm, the lowest concentration tested (Casanova et al., 1989). The earlier method, based on a dual-isotope ($^{3}H/^{14}C$) approach, measured the amount of residual formaldehyde bound to DNA in a solution of hydrolyzed DNA (Casanova-Schmitz et al. 1984; Casanova and Heck, 1987). Following the concerns raised by the EPA (1987a) and others about the dual-labelling technique, Casanova et al. (1989) developed their new methodology, based on high performance liquid chromotography (HPLC) to determine total formaldehyde bound to DNA. This method allows the

determination of the concentration-response curve for DNA-protein crosslinking by techniques that do not use ^{3}H-formaldehyde, that have a greater sensitivity for detection, and that accurately determine the amount of bound formaldehyde. Thus, the quality of the binding data now appears to overcome objections to use of the earlier binding data for risk assessment by Starr and colleagues (Starr 1983, 1987; Starr et al. 1984; Starr and Buck, 1984; Starr and Gibson, 1985).

Investigators at CIIT have also measured the extent of covalent binding in nasal DNA of rhesus monkeys exposed to ^{14}C-formaldehyde. Because the nasal passages of monkeys are morphologically closer to humans than to rats, the data obtained from monkeys may be more appropriate for human risk assessment purposes. Also, humans and monkeys can resort to mouth breathing if nasal irritation (as a result of chemical exposure) becomes too great, whereas all air that rats breathe must pass through their nasal passages and thus interacts most strongly with the cells of the nasal mucosa. While the carcinogenic significance of the different types of breathing patterns is not fully established, the oronasal pattern of respiration used by humans and monkeys would be expected to reduce the dose of formaldehyde received by the nose and to increase the dose delivered to the oral cavity and lower respiratory tract. The lack of cancer bioassay data for monkeys limits the usefulness of the binding data in monkeys, because it is not known how susceptible monkeys are to formaldehyde-induced carcinogenesis.

Heck et al. (1989) and Monticello and Morgan (1989a) evaluated the extent of DNA-protein crosslinking and pathologic lesions in the nasal passages and respiratory tract of rhesus monkeys. For the crosslinking experiments Heck et al. (1989) exposed male rhesus monkeys in a head-only inhalation chamber to 0.7, 2, or 6 ppm ^{14}C-formaldehyde for six hours. Immediately following the exposure period samples of respiratory mucosa were collected from the middle turbinates, anterior nasal walls and anterior septum, nasopharynx, maxillary sinuses, larynx, trachea, carina, major intrapulmonary airways, and proximal lung. The DNA from the samples was isolated, purified, and enzymatically hydrolyzed to deoxyribonucleosides, resulting in the dissociation of DNA-protein crosslinks and the quantitative release of ^{14}C-formaldehyde. Groups of F-344 rats were also exposed to either 0.3, 0.7, 2, 6, or 10 ppm formaldehyde for six hours, with nasal and respiratory DNA-protein crosslinks measured immediately after exposure. The authors stated that a similar region of the respiratory tract was selected for evaluation from both species, and that the mean concentration of crosslinks was weighted according to the amount of DNA in each tissue, to aid in the cross-species binding comparison (Heck et al., 1989).

The results demonstrated that monkeys had much lower (up to 10-fold) concentrations of crosslinks in the nasal turbinates and anterior nose than did rats at a given formaldehyde concentration. Crosslinking was also detected in the nasopharynx, the larynx-trachea-carina, and major intrapulmonary airways of the monkeys at the 2 and 6 ppm doses, indicating that formaldehyde can penetrate to deeper regions of the respiratory tract of monkeys than of rats. The authors speculated that the monkey may be more capable of eliminating absorbed formaldehyde or repairing DNA-protein crosslinks more efficiently than the rat (Heck et al., 1989).

Some important questions need to be considered when using the molecular dosimetry data to estimate cancer risk. First, are the observed DNA-protein crosslinks solely responsible for the carcinogenic effects, or do other factors, such as cell turnover, play a contributory role? Second, are binding data from an acute or subacute exposure period applicable to a two-year bioassay situation? Cell proliferation rates, significantly elevated following three days of exposure to formaldehyde, were reported to decrease substantially after ten days of exposure (Swenberg et al., 1983). It seems possible that adaptative mechanisms may be induced by repeated exposure, which could reduce the interactions of formaldehyde with the DNA. Third, are rats a good animal model to use for human extrapolation in view of their anatomic and morphologic differences and their breathing method? Heck et al. (1989) have shown there are significant differences in the binding characteristics of ^{14}C-formaldehyde between rats and monkeys. Such data are presently suggestive of such differences between rats and humans. Such questions do not eliminate the usefulness of the molecular dosimetry data, but it is prudent to be aware of any assumptions being made.

Dosimetric Model

The pharmacokinetic model outlined in this section provides a means of using the molecular dosimetry data from animal experiments to evaluate carcinogenic risks to humans resulting from breathing ambient levels of formaldehyde. The use of this model improves confidence in extrapolation of cancer rates measured at high exposures to those expected at low exposures. Such models also help to extrapolate across species, thus allowing animal bioassay data to be extrapolated more confidently to humans.

The recent data of Casanova et al. (1989) appear to be sufficiently accurate to provide a measure of the rate at which formaldehyde binds to rat nasal DNA. The binding occurred as protein-DNA crosslinks primarily in the anterior sections of the nasal cavity. A plot of the rate of binding of ^{14}C-formaldehyde as a function of formaldehyde exposure (their Figure 5) provides evidence for the saturation of the detoxification process. At low concentrations of formaldehyde the detoxification takes place more efficiently than at higher concentrations. At sufficiently high exposure concentrations the detoxification mechanisms become overwhelmed, leaving much of the adsorbed formaldehyde available for interaction with DNA and other cellular molecules.

A pharmacokinetic model for the binding of formaldehyde to DNA in the nasal mucosa is presented in Appendix A. This model equates the rate of cellular absorption from the nasal air stream to the combined rate of loss due to a saturable detoxification pathway and due to a first-order kinetic pathway. The model yields the following simplified relationship between y and X:

$$y + b_1 y/(c_1+y) = a_1 X, \qquad (1)$$

where y is the rate of binding of formaldehyde to DNA (which is used as a measure of dose rate of formaldehyde at the nasal target tissue), X is the applied exposure concentration (which is a measure of the rate of inhalation of formaldehyde in the air being breathed by the rats), and a_1,

b_1, and c_1 are parameters estimated from the binding data of Casanova et al. (1989) for a range of exposures from 0.3 ppm to 10 ppm.

Calculations for the parameters a_1, b_1 and c_1 of Equation 1 used the raw data for the DNA-binding rates obtained by Casanova et al. (1989) and summarized by Starr (1989,1990). In a personal communication, M. Casanova furnished the 15 raw data points, each of which was obtained by pooling the nasal mucosas of four rats that received the same exposure. See Table A-4 for raw data, which represent five different exposure levels.

The estimation method was to obtain an algebraic expression predicting y and then to use a non-linear least squares analysis that weighted each point by the inverse of the variance of the observations collected at that exposure level. This approach equalizes the contributions of each point to the weighted residuals of the sum of squares. See also the description in Appendix A.

The results of the minimization procedure, displayed in Table 1, give the point and interval estimates of the three parameters in Equation 1. The estimate of the parameter b did not reach statistical significance at the 95% confidence level with $p = 0.17$. This aspect of the results is a potential weakness in the analysis. Nevertheless, there are several reasons to accept the present characterization of the binding rate as the best available at this time. (1) The form chosen for the relationship, Equation 1, has a theoretical basis in pharmacokinetics. That form has the important characteristic of being linear at low exposures with a slope that differs from the asymptotic slope used for extrapolating to exposures above 10 ppm. (2) The parameter b represents the contribution of the non-linear (hyperbolic) term relative to the linear term in Equation 1. Exploratory analysis shows that a simple linear fit to the data, with or without a threshold, gives a much less satisfactory fit. (3) The estimates of the parameters are all statistically highly correlated, indicating that difficulties in obtaining statistical significance may be expected.

The model of Equation 1 appears to provide an adequate first approximation to the rate at which formaldehyde actually binds to DNA within the nasal tissue. Nevertheless, this metabolic system is complex, and additional data eventually may be obtained to permit descriptions of more complex models, which require estimation of further parameters.

Cancer Risk Predicted From Rat Bioassay

The mathematical model most appropriate for extrapolating predictions of cancer risk from the animal bioassay exposures to the human experience is the linearized multistage model (EPA, 1986, 1987b; DHS 1985). This class of models has gained acceptance for its biological plausibility and consistency with experimental data on cancer as well as its prediction of linearity at low dose. In recent years evidence for a small number of discernible stages of carcinogenesis has accumulated (Moolgavkar, 1988), and support for the multistage model has grown, especially when used with appropriate physiological and pharmacokinetic inputs. Other models are difficult to link to biological mechanisms of carcinogenesis but have been presented in risk assessments to emphasize uncertainities about the low

TABLE 1 PARAMETERS FOR PHARMACOKINETIC MODEL

Parameter	Point Estimate[a]	Confidence Interval[b]	Units[c]
a_1	7.3	1.7, 12.9	(pmol/mg-hr)/ppm
b_1	30.8	-14.7, 76.3	pmol/mg-hr
c_1	3.8	0.6, 7.0	pmol/mg-hr

[a] Point estimate obtained by least-squares fitting of the prediction of the model Equation (1), solved for y, to the raw data. Each term in the least-squares procedure is weighted by the inverse of the variance of that exposure group. Program was SYSTAT NONLIN.

[b] 95% confidence limits. If lower confidence limit for the parameter estimate is less than zero, then the result is not statistically significant at the 95% level.

[c] Units are in parts per million (ppm) formaldehyde exposure and picomoles (pmol) of formaldehyde bound per milligram (mg) of DNA per hour (hr) of exposure.

dose extrapolation. See the supporting document (EPA, 1987a) for their application to formaldehyde.

The present assessment first uses the linearized multistage model of Howe et al. (1986), as implemented in the GLOBAL86 program, to estimate the cancer potency of formaldehyde. That program accepts cancer bioassay data and computes maximum likelihood estimates (MLEs) and upper 95% confidence limits (UCLs) of risk associated with a particular dose. The linearization aspect of the model leads to estimates of upper confidence limits on risk which are generally regarded as protective of public health.

The multistage model is based on several assumptions about the process of carcinogenesis. It is assumed that cancer is an irreversible process which originates in a single cell and involves a number of biological events or stages. The probability of occurrence of each stage varies linearly with dose. In addition, it is assumed that the incidences of background and chemically-induced cancer are additive. In a one-stage model the carcinogen in question participates only in one stage of cell transformation. In a two-stage model the carcinogen participates first in a process that transforms the normal cell to a precancerous stage then in a second distinct process that transforms a precancerous cell to a cancer cell. More stages would require participation in further distinct transformations between normal and cancer cell. In assessing carcinogenesis for a specific chemical, the number of stages refers to only those stages in which that specific chemical participates in the transformations.

For purposes of computation the multistage model takes the form:

$$P(d) = 1 - \exp(-q_0 - q_1 d - q_2 d^2 - \ldots - q_n d^n), \qquad (2)$$

where P(d) is the lifetime probability of tumor developing at dose d,

exp is the exponential function,

n is the selected number of stages, generally the lowest number that provides an adequate fit of the data, $p < 0.05$,

p is the probability that the model does not contradict the observed incidence data.

$q_i \geq 0$, $i = 0, 1, 2, \ldots, n$, are coefficients calculated to give the best fit to the experimental data (maximum likelihood estimates) subject to the constraint that all q_i are greater than or equal to 0.

At low doses, the additional risk is approximated by:

$$P(d) = P(0) + (1-P(0))\, q_1 d. \qquad (3)$$

A computer program provides point estimates and 95% upper confidence limits on the coefficients q_i, $i = 0, 1, 2, \ldots, n$, and the extra risk at a given dose, by maximizing the likelihood function of the data. The 95% upper confidence limit of the coefficient q_1 is designated q_1^*, which is called here the UCL on unit risk and is expressed in units of inverse exposure.

TABLE 2 BIOASSAY DATA USED TO ESTIMATE RISK TO RATS

X: Exposure[a] (ppm HCHO)	y: Rate of DNA Binding[b] (pmol/mg-hr)	Lifetime Equivalent Metabolic Exposure[b] (ppm)	Incidence of Nasal Squamous Carcinomas[c]
0	0	0	0/156 = 0%
2	2.5	0.54	0/159 = 0%
5.6	15.9	3.4	2/153 = 1.3%
14.3	74.8	16.	94/140 = 67%

[a] Fischer 344 rats inhaled indicated concentrations of formaldehyde gas 6 hours per day, 5 days per week for 24 months.

[b] Estimates obtained as follows: For each X in column 1 of this table, solve for y in the pharmacokinetic model of Equation (1) fit to data of Casanova, Deyo and Heck (1989) for 6-hour exposure (Table 1). Multiply y in pmol/mg-hr by $(b_1+c_1)/a_1c_1$ = 1.20 ppm/(pmol/mg-hr) to obtain metabolic exposure. Multiply that result by 30 hr/wk / 168 hr/wk = 0.179 to obtain the lifetime equivalent.

[c] Based on data partially reported in Kerns et al. (1983). Numerator and denominator are those used by US EPA (1987a). Rats that died prior to the appearance of the first squamous cell carcinoma at 11 months are not considered at risk. Rats sacrificed at 12 and 18 months are treated as though they would have responded in the same proportion as the rats that remained alive at the respective sacrifice times. The numbers obtained from the complex calculation are rounded. These numbers are in close agreement to those obtained by simply omitting all sacrificed animals from consideration and considering the rats that died prior to 11 months not to be at risk.

TABLE 3 UNIT RISK ESTIMATES FOR RATS[a]

Exposure Measure	Stages(n)	p[b]	q_1^* (ppm^{-1})[c]
Metabolically corrected:	3	0.85	5.8×10^{-3} [d]
Applied:	5	0.89	15.0×10^{-3} [e]

[a] Obtained for multistage models fit to nasal squamous cell carcinoma incidence in rats (Table 2) by maximum likelihood estimation procedure that provides 95% upper confidence limit on linear coefficient, q_1 (GLOBAL 86). The estimates are calculated for both tissue dose-rate and applied exposure. See Appendix A for estimates of the other coefficients.

[b] Goodness of fit statistic. The fit of the model to the data is taken to be inadequate for p less than 0.05, following Howe et al. (1986).

[c] Linear coefficient of 95% upper confidence limit on risk due to lifetime exposure. These values are obtained by multiplying the coefficients from the analysis of the cancer bioassay by 168hr/30hr in order to obtain lifetime estimates from data obtained for partial exposure during each week.

[d] Provides accurate (linear) predictions only below 0.6 ppm. Above that concentration the prediction becomes nonlinear and requires a more complicated calculation, either estimation using an additional (nonlinear) term with the coefficient from Table A-1 or direct use of the GLOBAL 86 program for the appropriate exposure.

[e] Essentially agrees with EPA 1987a.

At low doses, q_1^* is used to obtain an upper confidence limit on the risk associated with a given dose and the lower confidence limit on dose producing a given risk. The computation provides generally for any dose the largest value of risk that is likely to be consistent with the data and the smallest dose corresponding to a fixed risk that is likely to be consistent with the data. GLOBAL86 incorporates a technique for assessing goodness of fit based on a Monte Carlo simulation (Howe et al., 1986).

The rat tumorigenicity data that are used here to obtain the parameters of the linearized multistage models are presented in Table 2. The two different measures of dose rate used in the models are exposure alone (ppm) and metabolic exposure. The metabolic exposure is calculated for each exposure by solving Equation (1) to obtain the tissue dose rate y and then scaling that value to the lifetime equivalent. Metabolic exposure is defined to be proportional to y in such a manner as to be essentially equal to applied exposure at low concentrations, as developed in Appendix A. The computer program allows exploration of the form each model takes with different numbers of stages.

The computations all determine q_0 to be zero; so the risk relationship has no background rate, in accordance with previous experience as well as the present control observations. The resulting values of q_1^*, adjusted for equivalent lifetime exposure by multiplying by (168 hr/wk)/(30 hr/wk) to account for partial lifetime exposure, are presented in Table 3, which also provides a measure of goodness of fit for each form of the model. Although linear predictions based on q_1^* provide accurate upper confidence limits (UCLs) for low dose extrapolations, predictions at higher doses require an additional coefficient for each model, presented in Table A-1 of Appendix A, which also presents the coefficients for the maximum likelihood estimates of risk.

The prediction of the lifetime unit risk for the three-stage model based on metabolic exposure (tissue dose rate) is $q_1^* = 5.8 \times 10^{-3}$ ppm^{-1} for the rat experiment. The corresponding prediction for the five-stage model based on applied exposure, used by EPA (1987a), is $q_1^* = 15.0 \times 10^{-3}$ ppm^{-1}. Both these forms of multistage model produce a good fit to the data, but the form using metabolic exposure has the advantage of the greater accuracy expected by using a measure that reflects actual dose rate to the affected tissue. Both these values of q_1^* are estimates of the upper 95% confidence limit on the slope of the cancer-risk relationship applicable for linear low dose extrapolation. As exposures increase up toward 1 ppm, the estimate of the 95% upper confidence limit for the three-stage model based on metabolic exposure develops significantly steepening curvilinearity when plotted against exposure (See Figure 1). The use of the simplified linear Equation 3 underpredicts risk for this model by 17% at 1 ppm. On the other hand, the full estimate of the 95% upper confidence limit for the five-stage model based on applied exposure remains nearly linear up to 3 ppm.

With the availability of long term cell proliferation data that might explain the degree of carcinogenesis of formaldehyde at high exposure, the assessment uses a set of mathematical modeling assumptions governing cell proliferation to explore the effect of the formaldehyde-induced proliferation on carcinogenesis. The modeling assumptions account for the effect of such proliferation on one or more of the following processes:

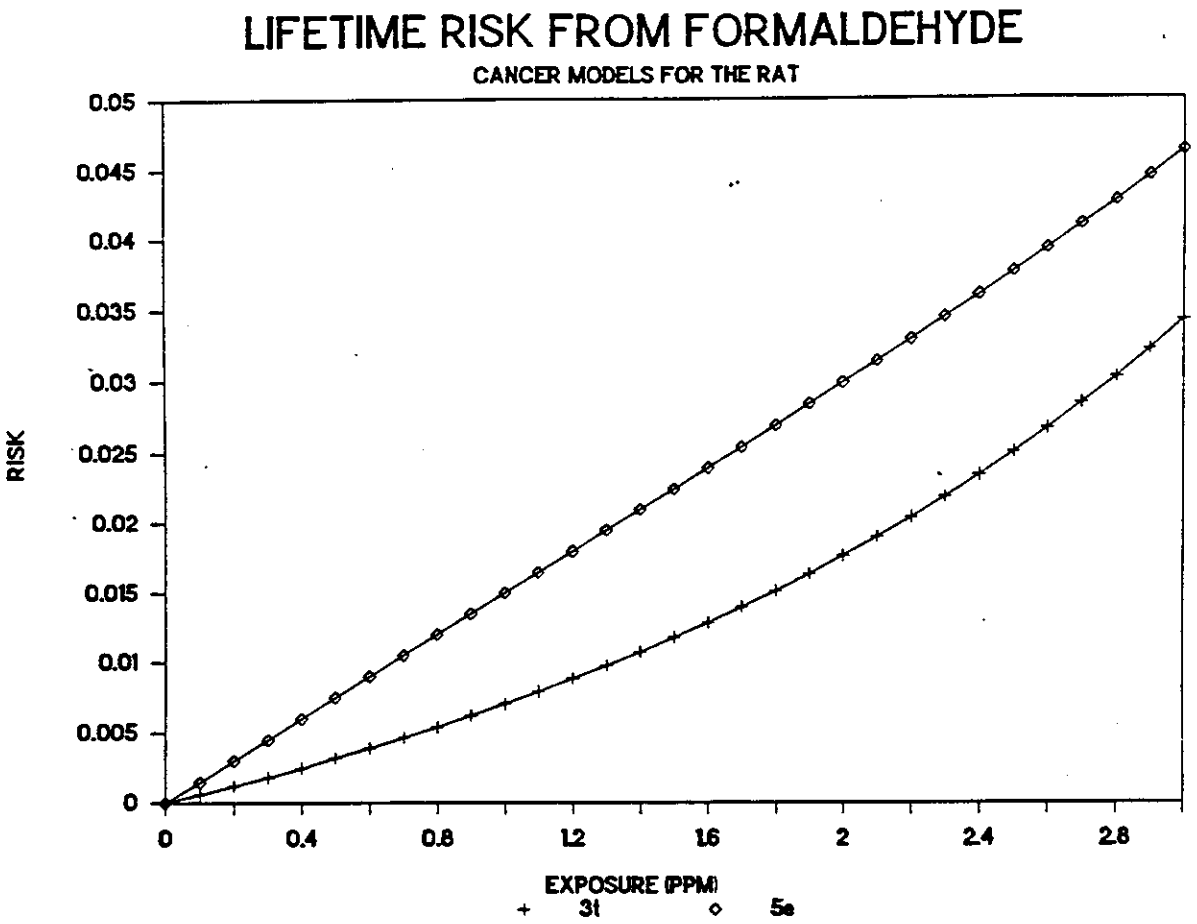


FIGURE 1 Two predictions of 95% upper confidence limit on lifetime risk of cancer from formaldehyde exposure. Both use the same data on cancer in the rat. The lower curve is for the three-stage model (3t), using metabolic exposure. The upper curve, which is nearly linear in this range, is for the five-stage exposure-based model (5e) using the applied exposure. The horizontal axis uses resting exposure in ppm to represent dose rate for both curves.

(1) the rate of mutation from normal cells to a premalignant cell, (2) the rate of mutation from premalignant cell to malignant cell, and (3) the rate of increase in the number of premalignant cells. These assumptions describe how the ratio of the exposure-dependent proliferation rate to the control rate might enter a well known approximate model formula that allows inclusion of proliferation effects. The likelihood calculations closely parelleled those of GLOBAL86. Five cases resulted in an excellent fit of the prediction of each to the data, and these five cases gave UCLs for unit risk (q_1^*) in the narrow range of 7.5×10^{-3} to 8.9×10^{-3} ppm^{-1}. This value is 30 to 50% above the UCL for the three-stage tissue-based model that did not explicity consider proliferation. Five additional cases could not be ruled out as being too unlikely statistically, showing that uncertainties prevented clear discrimination among cases. One of these additional cases gave a substantially different value of UCL on unit risk, $q_1^* = 1.0 \times 10^{-3}$ ppm^{-1}, resulting in a marginal fit, and three of these additional cases degenerated into that marginal case with this lower value of UCL on unit risk. In all cases the MLE exhibited strong linearity of the exposure-response relationship at low exposures when proliferation is taken into account, a result contrasting to results from models that do not take cell proliferation into account. See Appendix A for a description of methods and results.

Results of other multistage (and one single-stage) model analyses are offered here for comparison.

(1) In his latest approach, Starr (1989, 1990) used estimates of tissue dose in a three-stage model, with incidence data from the rat bioassay of Kerns et al. (1983). Starr's estimate after adjusting for lifetime exposure is 4.1×10^{-3} ppm^{-1}, which is 20% less than the UCL on unit risk in the present assessment. One reason for the difference is because Starr used tumor incidence data which did not subtract out early mortality in the denominator. The Office of Environmental Health Hazard Assessment, the U. S. Environmental Protection Agency (EPA) and others, have generally considered, that animals dying prior to the first cancer occurrence should not be counted as being at risk of cancer, in contrast to the approach of Starr. Another reason for the difference is because of Starr's use of a segmented linear interpolation of the DNA binding data instead of a metabolic model.

(2) In a study that included the effect of two different selections of incidence rates on the five-stage exposure model, K. Brown (1985) obtained UCLs on unit risk, which become 1.1×10^{-2} ppm^{-1} and 3.4×10^{-2} ppm^{-1} after adjusting for lifetime exposure. These values bracket the UCL on unit risk of the EPA five-stage exposure-based model, 15×10^{-3} ppm^{-1}. Brown also used a spectrum of models, affording the opportunity to compare results to the multistage model.

(3) OEHHA staff have recalculated the risks of cancer derived from the incidence data of Kerns et al. (1983) in order to investigate how the omission of the highest exposure group affects risk predictions. The highest exposure may have damaged nasal cells sufficiently to question the use of a multistage model that did not take into account cell kinetics. With the omission of the highest exposure group, a two-stage tissue-based model produces an excellent fit, and the resulting

UCL on unit risk, 8.4×10^{-3} ppm^{-1}, is 40% above the best estimate for the three-stage tissue-based model using all four dose groups and is the same value as for the most likely of the cell proliferation models. This result reflects, in part, greater uncertainty for the smaller number of data points.

(4) OEHHA staff calculated risk estimates for the nasal squamous cell carcinoma data from the Tobe et al. (1985) study using the incidence data as in EPA (1987a). The study had four dose groups, but a much smaller number of animals (30) started each exposure group, in comparison to the CIIT study (120 animals). The result of calculations for the three-stage tissue-based model using lifetime equivalent exposure is that the unit risk estimate 11.6×10^{-3} ppm^{-1} is two times greater than the corresponding present estimate based on the Kerns et al. (1983) study, in part reflecting the greater uncertainty as a result of the smaller number of animals.

(5) EPA (1987a) performed a calculation using polypoid adenoma data in a single-stage model based on applied exposure and obtained a unit risk value 13 times higher than their five-stage estimate using squamous cell carcinoma data. After an extensive discussion of that result, EPA decided not to use it in their quantitative risk assessment "because of uncertainties associated with the polypoid adenoma data set, its statistical significance, the manner of risk estimation, and the question of progression to malignant tumors." EPA considered that "There appears to be little credible evidence that the polypoid adenomas progress to any of the malignant tumors seen in the Kerns et al. (1983) study." On this basis OEHHA concurs with the EPA decision not to add the count of these benign tumors to the counts of squamous cell carcinomas. Nevertheless the observation of adenomas at the lowest exposure indicates a trend consistent with the linearized model.

This comparison provides some perspective on the present estimates. Not much change occurs for various ways of obtaining estimates based on the tumor incidence in the CIIT study, provided adenomas are omitted. Even using the much smaller Tobe study increases the unit risk by only a factor of two. The use of adenoma data from the CIIT study does, however, greatly increase the estimate of unit risk, by a factor of 13.

Extrapolation of Rodent Results to Human Risks

Extrapolating results of the risk analysis from the rodent model to humans presents one of the great challenges to the risk assessment. Bolt (1987) has listed difficulties in characterizing physiological mechanisms. These difficulties prevent confident extrapolation for formaldehyde. Interspecies extrapolations for cancer risk assessment presently rely on scaling factors applied to dose rate in such a way as to estimate the human response from the rat model. In its formaldehyde document the EPA (1987a) does not consider the need for any scaling factors across species and simply relies on the concentration of rat exposures as a measure of dose rate. This procedure is consistent with EPA practice for inhalation exposures, although EPA guidelines and procedures (EPA, 1986, 1987b) have specified the need for scaling factors in a number of circumstances. The

preliminary OSHA document (1985, pages 50455-6) has an extensive pragmatic discussion of some possible scaling factors, but OSHA (1985, page 50456; 1987, page 46218) ultimately rejected use of a scaling factor across species because of lack of persuasiveness of proponents' arguments in the regulatory record.

California guidelines (DHS, 1985) advocate a scaling factor based on the assumption that cancer risk across species depends upon intake rate of the carcinogen divided by body-surface area, mg/day-m^2, "in the absence of decisive empirical evidence" for some other scaling. The present assessment uses not only this default or body-surface-area scaling but also two modifications of it to take account formaldehyde's contact mechanism of carcinogenesis. All interpretations include adjustment for the greater percentage uptake of formaldehyde by the rat. See Appendix A for the mathematical treatment.

The default scaling factor predicts that risk is determined by uptake rate divided by body surface area (mg/day-m^2) with no explicit consideration for mechanism of action of formaldehyde. This scaling developed in the context of systemic carcinogens (EPA, 1985), for which it is appropriate to characterize risk by a measure of dose according to average body tissue concentration. The present calculations lead to value of 1.2 for this systemic scaling factor.

Formaldehyde, however, needs an alternative approach to take account the contact mechanism of carcinogenesis, in which the average concentration in the respiratory surface layer provides the measure of dose to characterize risk. The main evidence that formaldehyde acts as a contact carcinogen on the respiratory tract is that (1) the cancer sites clearly attributable to formaldehyde are on the exposed surface of conducting airways and (2) systemic formaldehyde levels do not become elevated in body fluids after substantial formaldehyde exposures.

Two different contact scaling factors take into account the evidence that inhaled formaldehyde is carcinogenic primarily on contact with the exposed surface tissue of the respiratory tract. Both contact scaling factors use an implicit systemic property of default scaling to establish a simple metabolic model for tissue concentration. The metabolic model equates the rate of uptake of parent carcinogen to a special form of the rate of metabolism of the parent carcinogen. The contact scalings apply the model to the intake surface--here the surface of the conducting airways--rather than to the whole body. Generic calculations using only allometric relationships across species lead to a contact scaling factor of 5.0. The dosimetrically adjusted approach to the contact scaling factor uses dosimetric data in the nasal passages of monkeys and rats to replace a general allometric relationship, leading to a scaling factor of 0.28.

The results of using the three scalings, the default scaling of 1.2, and the generic contact scaling of 5.0, and the dosimetric contact scaling factor of 0.28, give the estimates of UCL for lifetime human unit risk shown in Table 5 for the various models. The analysis developed the contact scalings in order to improve the accuracy of the predictions, but there is not a clear enough case for either contact scaling with presently

available data and models. Thus, the OEHHA staff have selected the body-surface-area (default) scaling as the best available choice.

There are a number of uncertainties in these scaling calculations, only in part represented by the given range of 0.28 to 5.0. Some of these uncertainties are due to lack of knowledge about the cancer process. There are two issues of species susceptibility that bear especially on the extrapolation from rat to human for formaldehyde.

(1) The first issue is that the epithelial lining of the lung airways in humans may be more susceptible to formaldehyde-induced carcinogenesis than the lining of the rat nasal passages. Although rat nasal surface concentrations are undoubtedly higher than human lung airway surface concentrations for a given applied exposure, the nasal passages generally are defended by a more copious mucus flow compared to the lung. Also, rat tissues have 10-25 times more glutathione than do humans (Meister, 1988) and rat lung tissues have about 3 times more glutathione activity than do human lung tissues. (Reitz et al, 1988), suggesting that rats may be able to detoxify formaldehyde more rapidly than humans. An experiment of Casanova and Heck (1987) has shown that formaldehyde exposure in rats with depleted glutathione levels results in a three to four times greater rate of DNA-binding than in rats with normal glutathione levels. The sensitivity of tissues also depends upon the amount of DNA at risk and therefore upon the number of cells exposed.

(2) The second issue concerning species-dependent susceptibility involves possible differences in the latency period for cancer development. The assumption used here, which is the same as used by EPA (1987a) and OSHA (1987), is that the time between exposure and tumor development is the same on the proportionate lifetime scale of the human and the animal. It may be, however, that the respiratory tract tumors have a more nearly chronological time scale and do not have adequate time to develop in the lifetime of the rat (two years) though they do in the lifetime of humans (70 years).

These susceptibility issues generally indicate a potential need for further upward scaling in extrapolating risk from the rat model to humans. It would be difficult to develop models that would confidently produce appropriate scaling factors in view of the complex interactions involved. For example, there may be pathways that compensate any lesser glutathione levels that may occur in the human respiratory tract lining, compared to the rat. Also, there is little information on relative rates of cell division of premalignant clones of cells.

Relationship of Predictions to Observed Human Cancer Rates

The quantitative results of the Blair study (1986), the largest and best documented epidemiology study, afford the opportunity to make a numerical comparison between observed risks of humans contracting cancer from formaldehyde exposure and predictions of risks for humans derived from animal studies. Among a cohort of 26,561 formaldehyde workers, Blair et al. (1986) observed significantly elevated relative risks of mortality both for lung cancers (relative risk for hourly workers who had the substantial formaldehyde exposures, was 1.35) and for nasopharyngeal cancer (relative

risk for wage earners was 2.0). As shown in the Table 4, the relative risk for this cohort for lung cancer translates into cohort work-exposure excess risk of 1.5×10^{-2}, while the equivalent translation for nasopharyngeal cancer produces the much smaller excess risk, 8×10^{-4}.

One can also estimate the risk of the cohort using potency estimates obtained from the animal bioassay. The corresponding predictions of risk based on the rat models require an estimate of exposure conditions for that cohort of workers. The estimated exposure is 1.0 ppm for the work week (a mid-range value). The corresponding ventilation-weighted exposure prior to either type of scaling is 2.0 ppm because the ventilation of the average worker has twice the sedentary value; so the dose rate applied to the same tissue has doubled. The resulting predictions of the UCL for risks due to total work exposure for the present models, extrapolated to humans with a generic contact scaling factor of 5, are 3.2×10^{-2} for the tissue-based model (3t) and 1.1×10^{-2} for the exposure-based model (5e). Use of the default scaling factor, 1.2, yields corresponding UCL risk predictions of 1.6×10^{-3} (3t) and 2.5×10^{-3} (5e). Both values assume a 40-hour work week and a 20-year exposure. For the generic contact scaling factor with the tissue-based model, the observed rate of cancer in the worker cohort, 1.5×10^{-2}, is about half the predicted UCL of risk and well within the confidence limit. For the contact scaling factor with the exposure-based model, the observed rate is above the predicted UCL of risk for the exposure-based model, although the predicted and measured confidence ranges do overlap. For the default scaling factor with either measure of dose rate, the observations are far above the predictions, and the dosimetric scaling-factor predictions are even below those of the default scaling factor. This outcome lends support for the tissue based model (3t) with generic contact scaling factor as an important estimate for UCL on unit risk. See Appendix A for the detailed calculations. The results are summarized in Table 4.

There are three main questions about the interpretations of the observation of excess lung cancer in the Blair study (1986) and about the exposure estimates obtained for the workers studied:

(1) Blair et al. (1987) suggested that inhaled particulate matter may have enhanced the delivery of formaldehyde to the respiratory tract of the exposed workers. If this is the case, exposure without particles would tend to be more in agreement with mid-range values of UCL on unit risk. Also, predictions from rodent studies using formaldehyde alone would have to be increased to account for the enhancement due to wood particles when such particles are present with formaldehyde exposure.

(2) Another possibility needs to be considered in any epidemiology study that did not obtain rates of smoking for the study groups. The more exposed groups with elevated rates of lung cancer may have contained more smokers than the unexposed group. EPA (1987) has argued persuasively that such is unlikely to be the situation in the present study because emphysema rates, which are strongly correlated to smoking, were actually larger in the unexposed group than in the exposed group.

TABLE 4 LUNG CANCER RISKS FOR BLAIR (1986) STUDY

Description	Values	
Relative risk observed[a]	1.35 (1.17-1.55)	
Equivalent individual risk[a,b]	1.5×10^{-2} (0.8×10^{-2}-2.7×10^{-2})	
Predictions of corresponding individual human risk from rat study[c]	Three-stage (3t) metabolic exposure	Five-stage (5e) applied exposure
Scaling factor = 5.0	3.2×10^{-2}	1.1×10^{-2}
Scaling factor = 1.2	1.6×10^{-3}	2.5×10^{-3}

[a] Values in parentheses represent 90% confidence intervals for the estimate preceding the parentheses.

[b] Calculated by multiplying the excess risk, which is the relative risk - 1, by the proportion of all deaths due to that form of cancer in the general population. For the period, 1960-1979, lung cancer accounted for 5% of all deaths.

[c] Values are 95% upper confidence limits. Model for nasal squamous cell carcinoma in rat is adjusted to humans for 20 years exposure at 40 hours per week. Predictions are assumed to be representative of the conducting airways of the entire respiratory tract of humans. The predictions assume an exposure of 1.0 ppm on average, which produces a ventilation-weighted average of 2.0 ppm for the work force, on the assumption that the average ventilation rate during working hours is twice that of the sedentary case.

(3) Another potential criticism of the observation of elevated lung cancers in the Blair et al. (1986) study is the apparent lack of a confirmatory trend of increasing lung cancer deaths with formaldehyde exposure. One possible explanation is that workers with increased sensitivity to formaldehyde, due to lower glutathione levels for example, may leave the highest exposed jobs sooner due to irritation, thus reducing the risk of respiratory cancer proportionally below what would be expected in the high exposure categories (Universities Associated for Research and Education in Pathology, Inc., 1988). Another possible explanation is that smokers may tend to leave the formaldehyde exposed jobs in inverse proportion to their rate of smoking because of excessive irritation. Thus, the dose-response relationship between lung cancer and formaldehyde may be masked by the decreased smoking contribution in the higher exposure categories (EPA, 1987a). This explanation is consistent with the decreased emphysema in the higher exposure categories. Also one study (Robins et al., 1988) has reported that non-malignant respiratory disease rate, which is highly correlated with smoking rate, decreased significantly with length of employment. Either of these explanations, irritation just from formaldehyde or irritation in connection with smoking, could account for the lack of dose-response relationship, thus lending support to the approximate validity of the number of lung cancers attributable to formaldehyde in the Blair study.

This risk assessment has mentioned uncertainties in the assumptions that produce the present predictions for humans. Rosenberg (1986) has developed an extensive outline of facts and controversies in the assessment of human risk to formaldehyde exposure. Starr (1990) has developed an adjustment of rat data to humans based on comparing DNA-binding data in monkeys and rats, producing lower estimates of risk. However, the monkey data do not appear to be adequate, in part because those data do not include the entire conducting airways, as would be necessary to extrapolate from rat nasal tumors to human lung tumors. Howlett et al. (1989) and L. Brown (1989) have criticized the use of the UCL of the linearized multistage model as giving unrealistically high risks for human exposure to formaldehyde. Both analyses are based only on the atmospheric exposure in the modeling. Beliles and Parker (1989) show that a dose parameter based on atmospheric concentration, breathing rate, and nasal surface area provides good agreement of observed and predicted risks between rats and mice in the cancer bioassays for formaldehyde exposure. However, OEHHA staff believe that use of a metabolic correction with a scaling factor based on a contact mechanism of carcinogenesis provides the best single estimate of risk with the least amount of uncertainty, considering the available scientific evidence.

Threshold Not Supported

The marked rise in observed cancer incidence in rats with increasing exposure (from 0% at 2 ppm to 1.3% at 5.6 ppm and to 67% at 14.3 ppm) suggests the possibility of a carcinogenic threshold for formaldehyde. However, a closer look at the biological processes involved suggests that this result is likely at least in part to be due to pharmacokinetics of normal detoxification processes and does not provide credible evidence that

there is a true threshold in the sense that there is negligible risk below some threshold level of formaldehyde exposure. The protective barrier function of the mucociliary apparatus, coupled with enzymatic detoxification and DNA repair processes, greatly reduces the effect of formaldehyde interacting with DNA. Because, these mechanisms are more effective at low formaldehyde concentrations, it is not surprising that only a very modest amount of formaldehyde binds to DNA at exposures of less than 1 ppm. Even so, Casanova et al. (1989) have identified DNA-protein crosslinks in the nasal mucosa of rats exposed to as little as 0.3 ppm formaldehyde, suggesting there is not an observable threshold for interaction of formaldehyde with DNA. Because formaldehyde is a known genotoxin and mutagen and has been shown to interact with DNA at such low exposure concentrations, the staff of OEHHA conclude that there is a strong basis to assume that formaldehyde does not have a carcinogenic threshold.

Specifying Risks to Humans

Table 5 displays the risk to humans calculated for the relevant combinations of risk models and scaling factors. The OEHHA staff have selected the three-stage tissue-based model with a body-surface area (default) scaling factor as providing the best value of upper confidence limit for unit risk to humans, $q_1^* = 7 \times 10^{-3}$ ppm^{-1}. This model uses in a consistent manner the best available scientific data on actual dose to target tissue and therefore appears to provide a sounder basis for prediction than the exposure-based estimate, which is higher. Models which include cell proliferation effects also give a higher unit risk, but those calculations are not well enough established to serve as a basis for the present best value. The body-surface-area (default) scaling factor serves as the best choice for scaling because of a lack of a clear case for using either the generic or the dosimetrically adjusted form of the contact scaling factor. The top of the range, $q_1^* = 40 \times 10^{-3}$ ppm^{-1}, occurs for using the generic form of the contact scaling factor and the results of using those cell proliferation models which fit the data well. The bottom of the range, $q_1^* = 0.3 \times 10^{-3}$ ppm^{-1}, occurs for using the dosimetrically adjusted scaling factor and the results of using a cell proliferation model which fits the data only marginally ($P = 0.05$).

TABLE 5 ESTIMATES OF UCL FOR UNIT RISK IN HUMANS[a]

Scaling type: (Scaling factor):	None[b] (1.0)	Systemic[c] (default) (1.2)	Contact, generic (5.0)	Contact, dosimetric (0.28)
Applied-Dose Model:				
5e [d]	15[q]	18	j	j
Tissue-Dose Model (DPX):				
3t [e]	5.8	7.0[o]	29	1.6
2t [b, p]	2.8			0.33
Tissue-Dose Models with Cell Proliferation[r]:				
1tn1[f,k] 1tx1[g], 1tg1[h]	8.4	10.1	42[m]	2.4
2tn1[f], 1tx0[g], 1tg0[h]	s	s	s	s
1tn2[i,k]	1.0	1.2	4.8	0.28[n]

[a] UCL values, expressed as 10^{-3} ppm^{-1}
[b] Values included for reference only.
[c] Also referred to as body-surface-area scaling.
[d] Five-stage exposure-based model, GLOBAL 86.
[e] Three-stage tissue-based model, GLOBAL 86.
[f] Two- or one-stage tissue-based model with proliferation affecting one mutation rate.
[g] One-stage tissue-based model with proliferation affecting no or one mutation rate and affecting exponential rate of premalignant cell increase.
[h] One-stage tissue-based model with proliferation affecting no or one mutation rate and affecting geometric rate of premalignant cell increase.
[i] One-stage tissue-based model with proliferation affecting two mutation rates.
[j] Improbable scaling because model makes no assumption about contact mechanism.
[k] Marginal fit, less likely model ($p = 0.05$).
[m] Top of the range.
[n] Bottom of the range.
[o] Present best estimate.
[p] Risks presented in Draft USEPA document (1991).
[q] Current EPA value based on 1987 document.
[r] See Table A-2 for values of related parameters.
[s] Values are near those of preceding line. See Table A-2 for exact values of unit risk without scaling factor.

APPENDIX A

MATHEMATICAL MODELS

This appendix provides a detailed account of the calculations in the main text that rely on special considerations for formaldehyde. The first section describes a pharmacokinetic model to estimate actual tissue-level dose rate as a function of exposure concentration. The second section gives the results of using the multistage model of carcinogenesis, both with the tissue concentrations from the pharmacokinetic model as a measure of dose rate and with the applied exposure concentration as a measure of dose rate. The third section describes the methods and results of a cancer risk model which considers cell proliferation explicitly. The fourth section develops three different scaling factors to be applied to the exposure measure in order to extrapolate rodent risks to humans. The fifth section gives an example of extrapolating the predictions based on rats to humans in the primary occupational study.

PHARMACOKINETIC MODEL

Accurate quantitative information about the actual concentration or rate of uptake of the chemical at the target tissue may provide a more accurate basis for estimating risk than simply using exposure concentration or applied dose. In the case of formaldehyde the tissue information is especially important because formaldehyde can be more efficiently metabolized or detoxified at low concentrations than at high concentrations in body tissues. So exposure alone may not be an accurate measure of concentration in the target tissue or of dose rate to the target tissue.

A recent paper of Casanova et al. (1989) provides data, interpreted by a pharmacokinetic model, to obtain a mathematical relationship between applied exposure and the dose rate to target tissue, which is given by the binding rate of formaldehyde to DNA in the tissues of the nasal passages of test animals. The mathematical model in Casanova et al. (1989) has a complicated derivation going back to a previous paper (Casanova et al., 1987), in which there was unjustified reliance on a simple dissociation-constant relationship for the equilibrium between free and glutathione-bound formaldehyde. Also, the earlier paper provides evidence that an important detoxification process of the saturable type is occurring in rats, even with the glutathione pathway depleted by pherone, yet the model is based on the assumption that only the glutathione pathway detoxifies the formaldehyde. The derivation that follows here takes a less specific approach to get a modified form of the important relationship between exposure and dose rate into the target tissue. The coefficients in this relationship do not have the specific interpretations of the earlier derivations, and the present approach does not use the unjustified assumptions of a simple dissociation constant between free and glutathione-bound formaldehyde in the derivations of Casanova et al. (1987, 1989).

The kinetic equations assumed to govern the rate of input of formaldehyde to DNA in the tissue are

$$r = k_1X - k_2F - V_mF/(K_m+F), \qquad \text{(A-1a)}$$

$$y = k_3F, \qquad \text{(A-1b)}$$

where F = concentration of free formaldehyde in tissue (pmol),
r = rate of accumulation of free formaldehyde in tissue (pmol/hr),
X = concentration of inhaled formaldehyde (ppm),
y = rate of binding of formaldehyde to DNA (pmol/mgDNA-hr),
k_1, k_2, k_3, V_m, K_m are constants.

Equation (A-1a), a mass balance, equates the rate of formaldehyde accumulation in the tissue to the difference between the input rate from the air stream and the sum of total diffusion rate of formaldehyde from the cell plus rate of conversion of formaldehyde ("detoxification") within the cell by a Michaelis-Menten mechanism (Savageau, 1976). Equation (A-1b) states that the rate of binding of formaldehyde to DNA is proportional to the concentration of free formaldehyde within the cell.

The present derivation assumes that Equations (A-1) are in the steady state during the course of the six-hour exposure. Thus r = 0, and Equations (A-1a) and (A-1b) combine to eliminate F and give a single equation:

$$a_1X = y + b_1y/(c_1+y), \qquad \text{(A-2)}$$

where a_1, b_1 and c_1 are parameters representing products and ratios of the original constants. This equation is essentially the same as that of Casanova et al. (1989). Solving Equation (A-2) for, y, which is the rate of binding, gives

$$y = 1/2(-b_1-c_1+a_1X+((b_1+c_1-a_1X)^2+4a_1c_1X)^{1/2}). \qquad \text{(A-3)}$$

The analysis fit the model predictions to the raw data of Casanova et al. (1989) for DNA-binding rate, as explained in the main text, which also presents and discusses the results. The analysis determined the parameters a1, b1 and c1 by minimizing the sum of the squared deviations between predictions and observations using inverse-variance weights on each of the squared deviations in the sum being minimized with respect to a1, b1 and c1.

The present analysis differs from that of Casanova et al. (1989) in the mechanistic interpretation of the parameters, though both calculations gave nearly the same values of point estimates of all three parameters. An advantage of the present calculation using the raw data is that two of the three parameter estimates are statistically significant, whereas none of the three parameter estimates is statistically significant in the analysis of Casanova et al. (1989), which used the meaned values of DNA-binding rates, with inverse variance weights at each exposure level.

The practical interpretation of subsequent risk calculations is aided by defining metabolic exposure as $Y = y(b_1+c_1)/a_1c_1$, where the constant multiplying y is chosen so that metabolic exposure has the units of ppm and becomes equal to applied exposure in the limit as concentration approaches 0. Evaluating Equation (A-3) with X very small verifies this statement. Metabolic exposure rises increasingly above applied exposure as exposure increases. The deviation is about 10% at 0.5 ppm applied exposure.

MULTISTAGE MODEL OF CANCER RISK

The multistage model to predict cancer risk for a given time period has the form,

$$P = 1 - \exp\left(-\sum_{i=0}^{n} q_i d^i\right), \qquad \text{(A-4)}$$

where P = probability of tumor in each animal,
$\exp(z)$ = exponential function, e^z,
q_i = coefficients,
d = measure of dose or dose rate,
Σ = summation of indicated terms,
n = number of stages.

A maximum likelihood procedure in a standard computer software package, GLOBAL 86, estimated the coefficients q_i from data on cancer incidence and the chosen measure of dose. The procedure also gave the 95% upper confidence level (UCL) of this estimate, which is generally used in risk assessment. Table A-1 gives the results of fitting models for both measures of dose rate, d, applied exposure and metabolic (or tissue) exposure.

CANCER RISK MODEL CONSIDERING CELL PROLIFERATION EXPLICITLY

The standard multistage extrapolation model does not explicitly consider effects such as cell proliferation. Data provided to the Office of Environmental Health Hazard Assessment by the CIIT during the comment period indicate that there is a substantial increase in cell proliferation in rat nasal cell mucosa at the highest exposure level of the bioassay. Furthermore, the concave curvature of the dose-response curve, even after adjustments for pharmacokinetics, indicates other mechanisms may be operating in the generation of nasal cancer in rats exposed to formaldehyde. Consequently, it was decided to consider whether the incorporation of cell proliferation data into the standard multistage model would substantially change the estimated cancer risk.

Background. At the highest exposure, 14.3 ppm, in the rat bioassay (Kerns et al., 1983) the cell structure of the nasal mucosa was severely affected but was substantially less affected at 5.6 ppm and 2.0 ppm, suggesting that cell proliferation rates may have been elevated at that highest exposure. Preliminary reports of long-term measurements have recently verified that at 6 and 12 months the rate of cell proliferation increased markedly at about that highest exposure and that an intermediate exposure produced an intermediate level of proliferation (Monticello and Morgan, 1990a; Monticello, 1990). These findings specifically suggest a role for cell proliferation in the carcinogenesis that occurred at the highest exposure, and the findings also furnish useful data for modelling considerations. Although the effect of cell proliferation may actually be incorporated in the GLOBAL86 results, explicit consideration of the cell kinetic models is instructive in this assessment.

TABLE A-1

COEFFICIENTS FOR LIFETIME RISK IN MULTISTAGE MODELS FOR NASAL SQUAMOUS CARCINOMA IN RATS[a]

Coefficient	Model[b]	
	3t[c]	5e[d]
q_1^* [e]	5.8×10^{-3} ppm^{-1}	1.5×10^{-2} ppm^{-1}
q_n^* [e]	2.5×10^{-4} ppm^{-3}	9.8×10^{-3} ppm^{-5}
q_2[f]	2.3×10^{-4} ppm^{-2}	
q_3[f]	2.6×10^{-5} ppm^{-3}	
q_4[f]		2.4×10^{-5} ppm^{-4}
q_5[f]		8.6×10^{-3} ppm^{-5}

[a] Incidence and exposure from Kerns et al. (1983), as selected by US EPA (1987). See Table 2 in main text.

[b] Abbreviated code: number of stages (n) followed by dose measure, indicated by t for tissue-based (metabolic) model and e for exposure-based (applied) model.

[c] Coefficients for tissue-based model require that d in Equation A-4 be expressed as lifetime equivalent metabolic exposure. See footnote b in Table 2.

[d] Coefficient for exposure-based model require that d in Equation A-4 be expressed as lifetime-equivalent ambient (applied) exposure.

[e] The q* are the coefficients of the polynomial for the 95% upper confidence limit in each multistage model.

[f] The q are the non-zero coefficients of the polynomial for the maximum likelihood estimate in each multistage model. The analysis determined q_0 and q_1 to be zero in all cases.

Moolgavkar and Luebeck (1990) have reviewed the work on two-stage probabilistic models that specifically take into account the kinetics of the cell populations involved in carcinogenesis. Many of the results are quite complicated, and the use of such models generally requires new information to select the parameters and functional forms of the models; yet appropriate experimental results are usually not available. Several investigators (Portier, 1987; Thorslund et al. 1987; Bogen, 1989, 1990) have used convenient formulas that can be obtained as special cases of an approximate formula of Moolgavkar et al. (1980). These formulas require only a small amount of new information in order to incorporate the effects of cell kinetics into the prediction of cancer risk. Those applications include diverse cases, but so far no one has provided results for formaldehyde.

Methods. This analysis uses a form of the simple approximate formula that takes cell kinetics into account and predicts cancer risks when the risks are not too large. The approximation derives from a more general two-stage probabilistic model of Moolgavkar and Venzon (1979), which assumes (1) that a first mutation occurs in the population of normal cells at a specifiable rate, producing an intermediate (premalignant) cell, (2) that the number of premalignant cells increases in a specifiable way, which may depend on exposure, and (3) that a second mutation occurs at a specifiable rate in the population of premalignant cells, producing a malignant cell that then leads to the formation of a cancer. The results of this analysis depend on the assumption that this two-stage model accurately specifies the role of cell proliferation in formaldehyde carcinogenesis. The approximation used to predict the risk for this set of hypotheses about a two-stage cancer process takes a simple form for the assumption that the underlying parameters are time independent,

$$P = 1 - \exp(- \mu_0 \mu_1 C_0 G), \qquad \text{(A-5)}$$

where P = the probability of carcinogenesis,
μ_0 = first mutation rate (lifetime^{-1}),
μ_1 = second mutation rate (lifetime^{-1}),
C_0 = the initial number of normal cells at risk,
G = a function that expresses the increase of risk due to the effect of an increased number of premalignant cells with the passage of time.

The present work uses two alternative forms for the function G (Bogen, 1989). The form that represents an exponential rate of increase of premalignant cells is

$$G_x(K_x,T) = [\exp(K_xT) - K_xT - 1] / K_x^2$$

The form that represents a geometric rate of increase of premalignant cells, in which the rate is proportional to the circumference of an expanding disk, is

$$G_g(K_g,T) = [(K_gT+1)^4 - 4K_gT - 1] / 12K_g^2,$$

where T = time, expressed in lifetimes,
K_x and K_g are time-independent quantities which parameterize the rate of increase and which are subscripted according to the assumed form of the rate of increase.

Assuming constant birth and death rates for the premalignant cells, both Portier (1987) and Thorslund et al. (1987) used the Moolgavkar approximation to obtain the above form for an exponential rate of increase in their versions of Equation A-5. Portier (1987) considered K_e and one mutation rate to be linear functions of dose. Thorslund et al. (1987) instead assumed that the ratio of liver weight to the control value was a log-logistic function of dose and that this function represented the amount by which proliferation increased the mutation rate. So their analysis multiplied the background (zero dose) mutation rate by that ratio. Those authors also found that the approximation becomes essentially the factorized form of the multistage model if the proliferation effect does not change with dose. Also assuming constant birth and death rates for the premalignant cells, Bogen (1989) derived both the above exponential form and the above form corresponding to a geometrical rate of increase. For both the exponential and geometrical forms, Bogen (1990) fitted a lognormal function to data on the percentage of cells in S-phase to obtain a measure of cell proliferation as a function of dose. He used this measure, multiplied by a constant, to specify the respective K's in the functions G.

The present work systematically explores the effect of various ways of using the cell proliferation data of Monticello and Morgan (1990) and Monticello (1990) in Equation A-5. The proliferation data are expressed as a ratio, R, for each level of exposure. The numerator of this ratio is the rate of cell proliferation, as measured by a labelling index per unit of basement membrane at the given metabolic exposure. The denominator is the background rate of cell proliferation. Using 12-month values, the present analysis assigns to the function R(X) the value 1 for applied exposures up to 6 ppm and assumes a linear rise with exposure at the higher exposures. Values of R(X) are 1 at 6 ppm, 4.3 at 10 ppm, and 9.8 at 15 ppm. The use of these values in the analysis is subject to uncertainty. Results from shorter exposure periods resulted in different values. Also, for the longer-term exposures including his 12-month exposures, Monticello (1990) determined the labelling index by the pump infusion method. That result can deviate from a strictly proportional relationship in representing the actual cell-division rate needed for the model.

The present analysis considered various combinations of the previous assumptions. First, the mutation rates were assumed to be linear functions of the tissue dose, expressed as metabolic exposure. Then a cell proliferation effect of formaldehyde, when present, is characterized by multiplying the mutation rate of normal cells and/or the mutation rate of premalignant cells by the function R. The biologic rationale for this approach is that mutation rate is proportional to cell turnover rate on the assumption that the preponderance of genetic damage occurs at mitosis, when cells may be most sensitive. Second, the parameter, either K_x or K_g, for the rate of increase of premalignant cells is expressed as a constant $\bar{K}$ times R to characterize that influence of formaldehyde when present. Otherwise, the K is taken to be constant. Figure A-1 shows schematically the various combinations of placements of R in the cell proliferation models.

With the assumptions of (1) linear mutation rates in response to metabolic exposure resulting in a product with a quadratic form, (2) one or two or no

mutation rate multiplied by R, and (3) the rate parameter in G either multiplied by R or not, Equation A-5 becomes

$$P = 1 - \exp(-(q_0+q_1Y+q_2Y^2)R^j(X)G(KR^m,T)/G(K,1)\ ), \qquad (A\text{-}6)$$

where q_i = lifetime risk coefficients, analogous to those in the linearized multistage model,
- i = 0,1,2, subscripts for the constant coefficients,
- Y = metabolic exposure concentration,
- X = administered exposure concentration,
- j = 0,1,2, the number of mutation rates which increase due to proliferation,
- m = 1 or 0 depending on whether or not formaldehyde increases the rate of increase of premalignant cells,
- K = a constant, either K_x or K_g, depending on the model for G.
- R(X) = proliferation ratio, implicitly a function of Y.

Because the function R(X) has the value 1 at and near zero exposure, the coefficient, q_1, gives the slope of the exposure-response relationship at small exposures in essentially the same way as in the standard multistage model. The function G indicates either G_x or G_g. The value G(K) in the denominator of Equation 2 insures that the q_i's can be used in the same way as those in the standard multistage model.

Equation A-6 indicates there are four parameters to estimate. With only four data points in the bioassay, the analysis proceeds by assuming that various of the coefficients, q_i, are zero and then estimating the remaining parameters for each possible set of values of m and j. In the computations reported in Table A-2 the shape of the cancer bioassay response causes practical calculations to make q_0 equal to zero as a result of the necessary application of a non-negativity constraint. Also, the historical background incidence of the nasal tumors in rats is extremely low. The analysis then proceeds to obtain the best fit models having non-negative parameters from the two appropriate pairs, either q_1,q_2 or q_1,K - - thus generating best fitting parameters for the twelve allowed cases below the first row of Table A-2.

The computations in SYSTAT NONLIN used unconstrained likelihood functions in obtaining maximum likelihood estimators for the best fit and in obtaining the 95% UCL on unit risk, q_1*, as used by GLOBAL86.

Results. Table A-2 reports the results of these calculations. The cases are identified by the code from the table, using the identifier in the left-hand column with the value of j at the top of the column adjoined to the right of the identifier.

Five cases, 1tx0, 1tg0, 1tx1, 1tg1, and 2tn1 fit the data well. The first four of these cases represent both exponential and geometric increases of premalignant cells, while the fifth case, represents two directly increased mutation rates and one mutation rate increased by proliferation. Because they provide by far the best fit of the data, these five cases emerge as the most likely present choices for modeling the effect of cell proliferation.

TABLE A-2

PARAMETER ESTIMATION FOR MODEL INCLUDING THE EFFECTS OF CELL PROLIFERATION

Case [a]	Quantity [b]	j = 0 [c]	j = 1	j = 2
3tn [d]	$-L_{max}$	99.32		
	q_1^*	5.8×10^{-3}		
2tn	$-L_{max}$		99.52	
	q_1		2.0×10^{-3}	
	q_1^*		3.0×10^{-3}	
	q_2		8.5×10^{-4}	
	q_2^*			
1tn	$-L_{max}$		100.52	100.83
	q_1		7.9×10^{-3}	0.89 x 10-3
	q_1^*		8.4×10^{-3}	1.0 x 10-3
1tx	$-L_{max}$	99.60	99.60	
	q_1	3.3×10^{-3}	3.3×10^{-3}	
	q_1^*	8.9×10^{-3}	8.4×10^{-3}	
	K_e	0.70(-2.6,4.0)	0.25(-4.7,5.2)	
	K_e^*	0.52	7.0×10^{-8}	
1tg	$-L_{max}$	99.60	99.60	
	q_1	3.3×10^{-3}	3.3×10^{-3}	
	q_1^*	8.9×10^{-3}	8.4×10^{-3}	
	K_g	1.8(-37,41)	0.19(-5.2,5.6)	
	K_g^*	0.72	1.1×10^{-6}	

[a] Number at beginning of each code below indicates the number of transitions in which formaldehyde produces mutations. The next letter, t, indicates that these cases use tissue dose converted to metabolic exposure. The letter at end of code indicates whether formaldehyde affects the rate of increase of premalignant cells in an exponential model (x) or affects the rate in a geometric model (g) or does not affect the rate of increase (n).

[b] L_{max} indicates the value of the maximum of the log-likelihood function, q_1 is the maximum likelihood estimator of unit risk (lifetime ppm)$^{-1}$; q_1^* is the 95% UCL value on unit risk; K_x,K_g are the coefficients for rate of increase of premalignant cells in the exponential and geometric models, respectively (lifetime)$^{-1}$; K_x^*,K_g^* are the coefficient values calculated for the given q_1^*.

[c] j indicates the number of mutation rates which formaldehyde directly increases. Numbers in parentheses represent 95% confidence limits on parameter.

[d] Results for the multistage model, which includes no explicit cell-proliferation effect, are included here for reference. See Table A-1 for further parameter values.

These five cases gave UCLs on unit risk, q_1^*, ranging from 7.5×10^{-3} to 8.9×10^{-3} ppm^{-1}. This range includes the value obtained for a multistage model computation rejecting the highest exposure group and is 30 to 50% higher than the UCL for unit risk for the three-stage tissue-based model including all exposure groups. Four of these cases all gave the same MLE value $q_1 = 3.3 \times 10^{-3}$ ppm^{-1} while the fifth gave $q_1 = 2.0 \times 10^{-3}$ ppm^{-1}. Quantitatively the essential differences among the five cases with excellent fit occur in the way the highest exposure point fixes the second parameter, either K, the parameter for rate of increase of premalignant cells in the first four cases, or q_2, the polynomial coefficient, in the fifth case.

Two cases, 1tn1 and 1tn2, in which formaldehyde directly increases one mutation rate and does not affect the growth rate of premalignant cells, gave only marginal fits of the data; that is, about a 95% chance of the MLE value not fitting the data. One of these cases, 1tn2, in which proliferation increases both mutation rates, gave a substantially lower value of the UCL on unit risk, $q_1^* = 1.0 \times 10^{-3}$ ppm^{-1}, than did any of the other cases. The other marginal case, 1tn1, in which proliferation increases one mutation rate, gave the same value of q_1^* as did the five cases with excellent fits. The range of uncertainty for estimates of the unit risk UCL includes 1.0×10^{-3}, the value for case 1tn2 with marginal fit.

The table omits the five cases which did not yield quantitatively satisfactory results, two cases because of a gross lack of fit of prediction to the data and the other three cases because the MLE of a parameter in each case had to be constrained to be zero to prevent an unintended negative value. The two cases that grossly fail to fit the data are 1tn0 and 2tn0, the one-stage and two-stage cases of the standard multistage model, with no proliferation effect. The three cases that gave a zero value for the constrained MLE of the second of their pair of parameters were cases 2tn2, 1tx2 and 1tg2. This resulted in their degenerating into the single case 1tn2, the case with the lower value of q1*, mentioned in the previous paragraph. These four cases have in common that proliferation induced by formaldehyde increases two mutation rates. The wide error bars incurred by using the presently available data do not permit ruling out statistically those cases that degenerated into the single case 1tn2.

The five cases that fit the data well and the two marginal cases gave substantial positive values for the MLE of q_1. In no case did the ratio, q_1^*/q_1, exceed 3. Thus, all these results of the proliferation modelling demonstrated the linearity of the MLE at low exposures.

Moolgavkar and Dewanji (1988) have pointed out that the approximation used to get these results should not be expected to be accurate in animal experiments in which a large proportion of animals develop tumors. Those authors do not specify the term, "a large proportion", but it is likely to be greater than 60% since it has been reported that the approximation is quite good when 50-60% of the animals develop tumors (Moolgavkar et al. 1988). In the present case 67% of the animals at the highest exposure developed tumors. So the approximation in this bioassay may be slightly inaccurate. However, the results for q_1^* appear to be reliable considering their similarity, even when a wide range of assumptions about modeling of proliferation effects are used.

Conclusion. The modeling of cell proliferation examined a variety of assumptions regarding the proliferation function R. Five cases resulted in an excellent fit of the data, and gave nearly the same UCL value for unit risk, $q_1^* = 8.4 \times 10^{-3}$ ppm^{-1}. Five additional cases could not be ruled out statistically, showing the range of uncertainty prevented clear discrimination among cases. One case, a marginal fit, gave a different value of $q_1^* = 1.0 \times 10^{-3}$ ppm^{-1}, and three cases degenerated into that marginal case with the lower value of UCL on unit risk. In all cases the MLE exhibited linearity of the exposure-response relationship at low exposures when proliferation was taken into account, in contrast to results that do not incorporate cell proliferation explicitly.

Among models that fit the data well, the results of incorporating cell proliferation do not substantially change the upper confidence limits on estimated cancer risk. Most of the models suggest an increase in risk while one model suggests a decrease in risk. The reason for this appears to be that, whether cell proliferation is modeled explicitly or not, the cancer incidence at the highest exposure level with no increased cell proliferation, 5.6 ppm, has most of the influence on the value of q1*. Thus, inclusion of the high exposure group in a sufficiently flexible model does not substantially change the results of the low-dose extrapolation. Considering the uncertainties in using these cell proliferation models and the slightly higher risks predicted by them in most cases, staff conclude that the standard multistage model provides a reasonable upper confidence limit for unit risk. The range of risk predicted by the cell proliferation model is informative, but no single cell-proliferation approach appears justified as a best value at this time. The use of further data to fix the parameters of the model may aid in selecting a model that is most consistent with the biology of the process.

INTERSPECIES SCALING

A scaling factor on applied dose allows the extrapolation to humans from the predictions of the cancer bioassays that used rodents. This section uses three approaches to develop scaling factors for formaldehyde. The first approach scales by intake rate per body-surface area. This is the default option of the California Department of Health Services guidelines for carcinogen risk assessments (DHS, 1985). The second approach develops a scaling factor using generic arguments that note the systemic nature of the default approach and then modifying that approach to take account of the evidence that formaldehyde acts by a mechanism of contact carcinogenesis of the respiratory tract. The third approach develops a scaling factor which is also based on a contact mechanism but which is dosimetrically adjusted to take account of data on the nasal passages of rats and monkeys.

Default Scaling. The default scaling adjusts dose on the basis that equal rates of uptake of carcinogen per body-surface area imply equal risks. Thus, the same risk occurs in both species when

$$I_{hum}/A_{hum} = I_{rod}/A_{rod}, \qquad \text{(A-7)}$$

where I = uptake rate (μg/day),
A = body surface area (m^2),
hum = subscript for human,

rod = subscript for rodent.

The relationship between uptake rate and the inhaled concentration is

$$I = aXV,$$

where a = proportion absorbed by the respiratory tract,
X = concentration of carcinogen being inhaled (mg/m^3),
V = volume of air inhaled per day (m^3).

Substituting for I in Equation (A-7) gives a scaling relationship in terms of inhaled concentration:

$$a_{hum}X_{hum}V_{hum}/A_{hum} = a_{rod}X_{rod}V_{rod}/A_{rod}.$$

Using this measure of dose rate to characterize risk across species, the equivalent rat concentration to scale the human concentration in the risk model results from solving the above equation for X_{rod}.

$$X_{rod} = [(a_{hum}/a_{rod})(V_{hum}/V_{rod})(A_{rod}/A_{hum})]X_{hum}, \qquad (A\text{-}8)$$

where the multiplier in brackets is the default scaling factor.

Weibel (1984) presented allometric relationships across species for the inhalation rate and geometric similarity furnishes a relationship for the body-surface area.:

$$V_{hum}/V_{rod} = (W_{hum}/W_{rod})^{3/4},$$

$$A_{hum}/A_{rod} = (W_{hum}/W_{rod})^{2/3},$$

where W = body mass (kg).

Hence, in Equation A-8

$$(V_{hum}/V_{rod})(A_{rod}/A_{hum}) = (W_{hum}/W_{rod})^{3/4}(W_{hum}/W_{rod})^{-2/3};$$

and Equation (A-8) becomes

$$X_{rod} = (a_{hum}/a_{rod})(W_{hum}/W_{rod})^{1/12}X_{hum}. \qquad (A\text{-}9)$$

In the present case for humans and rats,

$$W_{hum}/W_{rat} = 70 \text{ kg } /0.25 \text{ kg} = 280.$$

The absorption ratio for nasal breathing is obtained from observations that human respiratory uptake of formaldehyde at steady state is 75% (Raabe, 1988), while rat uptake is between 98% and 100% (Dallas, 1985).

$$a_{hum}/a_{rat} = 0.75/0.99 = 0.76.$$

Substituting these ratios into Equation (A-9) gives the default or body surface-area scaling factor for humans.

$$X_{rat}/X_{hum} = (0.76)(1.57) = \underline{1.2}$$

Therefore 1.2 is the default scaling factor for body-surface-area equivalence.

Contact Scaling, generic. The derivation of the generic contact scaling factor starts by identifying a basic property of default scaling and adapts that property to the process at the surface of entry of the carcinogen. The property applies in those cases in which a simple metabolic model having a very specific allometric relationship holds across species. This property is that the default scaling gives the same result as equating simple estimates of average body concentration across species. The generic approach to contact scaling adapts that systemic metabolic model to equate the toxicant concentrations in the entry surface layers of the two species rather than in the whole bodies. A contact scaling factor results from applying allometric relationships and determining the ratio of the applied exposure of the rodent to that of the human.

To get a consistent expression for tissue concentration the analysis starts by noting that, for default scaling, Equation A-7 above gives the same result as does

$$I_{hum}/(M_b)_{hum} = I_{rod}/(M_b)_{rod}, \qquad \text{(A-10)}$$

as long as M_b follows the allometric relationship,

$$M_b = m\ W^{2/3}, \qquad \text{(A-11)}$$

where M_b is the rate of metabolism of the mass of inhaled chemical in the whole body per unit of systemic concentration of the chemical, (L/sec)

m is the coefficient, considered to be constant across a class of animals ($L/sec\text{-}kg^{2/3}$).

Each side of Equation A-10 is just the average body concentration determined by solving for concentration in the mass balance which equates the overall rate of uptake of parent toxicant to its overall rate of metabolism at steady state, assuming no other significant means of loss of parent toxicant than by metabolism (Withey, 1985):

$$I = B\ M_b; \qquad \text{so} \qquad B = I/M_b,$$

where B = tissue concentration of carcinogen (ug/L).

To apply the concept of equal concentrations, used systemically in Equation A-10, to a contact surface the analysis treats concentration and reaction processes as though they are distributed uniformly throughout the designated volume of a thin layer on the intake surface of the body and nowhere else. The analysis assumes that the metabolism of mass per unit volume occurs in that layer at the same average rate as the average rate in the rest of the

body, which is $M_b/(W/D)$ per concentration per unit volume in the body. Using that value, the overall metabolism per concentration in the surface layer is

$$M_S = M_b\ D\ S\ t\ /\ W = m\ D\ S\ t\ W^{-1/3}, \qquad \text{(A-12)}$$

where D = average mass density of the body (kg/L),
S = surface area of the mucosal layer (cm^2),
t = average thickness of the layer (cm).

Each side of Equation A-10 now estimates the concentration in the surface layer when the expression for M_S in Equation A-12 replaces M_b in Equation A-10. With this replacement Equation A-10 specifies that the concentration in that contact layer is the same across species.

$$[aXW^{3/4}/(M_bStD/W)]_{hum} = [aXW^{3/4}/M_bStD/W)]_{rod}. \qquad \text{(A-13)}$$

Using Equation A-11 and assuming that the surface area of the lung airways has an allometric exponent of 3/4, which is the exponent estimated for "metabolic size" (Gross et al., 1982), this equation becomes

$$(aW^{1+3/4-3/4-2/3}mX/t)_{hum} = (aW^{1+3/4-3/4-2/3}mX/t)_{rod}.$$

Solving for the concentration breathed by the rodent and assuming that m is constant across species, this equation gives the applied rodent concentration that has the same risk as that predicted for humans breathing concentration X_{hum}.

$$X_{rod} = [(a/t)_{hum}(t/a)_{rod}(W_{hum}/W_{rod})^{1/3}]X_{hum}. \qquad \text{(A-14)}$$

The quantity in brackets multiplying X_{hum} is, thus, the expression sought for the generic contact scaling factor.

Assuming the same values for the parameters as in evaluating the default scaling factor for formaldehyde and assuming that the value of t is constant across species for tissue of the mucosal layer, Equation 12 gives the generic contact scaling factor for formaldehyde:

$$X_{rat}/X_{hum} = (0.76)(280)^{1/3} = \underline{5.0}$$

Contact scaling, dosimetrically adjusted. Comparison of the tissue binding data by Casanova et al. (1989) for rats and preliminary data by Heck et al. (1989) for monkeys exposed to formaldehyde suggests the need to scrutinize the assumptions of the generic contact scaling factor of Equation A-14. With subscripts changed from human to monkey, that equation predicts that the ratio of applied exposure concentration for rat to that for monkey, in order to achieve the same tissue concentration, is

$$X_{rat}/X_{monk} = (0.76)(12/.28)^{1/3} = 2.66, \qquad \text{(A-15)}$$

assuming that $t_{rat} = t_{monk}$ and that the absorption ratio for humans is the same as that for monkeys and using the 12 kg monkey and a 280 g rat of the experiments. For the case of low concentrations, at which proportionality prevails, this prediction is also for the ratio of average concentration in

the overall surface layer of the monkey airway to that in the rat, when both are identically exposed. Yet, the ratio of measured concentration of DNA-protein cross-links in the nasal airway of the monkeys to that of the rats in the two studies is about 0.1. Even though the prediction is for the overall airway and the measurement is just for the nasal passages, the 26-fold difference is large enough to suggest the need for investigation and reconciliation.

A local dosimetric approach explores how the use of this comparative data influences the contact scaling factor. This dosimetric approach computes the decreasing concentration of toxicant in the inspiratory gas along the airway for nasal breathing at steady state. The analysis then uses a local version of the balance of uptake rate and metabolic rate to estimate the tissue concentration at each point along the airway. This step adapts the suggestion of Heck et al. (1989), used to explain their cross-link data, that monkeys may be capable of eliminating absorbed formaldehyde or of repairing DNA-protein cross-links more efficiently than rats. The analysis goes on to estimate overall tissue dose for rats and monkeys, except that the allometric coefficients for metabolic rate are left unknown and possibly different in rats and monkeys. The ratio of measured tissue doses fixes the ratio of allometric coefficients. Assuming that humans and monkeys have the same allometric coefficient, further calculations of local variation lead to the dosimetric contact scaling factor from rats to humans.

The present analysis starts by using a formula for the local concentration of formaldehyde along the nasal airways of rats and of monkeys in order to predict the average rate of deposition in the nose of each, assuming that the monkeys as well as the rats are breathing nose only. Kleinman (1983) has noted a convenient approximate formula for the penetration P_a of contaminant gas along the airway.

$$P_a = X_a/X = \exp(-kS_a/V), \qquad \text{(A-16)}$$

where X_a = local concentration along the airway ($\mu g/m^3$),
X = atmospheric concentration ($\mu g/m^3$),
k = a constant for a particular airway geometry and contaminant gas (cm/sec)
S_a = surface of airway between point of entry and the location of X_a (cm^2),
V = volumetric flow rate of air into the nasal passages (cm^3/sec).

The rate of absorption of gas per unit of airway surface is then X_aU, and dividing this product by the per-unit-area version of the expression for metabolic rate in Equation A-12 (divide by S) gives an estimate of the local tissue concentration,

$$X_aU/mDtW^{-1/3}, \qquad \text{(A-17)}$$

where U = local deposition velocity, assumed constant throughout (cm/sec).

The next step is to obtain the average concentration in the nasal cavity by integrating the local tissue concentration along the nasal surface and dividing by the surface area. Using Equation A-16 for X_a and noting that X_a is the only quantity in this expression that varies with S_a gives

$$\int_0^S (X_a U/mDtW^{-1/3})dS_a/S = (XU/mSDtW^{-1/3})\int_0^S \exp(-kS_a/V)dS_a =$$

$$= (XUV/kmSDtW^{-1/3})(1-\exp(-kS/V)). \qquad \text{(A-18)}$$

where S = respiratory surface area from the point of entry to the location under consideration.

The resulting expression for the ratio of average concentration in the surface layers of the nasal airways in monkeys to that in rats is

$$\frac{y_{monk}}{y_{rat}} = \frac{k_{rat}}{k_{monk}} \frac{(1-P_{monk})}{(1-P_{rat})} \frac{(W_{monk})^{13/12}}{(W_{rat})^{13/12}} \frac{S_{rat}}{S_{monk}} \frac{m_{rat}}{m_{monk}}, \qquad \text{(A-19)}$$

assuming that the quantity U/t is the same for both species and that the allometric relationship for V uses $W^{3/4}$. If the metabolic rates in the surface layer of the nasal airways in monkeys and rats followed a single allometric relationship, then the values of m for both would be the same. Instead, the analysis assumes that the value of their ratio differs from unity and solves Equation A-19 for that value. Heck et al. (1989) have reported 0.10 for the value of y_{monk}/y_{rat}, and Table A-3 furnishes the other values of quantities needed to solve Equation A-19. In this calculation all of the quantities are evaluated for the nasal airways except for W. The resulting value of m_{monk}/m_{rat} is 106, very large compared to unity, the value assumed in generic scaling.

Equation A-19, evaluated for the entire respiratory tract and with the subscript for humans substituted for monkeys, now furnishes the contact scaling factor obtained from this local analysis. The analysis assumes here (1) that the nasal value of k_{rat} suffices for the calculation of the whole tract because the rats absorb nearly all of the toxicant in their nasal passages, (2) that humans are breathing nose only and k_{hum} has the same value as that used for the monkey nasal passage because absorption in the monkey upper airway and trachea appears to be the closest to the human airway of any measurements available for formaldehyde, (3) that the penetrations of the full respiratory tract are 0 for both species because this is the implication of estimates of the arguments of the respective exponents, (4) that both the airway surface areas of the whole respiratory tracts and the respiratory flow rates follow allometric relations using $W^{3/4}$ across species, as discussed above, and that (5) $m_{hum} = m_{monk}$, again on grounds of general similarity of these primate species. With these assumptions the equation analogous to Equation A-19 applied to the entire tract of conducting airways gives the scaling factor:

$$y_{hum}/y_{rat} = (km)_{rat}/(km)_{hum}(W_{hum}/W_{rat})^{1/3} = \underline{0.28}. \qquad \text{(A-20)}$$

This scaling factor is nearly 18-fold lower than the generically derived value, given by Equation A-14.

Conclusion. In addition to the default scaling factor, 1.2, this analysis has yielded a generically derived contact scaling factor, 5.0 and a dosimetrically adjusted contact scaling factor, 0.28. The purpose of developing the generic

TABLE A-3

PARAMETERS AND RESULTS FOR NASAL DEPOSITION

Quantity	Units	Rat	Monkey	Reference
Body mass, W	kg	0.28	12	Heck et al. (1989)
Nasal surface, S	cm^2	6.2	47.3	Heck et al. (1989)
Nasal penetration	-	0.03[a]	0.7[b]	Heck et al. (1989)
Flow rate, V	L/min	0.32	5.3	[c]
k	$L\text{-}min^{-1}\text{-}cm^{-2}$	0.125	0.028	Equation A-16[d]

[a] Upper bound (Dallas et al 1985).

[b] Estimated from the binding data at the highest exposure (6.0 ppm) to avoid the uncertainty of binding data obtained at lower exposures. The calculation of penetration used the local concentration of DNA-protein cross-links (DPX), 9.4 pmol/mg DNA, in the larynx-trachea-carina region to infer the airway formaldehyde concentration in that region. This DPX value is about half the 18.2 pmol/mg DNA in the turbinates and anterior nose, associated with the applied exposure of 6 ppm. Figure 5 of Casanova et al. (1991) provided the interpolation curve to obtain the airway concentration of approximately 4 ppm at that location for half the binding of the 6 ppm exposure. Thus, penetration is 4 ppm / 6 ppm = 0.7.

[c] Allometric relationship computed relative to standard 70 kg human.

[d] Thus the formula is $k = -(V/S)\,Ln(P)$.

contact scaling factor was to take more account of the specific mechanism of carcinogenesis than does the default procedure. Although some substances, for example oxygen (Weibel, 1984), follow a general allometric relationship with a constant coefficient for metabolism across a wide range of mammalian species, formaldehyde metabolism may follow quite different relationships in rats than in humans. If that difference were the case, then the generic contact scaling factor would not be appropriate. See Table 5 for the application of these scaling factors to the UCLs on unit risks determined from the rat bioassay.

The analysis for the dosimetric approach has provided evidence of a departure from a single allometric relationship. That analysis produced an estimate of a 100-fold greater allometric coefficient for metabolism in the monkey nasal epithelium compared to the rat, based on the observed greater concentration of DNA-protein crosslinks in the rat tissues. So if humans had the same allometric coefficient as has the monkey, then the dosimetrically adjusted scaling factor would be most likely to be appropriate. Yet measurements of blood plasma in rats had 10-25 times more glutathione concentration than did measurements in humans (Meister, 1988) and 3 times more glutathione activity (Reitz et al., 1988), suggesting that rats may develop less tissue concentration of formaldehyde and therefore may develop less DNA-adducts than humans experiencing the same exposure because of the central role of glutathione in the metabolism of formaldehyde. Casanova and Heck (1987) found that, following exposure to formaldehyde, rats with depleted glutathione developed three to four times more DNA-binding than did rats with normal glutathione concentrations.

Another major problem with using the dosimetric adjustment is the assumption of nose-only breathing in both humans and monkeys. The monkeys could have been breathing orally to a substantial degree, thus accounting in part for the lower rate of DNA-binding measured in the monkey nasal passages. How the partitioning between oral and nasal breathing may change due to increasing irritancy with increasing exposure is not known. For one monkey, Casanova et al. (1991) offer evidence of high DNA-binding in both nasal passages and lower airways, which implies substantial nasal breathing.

In conclusion conflicting evidence prevents making a clear case for using either form of contact scaling factor.

APPLICATION TO FORMALDEHYDE WORKER STUDY

An important example of the use of these results based on the rat bioassay is the prediction of risk of formaldehyde workers getting lung cancer in the cohort of the Blair (1986) study. The present calculation assumes that, when human exposures are expressed as rat equivalents, the risk of lifetime exposure of humans getting any respiratory tract tumor is the same as the rats getting any respiratory tract tumor. This assumption is consistent with the reports that the main human tumor is lung cancer and the main rat tumor is nasal squamous cell carcinoma by noting the corresponding differences in respiratory tract absorption characteristics.

In the calculation of scaling factors just completed, the atmospheric concentration scaled across species according to the ratio of ventilation rates, for example as in Equation A-6. Those calculations proceed on the assumption that the rodents and humans are in the same ventilation state,

namely the resting state. Hence, using data obtained on resting rats, as in the current bioassay, to extrapolate to human workers implies the need to calculate a further factor giving the ratio of the average rate of inhalation of a formaldehyde-exposed worker to that of a resting man. Using the standard inhalation rates of 1.25 m^3/hr for the industrial worker and 0.6 m^3/hr for the resting man this ratio is approximately 2. Thus, using the middle-of-the-range worker exposure, 1.0 ppm, estimated for the cohort of the Blair study, the ventilation-weighted exposure, which is proportional to applied dose rate, is taken as 2.0 ppm to take account that an approximate ventilation rate for such a work force is about twice the sedentary value.

The best-estimate calculation then proceeds by applying the contact scaling factor of 5 to the ventilation adjusted human exposure to obtain the rat-equivalent atmospheric exposure, X = 10 ppm, for use in the exposure-based model (5e) after adjusting to lifetime-equivalent exposure. The tissue-based model requires the further calculation of the metabolic exposure produced by the exposure of 10 ppm. The procedure of footnote b in Table 2 yields a binding rate y = 43.1 pmol/mg-hr, which when multiplied by the conversion factor, 1.2 ppm/(pmol/mg-hr), gives a metabolic exposure equal to 52 ppm, for use in the tissue-based model after adjusting to lifetime-equivalent exposure.

In both the exposure-based and tissue-based models the lifetime-equivalent exposures require multiplying each of these rat-equivalent exposures by (40/168) x (20/70) = 0.068 to account for the workers 40-hour week for 20 years. The resulting lifetime equivalent exposures are 0.68 ppm for the exposure-based (5e) model and 3.5 ppm metabolic exposure for the tissue-based (3t) model.

The polynomial forms of the two risk models then provide estimates of the individual risk in the workforce cohort, using the coefficients of Table A-1. The UCLs on unit risk follow from using the starred coefficients. For the exposure-based (5e) model, q_1^* and q_5^* enter, giving the risk of 1.1×10^{-2}. For the tissue-based (3t) model, q_1^* and q_3^* enter, giving the risk of 3.2×10^{-2}.

Analogously, using the default scaling factor of 1.2 yields X = 2.4 ppm and y = 3.3 pmol/mg-hr, corresponding to a metabolic exposure of 4.0 ppm, for rat-equivalent measures of exposure. The calculation then performed in the same way as for the contact scaling factor yields corresponding values of 95% UCL for individual worker risks in this cohort for the two models: 2.5×10^{-3} (5e) and 1.6×10^{-3} (3t).

TABLE A-4

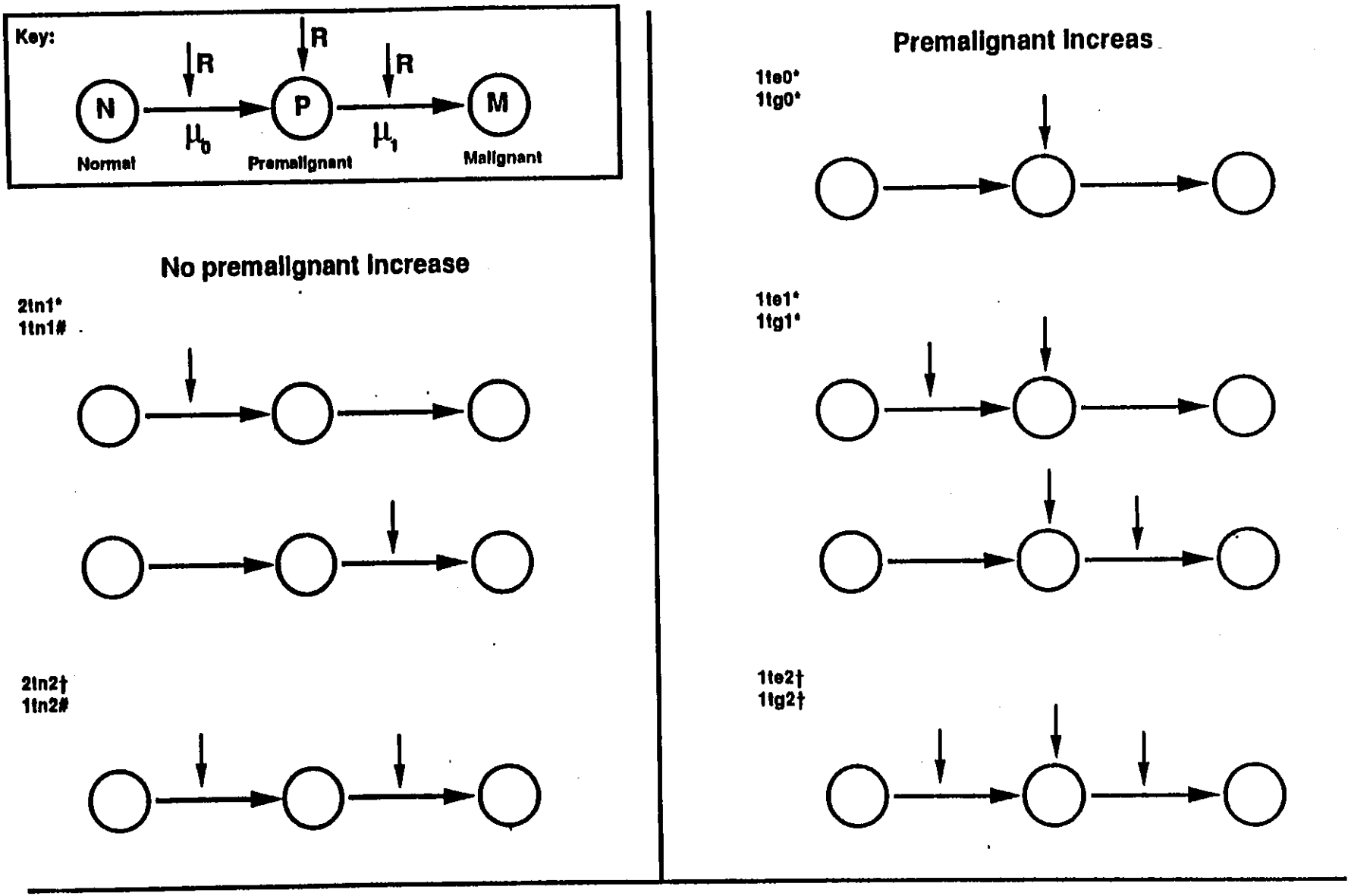
RAW DATA FOR RATE OF FORMATION OF DNA-PROTEIN CROSSLINKS IN NASAL MUCOSA OF RATS EXPOSED TO FORMALDEHYDE FOR 6 HR[a]

Exposure Concentration (ppm)	Binding Rate (pmole/mg-hr) observation[b]	standard error[c]
0.34	0.0728	0.6
0.312	0.214	0.6
0.305	0.4127	0.6
0.832	0.5167	0.4
0.65	0.745	0.4
0.637	0.6993	0.4
1.948	2.1	3.7
1.943	3.7933	3.7
1.912	4.0783	3.7
6.066	18.12	6
5.825	15.6733	6
5.877	18.9917	6
9.836	35.5917	30
9.904	44.2917	30
9.861	52.9983	30

[a] Courtesy of M. Casanova. Personal communication of data for Casanova et al. (1989).

[b] Each point obtained by pooling the nasal musosas of four rats receiving the same exposure.

[c] Standard error of the mean of the three binding rates reported at each exposure level.



TWO STAGE MODELS CONSIDERED FOR PROLIFERATION

* = GOOD FIT, # = MARGINAL FIT, † = DEGENERATES TO 1tn2

FIGURE A-1

APPENDIX B

REVIEW OF RECENT ANIMAL STUDIES

Since the publication of the 1987 EPA formaldehyde document, a number of additional animal studies have been conducted. While no new cancer bioassays suitable for risk assessment purposes have been reported, the new experiments add insights into both the general toxicology and the specific mechanisms associated with formaldehyde toxicity. These studies have been carried out mostly in rats and mice, although several reports describe the respiratory effect of formaldehyde in rhesus and cynomolgus monkeys.

In order to provide the most current status of information about the health effects associated with formaldehyde exposure, DHS staff have reviewed the relevant studies. These reviews are included in this appendix.

A) ACUTE AND SUBCHRONIC EFFECTS

Zwart et al. (1988) evaluated the cytotoxic and adaptive effects of formaldehyde on rat nasal epithelium. Male and female Wistar rats were exposed to 0, 0.3, 1 or 3 ppm formaldehyde for six hours/day, for either 3 days or five days/week for 13 weeks. Cell proliferation and morphologic effects were measured following the end of the exposure period. Formaldehyde-related histopathological changes in the nasal epithelium for the 3 ppm group ranged from cellular disarrangement to hyperplasia and squamous metaplasia in the anterior portion of the nose. These changes were not observed in the other dose groups. A strong correlation was found between cell turnover and exposure concentration for all dose groups three days after exposure began. The cell turnover rate following 13 weeks of exposure was markedly lower than after three days of exposure, suggesting that defense mechanisms and adaptation may blunt the cytotoxic effects of formaldehyde.

Maronpot et al. (1986) evaluated the subchronic toxicity of formaldehyde vapor in B6C3F1 mice. Both male and female mice were exposed to either 0, 2, 4, 10, 20, or 40 ppm formaldehyde for six hours/day, five days/week for 13 weeks. Mortality was high in the 40 ppm dose group, with eight out of ten exposed animals of both sexes dying before completion of the study. A number of pathologic changes were observed in the exposed animals. Squamous metaplasia and inflammation were present in nasal tissues of both sexes of mice in the 10, 20, and 40 ppm dose groups and in the larynx of the 20 and 40 ppm groups. Metaplasia of the bronchial epithelium was seen in the 40 ppm group. Squamous metaplasia and hyperplasia along with submucosal fibrosis and inflammation of the trachea were observed in animals in the 20 and 40 ppm group. Substantial weight loss was seen in the 40 ppm group; the high dose females also exhibited ovarian and uterine hypoplasia, thought to be attributable to general debility and weight loss resulting from formaldehyde exposure. Pathological changes were more prevalent in male mice than in females; no significant effects were observed at exposure levels below 10 ppm. This study suggests that the higher concentrations of formaldehyde penetrate deeper into the respiratory tract and produce laryngeal and tracheal lesions in addition to the nasal pathology.

Wilmer et al. (1987) compared the effects of an eight-hour intermittent versus an eight-hour continuous exposure to formaldehyde in male Wistar rats. Rats were exposed to either 5 or 10 ppm formaldehyde for eight continuous hours per day, five days/week for four weeks, or to 10 or 20 ppm formaldehyde interruptedly (eight 30-minute exposures each followed by 30 minutes of non-exposure). After either the third or the last exposure day, three rats per group were administered ^{3}H-thymidine by intraperitoneal injection. Two hours later the rats were sacrificed and the nasal cavities evaluated for cell turnover by autoradiography. All treated animals exhibited a marked increase in ^{3}H-labelled cells; the amount of labelling depended more on concentration than on dose. Focal thinning, disarrangement of the respiratory epithelium, squamous metaplasia, and basal cell hyperplasia were seen in a few of the 10 ppm rats and all of the 20 ppm group. Some degree of rhinitis was observed in all dose groups. More severe lesions were produced following intermittent exposure than continuous exposure.

Dallas et al. (1986) measured responses of the lower respiratory tract in male Sprague-Dawley rats to formaldehyde vapors. Animals were exposed to 0, 0.5 or 15 ppm formaldehyde for six hours/day, five days/week for 8 or 16 weeks by whole-body exposure, then challenged intratracheally with 30 ppm for ten minutes. The respiratory response of these pre-exposed animals to a 30 ppm challenge was then compared with the response of naive rats. Respiratory parameters measured were the minute volume, the respiratory rate, and the tidal volume. Challenge of naive rats resulted in minute volume depression and a decrease in tidal volume, while the respiratory rate remained relatively stable. The affected respiratory parameters had recovered almost completely by the end of the exposure period. Rats pre-exposed to formaldehyde exhibited a similar degree of minute volume decrement and tidal volume depression as a result of tracheal challenge with 30 ppm formaldehyde. The respiratory rate was not affected. Dallas et al. (1986) suggested that the lack of respiratory depression following intra-tracheal exposure to formaldehyde was because the challenge bypassed the upper respiratory tract, which contains receptors responsible for decreases in respiratory rate.

Adams et al. (1987) investigated the effect of formaldehyde on the mononuclear phagocyte system of mice. The mononuclear phagocyte system is a population of leukocytes with an ever-changing degree of maturation. Dean et al. (1984) had reported that formaldehyde enhanced certain functions of the mononuclear macrophage system. Female B6C3F1 mice were exposed to 15 ppm formaldehyde for six hours/day for three weeks. Peripheral leukocytes were recovered by peritoneal lavage from both control and treated mice two or three days after the final exposure. Formaldehyde exposure did not appreciably alter the number of resident macrophages in the peritoneal cavity. In addition, formaldehyde exposure did not induce systemic maturation of resident tissue macrophages. The primary finding from this study was an approximately two-fold increase in the ability of peritoneal macrophages to release hydrogen peroxide upon stimulation. Thus, although formaldehyde does not appear to have any major effect on the maturational status of peritoneal macrophages, it does increase the ability of the cells to release reactive oxygen intermediates (Adams et al., 1987).

Bogdanffy et al. (1987) reported the in vitro binding of ^{14}C-formaldehyde to rat and human nasal mucus samples. Rat mucus samples were pooled from the nasal washes of 15 rats, while human nasal mucus was obtained from a volunteer. Mucus preparations were incubated with 100 mM ^{14}C-formaldehyde for 30 minutes and subsequently analyzed for irreversibly bound formaldehyde. Additional experiments were performed to measure the binding of ^{14}C-formaldehyde to bovine serum albumin (BSA), a model protein similar to human albumin, a major protein component of human mucus. Formaldehyde was found to bind exclusively to one component of nasal mucus from both rats and humans. This fraction was thought to be albumin. The binding was reversible for the first 60 minutes, after which time it became irreversible. Formaldehyde was not found to react to any measurable extent with mucus glycoproteins, but solely with soluble protein. Bogdanffy et al. (1987) suggested that the binding of formaldehyde with mucosal albumin may alter the physical characteristics of mucus flow, potentially leading to the reduced mucus flow rates and mucostatis that have been reported following in vivo exposure to formaldehyde (Morgan et al., 1986).

Goering (1989) examined the effect of acute parenteral administration of formaldehyde on the induction of hepatic metallothionein synthesis. For the dose-response experiments adult male CF1 mice were given an intraperitoneal injection of either formaldehyde or saline at dose levels of 6.25, 12.5, 25, 50 or 100 mg/kg. Hepatic metallothionein, zinc, and copper levels were measured 24 hours after dosing. Hepatic metallothionein concentrations were increased 12- and 15-fold higher than control values after 50 or 100 mg/kg formaldehyde, respectively, but were not altered by the three lower doses. No induction of metallothionein was observed in non-hepatic tissues. Levels of hepatic zinc and copper were also increased by formaldehyde treatment. Glutathione depletion with phorone reduced the metallothionein induction response to formaldehyde, leading Goering (1989) to suggest that the induction may be partially due to a formaldehyde metabolite. Although only mild hepatotoxic changes were observed (an increase in plasma alanine aminotransferase activity), the changes in metallothionein synthesis and essential metal homeostasis may be part of cellular repair mechanisms resulting from acute administration of formaldehyde (Goering, 1989).

Investigators at the Chemical Industry Institute for Toxicology (CIIT) have continued their research into the toxicology of formaldehyde. Casanova et al. (1989) have developed new high-performance liquid chromatographic (HPLC) techniques that allow for more accurate measurement of DNA-protein crosslinks that occur after formaldehyde exposure. This new methodology replaces the dual isotope (^{3}H/^{14}C) approach previously used (Casanova-Schmitz et al., 1984), and provides several significant advantages. The new single isotope methodology with ^{14}C eliminates the isotope effect caused by ^{3}H-formaldehyde. This effect had resulted in an overestimation of the concentration of crosslinks. Additionally, since the shape of the concentration-response curve for DNA-protein crosslinking may have been inaccurate if the magnitude of the isotope effect was concentration-dependent, the new HPLC technique will avoid this methodological problem. Finally, the dual isotope method failed to detect crosslinks at exposure concentrations of less than 2 ppm, while the HPLC technique has identified crosslinks at exposures as low as 0.3 ppm formaldehyde.

The new technique involves enzymatic hydrolysis of the extracted DNA to deoxyribonucleosides with subsequent analysis by HPLC with liquid scintillation counting. Just prior to the hydrolysis step, the DNA was fractionated into an aqueous and an interfacial portion (which correspond to their location following organic extraction); formaldehyde was bound exclusively to the interfacial DNA, indicating that the formaldehyde was found as DNA-protein crosslinks. The hydrolysis of the DNA quantitatively released the formaldehyde, with no evidence supporting the formation of hydroxymethyl adducts. This finding is important, since it previously had been suggested (Beland et al., 1984) that formaldehyde could produce a deoxyadenosine adduct; Casanova et al. (1989) have suggested that the Beland et al. finding was artifactual, based on the use of an inappropriate buffer which caused the adduct to form during the analysis.

In their latest study Casanova et al. (1989) have demonstrated that rats exposed to 0.3, 0.7, 2, 6, or 10 ppm formaldehyde for six hours exhibited DNA-protein crosslinks and that the relationship between exposure and binding was non-linear. These findings have significant implications because earlier studies (Casanova-Schmitz et al., 1984) failed to detect crosslinking below 2 ppm. The data suggest that DNA-protein crosslinking can occur at exposure levels as low as 0.3 ppm, a concentration in the range of ambient air concentrations sometimes found in urban or indoor environments.

In several earlier publications, CIIT researchers discussed both the isotope effect and the effects of glutathione depletion on the binding of formaldehyde to rat nasal DNA. Casanova and Heck (1987) exposed male rats for three hours to ^{14}C- and ^{3}H-formaldehyde at concentrations of 0.9, 2, 4, 6, or 10 ppm, one day after a single three-hour pre-exposure to the same concentration of unlabelled formaldehyde. Two hours prior to the second exposure the animals were injected either with phorone (300 mg/kg) to deplete glutathione or with corn oil as a control. The metabolic incorporation of both radiolabels into DNA, RNA, and proteins in the respiratory and olfactory mucosa and bone marrow was significantly deceased, while DNA-protein crosslinking was significantly increased in the respiratory mucosa of phorone-treated animals, relative to corn-oil injected animals, at all formaldehyde concentrations. Casanova and Heck (1987) stated that the glutathione-dependent oxidation of formaldehyde by formaldehyde dehydrogenase is an important defense mechanism against the covalent interactions of formaldehyde with nucleic acids in the respiratory mucosa.

Heck and Casanova (1987) discussed isotope effects and their implications for the covalent binding of inhaled ^{3}H- and ^{14}C-formaldehyde in the rat nasal mucosa. In their previous paper Casanova and Heck (1987) observed that the $^{3}H/^{14}C$ of the fraction of the DNA that was crosslinked to proteins in the nasal mucosa of glutathione-depleted rats exposed to 10 ppm formaldehyde was significantly (39 $\pm$ 6%) higher than that of the inhaled gas. This finding suggested an isotope effect, either on the formation of DNA-protein crosslinks by labelled formaldehyde or on the oxidation of labelled formaldehyde by either formaldehyde or aldehyde dehydrogenase. In vitro incubation of rat nasal homogenates with ^{3}H- and ^{14}C-formaldehyde also led to the appearance of an isotope effect. Although Heck and Casanova (1987) speculated that the unmetabolized formaldehyde available to

interact with the cellular DNA was somehow enriched in ^{3}H-formaldehyde, subsequent work (Casanova et al., 1989) has shown the isotope effect to be an artifact of the methodology employed, and not a true biological effect. This approach, using the dual isotopes, has since been replaced by a more sensitive method (Casanova et al., 1989).

Several studies have evaluated the effects of formaldehyde exposure on the respiratory tract of non-human primates. Monticello et al. (1989) described the effects of formaldehyde on the respiratory tract of rhesus monkeys. In this study, groups of three adult rhesus monkeys were exposed to either room air or to 6 ppm formaldehyde for five days/week for either one or six weeks. The nature and extent of histologic responses and changes in the epithelial cell proliferation rate were then compared among the groups. The primary lesions identified were mild cellular degeneration and early squamous metaplasia confined to specific regions of transitional and respiratory epithelia of the nasal passages and the respiratory epithelium of the trachea and major bronchi. Although there was minimal progression of the histologic changes between the one-week and the six-week exposure periods, the percent of the nasal surface area affected was significantly increased at six weeks. Cell proliferation rates in the damaged tissues were elevated as much as 18-fold above control levels. These histologic lesions and increased cell proliferation rates were most abundant in the nasal passages and less extensive in the lower airways. The maxillary sinuses exhibited no evidence of a pathologic response to formaldehyde.

In a preliminary report Monticello and Morgan (1989) obtained data describing nasal tract lesions and cell proliferation rates in rats exposed to formaldehyde and compared the rat data to that obtained for monkeys (Monticello et al, 1989). The nasal lesions in rhesus monkeys were found to be more widespread than in the rat. Formaldehyde-induced lesions of the trachea and bronchial bifurcation were identified in the rhesus monkey (Monticello et al., 1989), while no such lesions have been observed in rats (Monticello and Morgan, 1989). Monticello et al. (1989) have suggested these site-specific differences may be attributable to differences in respiration patterns between the two species, where partial mouth breathing by the monkeys would bypass the nasal tissue to some extent, and thus allow a deeper penetration of formaldehyde into the lower airways.

In another preliminary report Heck et al. (1989) compared the extent of DNA-protein crosslinking between rats and rhesus monkeys following a single six-hour exposure to formaldehyde. In this study, rats were exposed to ^{14}C-formaldehyde concentrations of 0.3, 0.7, 2, 6, or 10 ppm in a nose-only inhalation chamber. Rhesus monkeys were exposed (head only) to either 0.7, 2, or 6 ppm ^{14}C-formaldehyde. Immediately following exposure, both groups of animals were sacrificed and tissue samples taken from all levels of the respiratory tract. The DNA was then extracted from the different tissue samples and enzymatically hydrolyzed to deoxyribonucleosides, allowing for the dissociation of DNA-protein crosslinks and for the quantitative release of ^{14}C-formaldehyde. Monkeys had much lower concentrations of crosslinks in the nasal turbinates and anterior nose than did rats for a given formaldehyde concentration. DNA-protein crosslinks in monkeys were also identified in the larynx, trachea, and major intrapulmonary airways greater than 2 mm in diameter. These data are consistent with the histologic

findings, which identified lesions deeper in the respiratory tract for monkeys than for rats. Depending on dose, there was a six- to ten-fold increase in the concentration of crosslinks in the upper respiratory system of rats compared to monkeys. Heck et al. (1989) suggested that this difference may be due to a more efficient elimination of formaldehyde by monkeys, or better repair of the DNA-protein crosslinks. Saturation of these defense mechanisms could help explain the non-linear dependence of DNA-protein crosslinks on the exposure concentration of formaldehyde.

Biagini et al. (1989) examined the effects of formaldehyde exposure on acute airway narrowing in non-human primates. Nine adult male cynomolgus monkeys were tranquilized prior to exposure to 2.55 ppm formaldehyde for ten minutes. Airway pulmonary flow resistance was measured at two, five, and ten minutes post-exposure. The monkeys were exposed by means of an endotracheal catheter placed sub-laryngeally in an attempt to deliver the formaldehyde dose to the lungs and not just to the nose and upper respiratory tract. Airway resistance was significantly increased over control values for all time points measured, demonstrating the ability of formaldehyde to exert effects on the lower respiratory tract. The results of the study by Biagini et al. (1989) demonstrated that increased airway resistance in the lung can occur for at least 10 minutes following exposure to 2.55 ppm formaldehyde. The authors concluded by suggesting that this system could easily be modified to challenge humans having suspected formaldehyde hypersensitivity.

Several aspects of the Biagini et al. (1989) study were atypical of normal toxicity testing. First, all the animals had previous repeated exposure to either hexachloroplatinate salts, vanadium pentoxide dust, or cotton dust extract; however, no animal had either any known previous exposure to formaldehyde or any experimental exposure for at least one year before the present study. Second, all monkeys were known to have airways that were hyperreactive to methacholine. Methacholine is a cholinergic agonist commonly used to evaluate airway reactivity; monkeys with hyperreactive airways were used for this experiment to mimic the ranges of bronchial hyperreactivity that would be observed in a normal and asthmatic human population. Third, formaldehyde was generated by heating diluted formalin (37% formaldehyde solution, with 10-15% methanol as a stabilizing agent) instead of heating paraformaldehyde (the polymerized form of formaldehyde). Thus the monkeys also had a simultaneous exposure to "very low levels of methanol vapor." The estimated methanol vapor concentration of 0.3-0.4 ppm was stated by the authors to be well under methanol concentrations known to cause negative effects on the respiratory system. Fourth, formaldehyde was delivered directly to the lungs by means of a sub-laryngeal catheter. This delivery system was chosen so as to bypass nasal breathing and interaction of formaldehyde with the nasal and respiratory mucosa, and instead deliver the dose directly to the lungs.

Til et al. (1988) conducted an oral subacute toxicity study by adjusting formaldehyde to deliver 5, 25 or 125 mg/kg/day to rats in their drinking water for four weeks. Significant toxic effects were observed only in the highest dose group and consisted of yellow discoloration of the fur, decreased blood protein and albumin levels, hyperkeratosis of the forestomach, and focal gastritis in the glandular stomach. These gastric changes were thought to be due to the irritating properties of

formaldehyde. The authors concluded that a no-observed-adverse-effect level (NOAEL) for administration of formaldehyde in drinking water was 25 mg/kg/day.

Upreti et al. (1987) evaluated the pharmacokinetics and covalent binding of ^{14}C-formaldehyde following a single intraperitoneal injection in male Sprague-Dawley rats. The animals were given 72 mg/kg ^{14}C-formaldehyde, and excretion, tissue distribution, and binding measured for up to 72 hours. Within 30 minutes after dosing, 10% of the dose was recovered in expired air as $^{14}CO_2$, and 41% recovered from exhalation by 72 hours. Feces and urine contained 15% of the radioactivity within 72 hours post-dosing. Radioactivity was measured in a number of tissues, with the liver and spleen having the greatest amount of ^{14}C. Binding to DNA and RNA was also observed, even at 72 hours post-dosing; the maximum extent of DNA binding was observed at 12 hours after ^{14}C-formaldehyde administration.

B) CHRONIC EFFECTS

Feron et al. (1988) investigated the effects of a relatively short-term exposure to formaldehyde on chronic changes in the nasal tissue of rats. Male Wistar rats were exposed to either 10 or 20 ppm formaldehyde vapors six hours/day, five days/week for four, eight, or 13 weeks, and then observed for up to 126 weeks. Rats exposed to 20 ppm formaldehyde had reduced body weight gain for all exposure periods, which eventually returned to normal following termination of exposure. Rats exposed for 8 or 13 weeks to 10 ppm formaldehyde had slightly lower body weights than did control animals, but also returned to normal values during the observation period. Formaldehyde-related changes in nasal tissue observed immediately after termination of the 20 ppm exposure included varying degrees of hyperplasia, metaplasia, and rhinitis in both the olfactory and respiratory epithelium. Similar lesions were found in the respiratory epithelium of rats exposed to 10 ppm, but were more focal and less severe. The olfactory epithelium was not visibly damaged at 10 ppm. A total of 14 nasal tumors was found in rats exposed to formaldehyde. Both the control group and the 10 ppm groups each had two squamous cell carcinomas. The 20 ppm groups had five squamous cell carcinomas, two polypoid adenomas, one carcinoma in situ, one cystic squamous cell carcinoma, and one ameloblastoma. The group of rats exposed to 20 ppm for 13 weeks had the highest incidence of nasal tumors (6/44). The authors concluded that nasal tissue severely damaged by formaldehyde exposure often may be unable to repair itself, and the lesions may progress to tumors (Feron et al., 1988).

Woutersen et al. (1989) measured nasal tumor induction in rats following severe injury to the nasal mucosa and subsequent prolonged exposure to varying concentrations of formaldehyde. Rats were initially divided into two separate groups, one of which was subjected to bilateral intranasal electrocoagulation, while the other group was left intact. This approach was used to test the hypothesis that subcytotoxic concentrations of formaldehyde are able to induce cancer only in damaged tissues. Thus, the tumorigenic response of the group subjected to intranasal electrocoagulation was compared to undamaged animals exposed to formaldehyde. Following the electrocoagulation, the animal groups were divided so that half the animals were exposed (six hours/day, five days/week) for either three or 28 months. All surviving animals were

killed at 29 months for pathological examination. Formaldehyde exposure levels were either 0, 0.1, 1.0, or 10 ppm. Exposure of rats with a damaged nasal mucosa to 0.1 or 1 ppm formaldehyde for 28 months, or to 0.1, 1, or 10 ppm formaldehyde for three months did not result in a significant increase in nasal tumors. Intact animals exposed to 10 ppm formaldehyde for 28 months also failed to exhibit any increase in nasal tumors above control levels. Animals with an injured nasal epithelium and chronically exposed to 10 ppm formaldehyde demonstrated a significant increase in nasal tumors (17/58 vs. 1/54 for injured controls), primarily squamous cell carcinomas derived from the respiratory epithelium. Woutersen et al. (1989) concluded that severe damage to the nasal mucosa is an important contributory factor for the induction of nasal tumors by formaldehyde.

Iversen (1988) evaluated the dermal tumorigenicity of formaldehyde in SENCAR mice, a strain bred for maximum sensitivity to chemical tumorigenesis. Topical skin application of a 4% formaldehyde solution twice a week for 58 weeks resulted in two animals each developing one small benign papilloma. A separate group of SENCAR mice were given 51.2 μg dimethylbenzanthracene (DMBA) preceeded by twice-weekly application of 1% formaldehyde. Tumor rates for these animals were compared with a group given 51.2 μg DMBA plus twice-weekly applications of 4% formaldehyde and an additional group administered just DMBA. No statistically significant difference in tumor incidence was observed between the groups of mice that received DMBA alone or in combination with formaldehyde. Iversen (1988) concluded that formaldehyde has no skin tumorigenic or carcinogenic potency of its own, nor does it appear to have any significant influence on DMBA-induced carcinogenesis.

APPENDIX C

REVIEW OF EPIDEMIOLOGICAL STUDIES OF CANCER AND EXPOSURE TO FORMALDEHYDE

Epidemiological studies have been divided into three sections. The first section deals with exposure to formaldehyde in preservative and fixing solutions. The second section deals with industrial workers. The third section deals with studies in the general population. In addition, the combined evidence concerning individual cancer sites is presented in Table C-4.

Effect measures have been presented with 90% confidence intervals when possible. When an author presented 95% confidence intervals, they were presented as such if there was insufficient data given to allow the 90% limits to be calculated.

Each reviewed study is summarized in the accompanying tables. When the published studies gave information concerning brain cancer, leukemia, respiratory or lung cancer, nasal cancer, or buccal/pharyngeal cancer, then the findings for those sites are given in the tables. In addition, separate tables have been produced for each site.

OCCUPATIONS EXPOSED TO FORMALDEHYDE IN FIXING SOLUTIONS

Pathologists, undertakers, and anatomists are exposed to formaldehyde in the preservatives and fixatives they work with. These preservatives generally contain formalin, which is an aqueous solution of formaldehyde.

Several studies have examined the effect of exposure to formaldehyde among pathologists (Harrington and Shannon, 1975; Harrington and Oakes, 1984; Jensen and Anderson, 1982), undertakers (Levine *et al.*, 1984; Walrath and Fraumeni, 1983; Walrath and Fraumeni, 1984), and anatomists (Stroup *et al.*, 1986). These studies are summarized in Table C-1.

Cohort Studies of Occupations Exposed to Formaldehyde in Fixing Solutions

One study involved 2,079 male British pathologists who were members of the Royal College of Pathologists between 1955 and 1973 (Harrington and Shannon, 1975). Exposure levels were not given or estimated. The only increase in cancer rates reported was in lymphomas and haematomas (Standardized Mortality Ratio or SMR: 2.00; 90% Confidence Interval or CI: 1.00-3.61). (See Table C-1.) There was a deficit of lung cancer (SMR: 0.39; 90% CI: 0.22-0.65) and leukemia (SMR: 0.63, 90% CI: 0.03-2.96). No cases of nasal cancer were observed and brain cancer was not reported.

A later study by the same author examined 2,307 male British pathologists who were members of the Royal College of Pathologists from 1974 to 1980 (Harrington and Oakes, 1984). Like the previous study, exposure levels were neither measured nor estimated. This study found an increase in brain cancer (SMR: 3.31; 90% CI: 1.13-7.62), but no increase in leukemia (SMR: 0.90; 90% CI: 0.04-4.29). A reduced rate of lung cancer was reported (SMR: 0.41; 90% CI: 0.21-0.71) and no cases of nasal cancer were observed.

A study of 1,477 male undertakers in Ontario, first licensed during 1928-1957 (Levine *et al.*, 1984), reported a leukemia SMR of 1.60 (90% CI: 0.54-3.66) and a brain cancer SMR of 1.15 (90% CI: 0.31-2.98). (See Table C-1.) There was no increase in buccal/pharyngeal cancer (SMR: 0.48; 90% CI: 0.02-2.25) or lung cancer (SMR: 0.94; 90% CI: 0.62-1.38) and no cases of nasal cancer. This study reported no difference in the cancer risks when a 20-year latency restriction was imposed (numbers not given in paper). This study measured the mean time-weighted-average formaldehyde concentration during the embalming of intact bodies to be 0.3 ppm and during the embalming of autopsied bodies to be 0.9 ppm. Peak half-hour concentrations were estimated between 0.4 ppm and 2.1 ppm. Using an estimate of one hour to prepare an intact body and two hours to prepare an autopsied body (taken from Williams *et al.*, 1984) and assuming, as in a West Virginia survey (Levine *et al.*, 1984), that embalmers prepare 75 bodies a year, 15 of which are autopsied, the time-weighted average concentration for a 40-hour work week, 50 weeks per year, was estimated to be 0.02 ppm.

The final cohort study among professionals involved 2,317 male anatomists who joined the American Association of Anatomists between 1888 and 1969 (Stroup *et al.*, 1986). (Table C-1.) This study reported an increased risk of brain cancer (SMR: 2.70; 90% CI: 1.47-4.58), which remained when comparing this cohort to psychiatrists (SMR: 6.00; 90% CI: 3.13-10.47) and which increased with length of membership in the association (1-19 years membership, SMR: 2.00; 90% CI: 0.68-4.57; 20-39 years membership, SMR: 2.80; 90% CI: 0.95- 6.40; 40-69 years membership, SMR: 7.00; 90% CI: 1.19- 21.67). Leukemia mortality was increased when comparing the cohort to the general population (SMR: 1.47; 90% CI: 0.80-2.50) but not when comparing them to psychiatrists (SMR: 0.80; 90% CI: 0.23-2.15). There were reduced rates of cancer of the buccal/pharynx (SMR: 0.15; 90% CI: 0.01-0.70) and lung cancer (SMR: 0.28; 90% CI: 0.16-0.45). Lung cancer rates were also reduced when psychiatrists were used as the referent group (SMR: 0.50; 90% CI: 0.23-0.93), and did not increase with years of membership in the association (1-19 years membership, SMR: 0.40; 90% CI: 0.17-0.79; 20-39 years membership, SMR: 0.20; 90% CI: 0.07-0.46; 40-69 years membership, SMR: 0.30; 90% CI: 0.05-0.94). There were no cases of nasal cancer reported. Exposure estimates were reported to be between 1 and 3 ppm in anatomy or embalming areas based on a review of formaldehyde exposure in various settings (EPA 1984). To examine the effect at different formaldehyde exposure levels, the authors compared the rate of brain cancer in anatomists specializing in gross anatomy (629 anatomists, SMR: 3.90; 90% CI: 1.32-8.88) to that in anatomists specializing in microanatomy (673 anatomists, SMR: 2.8; 90% CI: 0.76-7.24) and found no difference, even though it appeared that gross anatomists were exposed to formaldehyde more frequently than were microanatomists. However, no estimates of the duration of exposure were given in terms of the proportion of worktime at the exposure levels quoted. Anatomists probably spend only a small percentage of their work time at the exposure levels quoted. Thus, the overall time-weighted average exposure levels were probably much lower than 1 ppm for the groups in the study.

Case-Control Study of Occupations Exposed to Formaldehyde in Fixing Solutions

Only one case-control study was found giving results concerning anatomists (Jensen and Anderson, 1982). It examined lung cancer in Danish male physicians

and found that the proportion who had ever worked in pathology, forensic medicine, or anatomy was the same among cases and controls (Odds Ratio or OR: 1.00; 95% CI: 0.40-2.40).

Proportionate Mortality Studies of Occupations Exposed to Formaldehyde in Fixing Solutions

A proportionate mortality study of 1,132 New York embalmers (Walrath and Fraumeni, 1983) found a brain cancer Proportionate Mortality Ratio or PMR of 1.56 (90% CI: 0.81- 2.71) and a leukemia PMR of 1.40 (90% CI: 0.81-2.29). (See Table 1.) The lung cancer PMR was 1.08 (90% CI: 0.88-1.31). For the subgroup of "embalmers only," who may have had heavier exposure, the PMR for brain cancer was 2.34 (90% CI: 1.00-4.55).

A similar study of 1,109 California embalmers (Walrath and Fraumeni, 1984) found elevations of all cancers combined, including cancers of the brain (PMR: 1.94; 90% CI: 1.00- 3.34), buccal/pharynx (PMR: 1.31; 90% CI: 0.65-2.36), and colon (PMR: 1.87; 1.35-2.54), and leukemia (PMR: 1.75; 90% CI: 1.00-2.82). Lung cancer PMR was 0.96 (90% CI: 0.72- 1.24). When length of licensure was examined, leukemia increased in those licensed for more than 20 years (PMR: 2.21; 90% CI 1.10-3.99) compared to those licensed less than 20 years (PMR: 1.24; 90% CI: 0.42-2.83), while the risk of brain cancer remained unchanged (<20 years PMR: 1.98; 90% CI: 0.78-4.15; >20 years PMR: 1.89; 90% CI: 0.64-4.31).

STUDIES OF INDUSTRIAL WORKERS EXPOSED TO FORMALDEHYDE

Industrial workers are exposed to air-borne formaldehyde while working in the following industries: formaldehyde production, resin and plastic materials and manufacture, apparel manufacture, plywood particle board and wood furniture manufacture, and paper and paperboard manufacture.

Cancer risks in industrial workers exposed to formaldehyde are summarized in Table C-2.

Cohort Studies of Industrial Workers Exposed to Formaldehyde

The largest cohort study examining cancer risks and formaldehyde exposure involved 26,561 industrial workers exposed to formaldehyde (Blair *et al.*, 1986; Blair *et al.*, 1987; Tamburro and Waddell, 1987; Collins *et al.*, 1988; Sterling and Weinkam, 1988). These employees worked at one of ten formaldehyde-using plants in the United States, including factories producing resin products, formaldehyde, molding compounds, plywood, photographic film, decorative laminates, and hexamethylenetetramine.

The study estimated 8-hour TWA exposure to formaldehyde in five categories (trace, <0.1 ppm, 0.1-<0.5 ppm, 0.5-<2.0 ppm, and >2.0 ppm) and level and frequency of peak exposures (an excursion of generally less than 15 minutes that exceeded the upper level of the job's TWA category). The following sources of information were used.

1. Industrial hygienists working on the study prepared exposure matrices of job-work area-calendar year combinations for 6,700 job titles using the five categories defined above. These were based on a plant walk-through

and company monitoring data (the amount and quality of which varied from plant to plant);

2. The list of each job by formaldehyde exposure category was reviewed by each plant's industrial hygienist; and

3. Formaldehyde levels were monitored at each plant during the summer and the winter of 1983-84 using standard NIOSH methods.

The study then examined workers exposed to formaldehyde levels above 0.1 ppm TWA. These workers had SMRs for laryngeal cancer of 1.42 (90% CI: 0.87-2.43) and for lung cancer of 1.11 (90% CI: 0.98-1.24). The lung cancer SMR increased to 1.35 (90% CI: 1.17-1.55) when the analysis was restricted to wage employees with exposure over 0.5 ppm- years and 20+ years of latency, but there was no increase of lung cancer within this group with increasing exposure. There was no increase in SMRs for cancer of the buccal cavity and pharynx (SMR: 0.96; 90% CI: 0.61-1.41), nose (SMR: 0.91; 90% CI: 0.16-2.86), brain (SMR: 0.81; 90% CI: 0.52-1.21) or leukemia (SMR: 0.80; 90% CI: 0.52-1.16). (See Table C-2.)

Workers with non-zero formaldehyde exposure were used to study subsites of cancer of the buccal cavity and pharynx. Although there had been no overall increase in buccal/pharyngeal cancer, there was an increase in cancer of the oropharynx (SMR: 1.92; 90% CI: 0.76-4.04) and nasopharynx (SMR: 3.00; 90% CI: 1.30-5.92), but no increase in cancer of the hypopharynx (SMR: 0.59; 90% CI: 0.02-2.78).

None of the cancers (including laryngeal, lung, oropharyngeal, or hypopharyngeal) displayed a clear trend of increasing risk with increasing intensity of exposure or with increasing cumulative exposure.

A 1984 cohort study examined the cancer risk of 7,680 men working with formaldehyde in five plants in the British chemical and plastics industry (Acheson *et al.*, 1984; Acheson *et al.*, 1984; Infante and Schneiderman, 1986). This study estimated exposure levels by categorizing the formaldehyde exposure for each job title into high, moderate, low, or background on the basis of subjective information collected from persons with long experience of the working conditions. Recollections by workers about the occurrence rate of acute symptoms of irritation were used in an attempt to match these exposure groupings to the following levels: >2.0 ppm, 0.6-2.0 ppm, 0.1-0.5 ppm and <0.1 ppm.

No cases of nasal cancers were found, but only 1.07 cases were expected. When comparing the lung cancer mortality incidence to local rates, there was a slight trend of increasing risk with increasing exposure. The lung cancer SMR for the entire cohort was 0.95 (90% CI: 0.85-1.07), for the factory (British Industrial Plastics or BIP) whose workers had the longest and most intense formaldehyde exposure it was 1.04 (90% CI: 0.89-1.21), and for the workers at the BIP factory with exposures over 2 ppm it was 1.18 (90% CI: 1.00-1.38). Using national rates, the lung cancer SMR for BIP workers increased to 1.24 (90% CI: 1.07- 1.44) and in the high-exposure employees it increased to 1.41 (90% CI: 1.19-1.66). However, when examining the workers in this most highly exposed group, there was no trend for increasing risk of lung cancer with increasing length of employment (the greatest SMR of 1.83 (90% CI: 1.22-2.63) was in workers employed for only 6 to 11 months). An important issue in this

study is which comparison population is most appropriate. Local mortality rates are generally superior to national mortality rates from the point of view of confounding. However, in highly industrial areas, local rates may be influenced by other industries with increased lung cancer rates. In this instance, there is an excess lung cancer rate among BIP factory workers with exposure over 2 ppm using either approach. However, the SMR of 1.18 using local rates increased to 1.44 using national rates. An estimate of increased risk due to occupational exposure compared to men non-occupationally exposed to lung carcinogens probably lies somewhere in this range.

Finally, a small increase in mortality due to diseases of the respiratory system was noted (SMR: 1.17; 90% CI: 1.01- 1.34), raising the possibility of some confounding from smoking.

A subsequent report by the same author (Acheson *et al.*, 1984) addressed the relationship of SMR to cumulative exposure and found no trend of increasing cancer risk with increasing cumulative dose for the BIP factory workers. However, they noted that comparatively few workers were exposed to high levels of formaldehyde for more than 5 years.

A 1988 study (Stayner *et al.*, 1988) examined a cohort of 11,030 predominantly female workers employed for at least three months at one of three garment factories (two of which were examined in an earlier proportionate mortality study (Stayner *et al.*, 1985) and a third added for this study). The air levels of formaldehyde were found to have a geometric mean of 0.15 ppm in 1981, with no substantial peak levels (although past levels were presumed higher and short-term 10 minute air levels had been measured in similar settings between 0.3 and 2.7 ppm). This study reported an SMR of 1.55 (90% CI: 0.68-3.07) for buccal/pharyngeal cancers, due to an increase in buccal cancers (SMR: 3.43; 90% CI: 1.18-7.86). It also reported a lung cancer SMR of 1.14 (90% CI: 0.86-1.49). There was no increase in brain cancer (SMR: 0.71; 90% CI: 0.28-1.49) and no cases of nasal cancer were reported. (See Table C-2.)

When these cancers were stratified by latency and duration of exposure, there was increasing risk with increasing latency for various cancers, with the greatest increase being in cancer of the buccal cavity and leukemia in workers with 20 or more years of latency. However, the risk of cancer of the trachea, bronchus, and lung actually tended to decrease with increasing duration of employment.

A cohort study involved 1,332 resin workers (Bertazzi *et al.*, 1986) who were exposed to airborne concentrations of formaldehyde estimated between 0.23 and 2.53 ppm, based on fixed area samples taken between 1974 and 1979 which were judged to be "typical" ambient air concentrations by plant technicians. This study found an increase in lung cancer when examining the entire cohort (18 cases, SMR: 1.86; 90% CI: 1.20-2.75). However, when the analysis excluded workers with no formaldehyde exposure and those with unknown exposure, the lung cancer SMR dropped to 1.36 (5 cases, 90% CI: 0.54-2.87). Numbers were too small to assess latency and duration of employment adequately, but some of the findings are shown in Table C-2.

The final cohort study examined 2,026 workers exposed to formaldehyde in a chemical plant which was one of the largest producers of formaldehyde in the U.S (Wong, 1983). This study did not measure or estimate the level of

formaldehyde exposure, nor did it divide the cohort into high and low exposure categories. A variety of products and processes had been introduced over the years with potential for exposure to benzene, asbestos, pigments, etc. The author reported no cases of nasal cancer (expected number not stated) and no increase in lung cancer (SMR: 0.94; 90% CI: 0.53-1.56). There was a brain cancer SMR of 1.86 (90% CI: 0.50-4.81). Lung cancer risks were higher in workers starting employment after 1961 (SMR: 2.82; 90% CI: 0.49- 8.85) than in those starting employment before 1960 (SMR: 0.82; 90% CI: 0.43-1.43). Although the small numbers made further stratification difficult, there was no difference in the risk of lung cancer or brain cancer when comparing subcohorts with 10 or 20 years latency. Cancer of the respiratory system was highest in workers with less than 5 years of employment (SMR: 2.40; 90% CI: 1.04-4.74 based on 6 cases).

Nested Case-Control Studies of Industrial Workers Exposed to Formaldehyde

A 1985 nested case-control study examined 57 cases of respiratory cancer in Finnish woodworkers (Partanen *et al.*, 1985). Exposure levels were estimated for each job title. The estimated time-weighted mean exposure levels were broken into three categories: 0.1-1 ppm; 1-2 ppm, and >2 ppm. Cumulative exposures were the product of exposure level and exposure time, summed up over all exposure periods. Smoking was controlled for, but stratified only as <35 years and >35 years. This study reported a respiratory cancer OR of 1.44 (90% CI: 0.69-3.00) in workers exposed to a minimum formaldehyde dose of 3 ppm months, and this increased when attention was confined to workers with a minimum latency of 10 years with an adjustment for smoking (OR: 1.60; CI not given). For the small number of workers with peak exposures over 1 ppm the OR was 1.35 (90% CI: 0.35-5.26).

A matched case-control study of 481 cancer deaths among workers at eight DuPont chemical plants (Fayerweather *et al.*, 1982) examined three broad exposure categories (which were "extrapolated from air monitoring data whenever possible"): continuous-direct exposure, intermittent exposure, and background exposure.

These were further broken down within continuous-direct exposure into approximate eight-hour time-weighted average concentrations of <0.1 ppm, 0.1-2 ppm, and >2 ppm, and within intermittent exposure into two categories: exposures to 2 ppm concentrations unlikely and exposures to 2 ppm concentrations likely. Smoking histories were also collected. Many different analyses were presented, and it was not always clear how results were obtained. In one analysis, when smoking was controlled for, lung cancer deaths increased in employees with increasing latency of exposure to formaldehyde to an odds ratio of 1.46 (number involved and CI not given) for the group with more than 20 years latency. In other analyses, which were not adjusted for smoking, the 20+ year latency group's odds ratio was only 1.00 (CI not given). However, exposure was less common in the workers who smoked more than half a pack per day than in workers smoking less than half a pack a day, so negative confounding would be expected. There were no cases of nasal cancer reported, and no increase in cancer of the buccal cavity (OR: 1.00; CI not given) or cancer of the brain (OR: 0.50; CI not given).

A study of 308 lung cancer deaths in 19,608 Dow Chemical workers (Bond *et al.*, 1986) found no increase among those exposed to formaldehyde (OR: 0.62; 95% CI:

0.29-1.34). However, only 9 cases were reported to have been exposed to formaldehyde, and formaldehyde exposure levels were neither measured nor estimated.

Proportionate Mortality Studies of Industrial Workers Exposed to Formaldehyde

A study of 256 deaths of primarily female workers at three garment factories (Stayner *et al.*, 1985) found that, at air levels measured between 0.1 ppm and 1 ppm (past exposures were presumed higher, but no estimate was stated), buccal/pharyngeal cancer was elevated (PMR: 2.29; 90% CI: 0.62-5.92), due to an increase in cancer of the buccal cavity (PMR: 7.50; 90% CI: 2.04-19.39). Both of these were more elevated in the group with latency and duration over ten years (buccal/pharyngeal PMR: 2.86; 90% CI: 0.49-9.98; buccal PMR: 9.52; 90% CI: 1.73-31.42). However, these numbers were based on three cases. Lung cancer was not elevated (PMR: 0.95; 90% CI: 0.53-1.57). A full cohort study with estimation of SMRs was later done and has been described in the section on cohort studies.

A study of 136 deaths among men employed in a chemical plant (Marsh, 1982) showed no overall elevation in respiratory cancer (PMR: 0.80; 90% CI: 0.35-1.58). Respiratory cancer rates were higher in those employed before 1959 (based on only two cases), when exposure levels were presumed higher (PMR: 2.37; 90% CI: 0.41-7.48), compared to those employed after 1959 (PMR: 0.61; 90% CI: 0.21-1.39). Respiratory cancer was also increased in workers employed more than 5 years (PMR: 1.53; 90% CI: 0.52-3.50) compared to those working less than 5 years (PMR: 0.41; 90% CI: 0.07-1.28). No data were presented concerning upper respiratory tract cancer. This study reported no exposure measures or estimates.

A later study of the same plant (Liebling *et al.*, 1984) examined the proportionate mortality in workers who had died since the previous study. This study reported measured air samples to be between 0.05 and 5 ppm, with an average of 1 ppm (based on 20 grab air samples available from 1977). This study found an elevated buccal cancer rate (PMR: 8.70; 90% CI: 1.50-27.33). Respiratory cancer had a PMR of 1.29 (90% CI: 0.35-3.37).

POPULATION-BASED CASE-CONTROL STUDIES

Cancer risks in population-based case-control studies of formaldehyde exposure are summarized in Table C-3.

Upper Respiratory Tract Cancer

Several population-based case-control studies examine the relationship between formaldehyde exposure and sinonasal cancer.

One study (Vaughan *et al.*, 1986) examined the relation between residential exposure to formaldehyde (through exposure to particle boards and plywood in renovation, recent construction, and, particularly, living in a mobile home) and cancers of the pharynx, sinus, and nasal cavities. It found an increase in nasopharyngeal cancer in subjects living in a mobile home park for 1-9 years (OR: 2.1; 95% CI: 0.7-6.6) and a greater increase for those living in a mobile home park for more than 10 years (OR: 5.5; 95% CI: 1.6-19.4) when smoking history and ethnic origin were controlled for. It found no increase in cancers

of the oro/hypopharynx or of the sinonasal cavities and no effect of particle board exposure. It also found an increased risk of nasopharyngeal cancer for subjects having both residential and occupational exposure to formaldehyde (OR: 6.7; 95% CI: 1.2-38.9) when compared to subjects with neither source of exposure, which was greater than the risk for subjects with only one source of exposure.

A companion study (Vaughan *et al.*, 1986) examined occupational exposures to formaldehyde. Exposure levels were estimated by linking each job to a job-exposure matrix listing probability of exposure and level of exposure. There was no increase in cancer when comparing the four different exposure groups (probable exposure to high levels, probable exposure to low levels, possible exposure to any level, and background), but only 7 subjects had high exposure. There was a trend towards increased risk of oro/hypopharyngeal cancer and nasopharyngeal cancer for those subjects exposed for the longest time and those subjects with the highest exposure score (computed by multiplying level of exposure by years worked), but the numbers were too small to achieve any clear result. The risks were slightly increased when only live interviews were included.

A study of 759 cases of sinonasal cancers in Denmark (Olsen and Asnaes, 1986) reported an increase in squamous cell cancer and adenocarcinoma of the nasal cavity in cases exposed to formaldehyde (RR: 2.3; 95% CI: 0.9-5.8 and RR: 2.2; 95% CI: 0.7-7.2 respectively) which remained when limited to those with a 10-year latency (RR: 2.4; 95% CI: 0.8-7.4 and RR: 1.8; 95% CI: 0.5-6.0) (these numbers controlled for wood dust exposure, but not for smoking). An earlier study by the same author (Olsen *et al.*, 1984) involved 839 cases of nasal cancer in Denmark and found an association between nasal cancer and formaldehyde exposure (RR: 2.8; 95% CI: 1.8-4.3). However, when adjusted for wood-dust exposure, the relative risk dropped to 1.6 (95% CI: 0.7-3.6)

A study of 116 cases of nasal cancer in the Netherlands (Hayes *et al.*, 1986) reported a relationship between nasal cancer and occupational exposure to formaldehyde (RR: 2.5; 90% CI: 1.2-5.0), which remained after adjusting for smoking and wood dust exposure, and increased with increasing formaldehyde level. This increase was seen primarily in squamous cell nasal cancer.

A study of 160 hospital patients (Brinton *et al.*, 1984) found no relationship between cancers of the nasal cavity and sinuses and occupational exposure to formaldehyde (RR: 0.35; 95% CI: 0.1-1.8).

A study of incident cases recorded by the Connecticut Tumor Registry (Roush *et al.*, 1987) examined 198 cases of sinonasal cancer and 173 cases of nasopharyngeal cancer and related them to formaldehyde exposure at three levels (background, <1 ppm and >1 ppm) based on the classification of an industrial hygienist reviewing each subject's work history. There was only a slight increase in sinonasal cancer among those exposed to a high level of formaldehyde with 20 year latency (RR: 1.4; 95% CI: 0.6-3.1) and no effect in any of the lesser exposed groups. Nasopharyngeal cancer risks were slightly increased in the high-exposure group (RR: 1.5; 95% CI: 0.6-2.9), and increased even more in those with a 20-year latency (RR: 2.3; 95% CI: 0.9-6.0).

Lung Cancer

The final population-based case-control study (Coggon *et al.*, 1984) explored the relation between formaldehyde exposure and lung cancer in a population-based case-control study involving 598 lung cancers deaths. The exposure categories were based on a job-exposure matrix linking each job to high, low, or no exposure. The relative risk of lung cancer among the 296 subjects exposed to formaldehyde was 1.5 (95% CI: 1.2-1.8). However, in those classified as having high exposure, the relative risk was only 0.9 (95% CI: 0.6-1.4). The jobs involved were not identified, and the exposure classification relied on industrial hygienist assessment of job names alone.

TABLE C-1: OCCUPATIONS EXPOSED TO FORMALDEHYDE IN FIXING SOLUTIONS

Cohort Studies

Author	Cancer site	Obs	Exp	SMR	90% CI Low	90% CI Upp
Harrington, 1975	leukemia	1	1.6	0.63	0.03	2.96
2,079 Pathologists	lung/trachea	11	27.9	0.39	0.22	0.65
No exposure data given	lymphoma/haematoma	8	4	2.00	1.00	3.61
Harrington, 1984	brain	4	1.2	3.31	1.13	7.62
2,307 pathologists	leukemia	1	1.1	0.90	0.04	4.29
No exposure data given	lung	9	22	0.41	0.21	0.71
	nasal	0	0.12	0.00	----	----
Levine, 1984	brain	3	2.6	1.15	0.31	2.98
1,477 undertakers	leukemia	4	2.5	1.60	0.54	3.66
Exposure while embalming:	buccal/pharynx	1	2.1	0.48	0.02	2.25
MTWA: 0.3-0.9 ppm	lung	19	20.2	0.94	0.62	1.38
peak: 0.4-2.1 ppm	nasal	0	0.2	0.00	----	----
Overall TWA: 0.02 ppm	skin	0	0.9	0.00	----	----
Stroup, 1986	brain	10	3.7	2.70	1.47	4.58
2,317 anatomists	1-19 yrs exp	4	2	2.00	0.68	4.57
Exposure: 1-3 ppm	20-39 yrs exp	4	1.43	2.80	0.95	6.40
Proportion of time at	40-69 yrs exp	2	0.29	7.00	1.19	21.67
these exposure not given	psychiatrist refer	9	1.5	6.00	3.13	10.47
	gross anatomy	4	1.03	3.90	1.32	8.88
	microanatomy	3	1.07	2.80	0.76	7.24
	leukemia	10	6.8	1.47	0.80	2.50
	psychiatrist refer	3	3.6	0.80	0.23	2.15
	buccal/pharynx	1	6.8	0.15	0.01	0.70
	lung	12	43.1	0.28	0.16	0.45
	1-19 yrs exp	6	15	0.40	0.17	0.79
	20-39 yrs exp	4	20	0.20	0.07	0.46
	40-69 yrs exp	2	6.7	0.30	0.05	0.94
	psychiatrist refer	7	14.2	0.50	0.23	0.93
	nasal	0	0.5	0.00	----	----

Case-control Study

Author	Cancer site	Exposed Cases	Exposed Controls	OR	95% CI Low	95% CI Upp
Jensen, 1982	lung	8	23	1.00	0.4	2.4
79 cases, 252 controls						
pathologists						
No exposure data given						

Proportionate Mortality Studies

Author	Cancer site	Obs	Exp	SMR	90% CI Low	90% CI Upp
Walrath, 1983	brain	9	5.8	1.56	0.81	2.71
1,132 embalmers	embalmers only	6	2.6	2.34	1.00	4.55
Exposure 0.25-1.39 ppm	leukemia	12	8.5	1.40	0.81	2.29
presumed during embalming	buccal/pharynx	8	7.1	1.13	0.56	2.03
	lung	72	66.8	1.08	0.88	1.31
	colon	29	20.3	1.43	1.02	1.95
	skin	8	3.6	2.21	1.11	4.01
Walrath, 1984	brain	9	4.7	1.94	1.00	3.34
1,109 embalmers	<20 years licensed	5	2.53	1.98	0.78	4.15
Exposure 0.25-1.4 ppm	>20 years licensed	4	2.12	1.89	0.64	4.31
presumed during embalming	leukemia	12	6.9	1.75	1.00	2.82
	<20 years licensed	4	3.23	1.24	0.42	2.83
	>20 years licensed	8	3.62	2.21	1.10	3.99
	buccal/pharynx	8	6.1	1.31	0.65	2.36
	lung	41	42.9	0.96	0.72	1.24
	nasal	0	0.6	0.00	----	----
	colon	30	16	1.87	1.35	2.54
	prostate	23	13.1	1.75	1.20	2.49
	skin	2	3.4	0.59	0.10	1.85

TABLE C-2: INDUSTRIAL EXPOSURE TO FORMALDEHYDE

Cohort Studies

Author	Cancer site	Obs	Exp	SMR	90% CI Low	90% CI Upp
Blair, 1986	brain	17	21	0.81	0.52	1.21
26,561 industry workers	leukemia	19	24	0.80	0.52	1.16
Exposure: 0.1 - >2.0 ppm TWA	buccal/pharynx	18	19	0.96	0.61	1.41
	lung	201	182	1.11	0.98	1.24
	larynx	12	8	1.42	0.87	2.43
	nasal	2	2.2	0.91	0.16	2.86
Exposure: >0 - >5.5 ppm-yr	lung, 20 year latency	146	108	1.35	1.17	1.55
	hypopharynx	1	1.7	0.59	0.02	2.78
	nasopharynx	6	2.0	3.00	1.30	5.92
	oropharynx	5	2.6	1.92	0.76	4.04
Acheson, 1984	brain	5	12.5	0.40	0.16	0.84
7,680 chemical workers	leukemia	9	11.4	0.79	0.41	1.38
Exposure: 0 - >2.0 ppm	buccal/pharynx	5	4.6	1.09	0.43	2.28
based on subjective recall	nasopharynx	0	NG	0.00	----	----
of symptom occurrence	lung	205	215	0.95	0.85	1.07
	BIP (local)	128	123	1.04	0.89	1.21
	(nat'l)	128	103	1.24	1.07	1.44
	larynx	4	4.5	0.89	0.30	2.03
	nasal	0	1.1	0.00	----	----
Exposure: >2.0 ppm	lung BIP (local)	106	90	1.18	1.00	1.38
	(nat'l)	106	75	1.41	1.19	1.66
Stayner, 1988	brain	5	7	0.71	0.28	1.49
11,030 garment workers	leukemia	9	7.9	1.14	0.60	2.00
Exposure: 0.15 ppm	buccal/pharynx	6	3.9	1.55	0.68	3.07
in 1981 (geometric mean)	buccal	4	1.2	3.43	1.18	7.86
Earlier short-term	lung	39	34.1	1.14	0.86	1.49
exposures: 0.3 - 2.7 ppm	nasal	0	NG	0.00	----	----
	connective tissues	4	1.1	3.64	1.23	8.25
Bertazzi, 1986						
1,332 resin workers						
Exposure: 0-2.53 ppm	lung, all employees	18	9.7	1.86	1.20	2.75
	nasal, all employees	0	0.03	0.00	----	----
Exposure: 0.13-2.53 ppm	lung, known exposure	5	3.7	1.36	0.54	2.87
Average of "typical"	<4 yrs latency	1	0.49	2.03	0.08	9.65
levels between 1974 and 1979	>15 yrs latency	2	1.55	1.29	0.22	4.06
	<4 yrs employment	2	1.77	1.13	0.20	3.55
	>15 yrs employment	1	0.41	2.47	0.10	11.53

Wong, 1983	brain	3	1.6	1.86	0.50	4.81
2,026 chemical workers	leukemia	2	1.7	1.18	0.20	3.70
Exposure data not given	10 yr latency	2	1.20	1.67	0.29	5.24
	20 yr latency	2	0.65	3.06	0.53	9.67
	lung	11	11.7	0.94	0.53	1.56
	pre-1960	9	10.96	0.82	0.43	1.43
	post-1960	2	0.71	2.82	0.49	8.85
	respiratory					
	<5 yrs employment	6	2.5	2.40	1.04	4.74
	15-19 yrs employment	3	1.91	1.57	0.42	4.06
	nasal	0	NG	0	----	----

Nested Case-Control Studies

Author	Cancer site	Exposed Cases	Exposed Controls	OR	90% CI Low	90% CI Upp
Partanen, 1985	respiratory	13	45		1.44	0.693.00
57 cases/71 controls	10 yr latency	8	NG	1.60	NG	NG
among 3,805 woodworkers	>1 ppm	3	18	1.35	0.35	5.26
Exposure: 0.1->2 ppm TWA						
Fayerweather, 1982	brain, 15+ yrs latency	1	2	0.50	NG	NG
481 cases/481 controls	buccal, 20+ yrs latency	1	1	1.00	NG	NG
among Du Pont workers	lung, 20+ yrs latency	39	39	1.00	NG	NG
Exposure: 0.1->2 ppm TWA	adjusted for smoking	NG	NG	1.46	NG	NG
	prostate	8	3	2.50	NG	NG

					95% CI Low	95% CI Upp
Bond, 1986	lung	9	27	0.62	0.29	1.34
308 cases/588 controls	15 yr latency	4	24	0.31	0.11	0.86
among 19,608 Dow Chemical workers						
Exposure data not given						

Proportionate Mortality Studies

Author	Cancer site	Obs	Exp	PMR	95% CI Low	95% CI Upp
Stayner, 1984	brain	1	2.14	0.47	0.02	2.21
256 garment workers	leukemia	4	2.38	1.68	0.57	3.85
Exposure: 0.01-1 ppm	buccal/pharynx	3	1.3	2.29	0.62	5.92
	> 10yrs lat/dur	2	0.7	2.86	0.49	9.98
	buccal	3	0.40	7.50	2.04	19.39
	> 10yrs lat/dur	2	0.2	9.52	1.73	31.42
	lung	11	11.62	0.95	0.53	1.57

Marsh, 1982	respiratory	6	7.5	0.80	0.35	1.58
136 chemical workers	pre-1959	2	0.84	2.37	0.41	7.48
Exposure data not given	post-1959	4	6.6	0.61	0.21	1.39
	< 5 yrs exposure	2	4.9	0.41	0.07	1.28
	> 5 yrs exposure	4	2.61	1.53	0.52	3.50
	< 20 yr latency	3	3.90	0.77	0.21	1.99
	> 20 yr latency	3	3.61	0.83	0.22	2.15
Liebling, 1984	buccal/pharynx	2	0.23	8.70	1.50	27.33
24 chemical workers	respiratory	3	2.3	1.29	0.35	3.37
Exposure: 1 ppm average	colon	4	0.57	7.02	2.39	16.05

TABLE C-3: POPULATION-BASED STUDIES OF FORMALDEHYDE

Author	Cancer site	Exposed Cases	Exposed Controls	OR	95% CI Low	95% CI Upp
Vaughan, 1986 residential						
53 cases/552 controls	sinonasal					
	1-9 years exposure	5	82	0.60	0.20	1.70
205 cases/552 controls	oropharynx					
	1-9 years exposure	21	64	0.90	0.50	1.80
	10+ years	7	18	0.80	0.20	2.70
27 cases/552 controls	nasopharynx					
	1-9 years exposure	4	64	2.10	0.70	6.60
	10+ years	4	18	5.50	1.60	19.40
Vaughan, 1986 occupational						
205 cases/552 controls	oropharynx	58	171	1.70	0.60	4.60
27 cases/552 controls	nasopharynx	11	171	3.10	0.60	15.40
Olsen, 1986	sinonasal, squamous	13	NG	2.30	0.90	5.80
759 cases, 2,465 controls	10 year latency	8	NG	2.40	0.80	7.40
	sinonasal, adeno.	17	NG	2.20	0.70	7.20
	10 year latency	12	NG	1.80	0.50	6.00
Olsen, 1984	sinonasal	33	NG	2.80	1.80	4.30
839 cases, 2,465 controls	10 year latency	23	NG	3.10	1.80	5.30
	sinonasal, wood dust	33	NG	1.60	NG	NG
	10 year latency	23	NG	1.60	0.70	3.60
	nasopharyngeal	NG	NG	0.70	0.30	1.70
Hayes, 1986	nasal/sinonasal					
63 cases, 161 controls	any exposure	24	44	1.64	0.90	2.80
	high exposure	17	24	2.12	1.10	4.10
Brinton, 1984	nasal/sinonasal	2	10	0.35	0.1	1.8
160 cases, 290 controls						
Roush, 1987						
Exposure >1 ppm						
198 cases/605 controls	sinonasal	NG	NG	1.00	0.50	2.20
	20 year latency	NG	NG	1.50	0.60	3.90
173 cases/605 controls	nasopharyngeal	NG	NG	1.40	0.60	3.10
	20 year latency	NG	NG	2.30	0.90	6.00
Coggon, 1984	lung	296	472	1.50	1.20	1.80
598 cases, 1,180 controls	high exposure	44	90	0.90	0.60	1.40

TABLE C-4: FORMALDEHYDE CANCER SITES

Study type/Author	Cancer site	Relative Risk	CI Low	CI Upp
Professional Cohort				
Levine, 1984	buccal/pharynx	0.48	0.02	2.25
Stroup, 1986	buccal/pharynx	0.15	0.01	0.70
Professional PMR				
Walrath, 1983	buccal/pharynx	1.13	0.56	2.03
Walrath, 1984	buccal/pharynx	1.31	0.65	2.36
Industrial Cohort				
Acheson, 1984	buccal/pharynx	1.09	0.43	2.28
Blair, 1986	buccal/pharynx	0.96	0.61	1.41
Stayner, 1988	buccal/pharynx	1.55	0.68	3.07
Industrial PMR				
Liebling, 1984	buccal/pharynx	8.70	1.50	27.33
Stayner, 1984	buccal/pharynx	2.29	0.62	5.92
	> 10yrs lat/dur	2.86	0.49	9.98
Industrial Cohort				
Stayner, 1988	buccal	3.43	1.18	7.86
Industrial Case-Control				
Fayerweather, 1982	buccal, 20+ yrs latency	1.00	NG	NG
Industrial PMR				
Stayner, 1984	buccal	7.50	2.04	19.39
	> 10yrs lat/dur	9.52	1.73	31.42
Industrial Cohort				
Acheson, 1984	nasopharynx	0.00	----	----
Blair, 1986	nasopharynx	3.00	1.30	5.92
Population-Based Case Control				
Olsen, 1984	nasopharynx	0.70	0.30	1.70
Roush, 1987	nasopharynx	1.40	0.60	3.10
	20 year latency	2.30	0.90	6.00
Vaughan, 1986 residential	nasopharynx			
	1-9 years exposure	2.10	0.70	6.60
	10+ years	5.50	1.60	19.40
Vaughan, 1986 occupational	nasopharynx	3.10	0.60	15.40
Industrial Cohort				
Blair, 1986	oropharynx	1.92	0.76	4.04

Population-Based Case Control				
Vaughan, 1986 residential	oropharynx			
	1-9 years exposure	0.90	0.50	1.80
	10+ years	0.80	0.20	2.70
Vaughan, 1986 occupational	oropharynx	1.70	0.60	4.60
Industrial Cohort				
Blair, 1986	hypopharynx	0.59	0.02	2.78
Professional Cohort				
Harrington, 1984	nasal	0.00	----	----
Levine, 1984	nasal	0.00	----	----
Stroup, 1986	nasal	0.00	----	----
Professional PMR				
Walrath, 1984	nasal	0.00	----	----
Industrial Cohort				
Acheson, 1984	nasal	0.00	----	----
Bertazzi, 1986	nasal	0.00	----	----
Blair, 1986	nasal	0.91	0.16	2.86
Stayner, 1988	nasal	0.00	----	----
Wong, 1983	nasal	0	----	----
Population-Based Case Control				
Brinton, 1984	nasal/sinonasal	0.35	0.1	1.8
Hayes, 1986	nasal/sinonasal			
	any exposure	1.64	0.90	2.80
	high exposure	2.12	1.10	4.10
Olsen, 1984	sinonasal	2.80	1.80	4.30
	10 year latency	3.10	1.80	5.30
	sinonasal, wood dust	1.60	NG	NG
	10 year latency	1.60	0.70	3.60
Olsen, 1986	sinonasal, squamous	2.30	0.90	5.80
	10 year latency	2.40	0.80	7.40
	sinonasal, adeno.	2.20	0.70	7.20
	10 year latency	1.80	0.50	6.00
Roush, 1987	sinonasal	1.00	0.50	2.20
	20 year latency	1.50	0.60	3.90
Vaughan, 1986 residential	sinonasal			
	1-9 years exposure	0.60	0.20	1.70

Industrial Cohort				
Acheson, 1984	larynx	0.89	0.30	2.03
Blair, 1986	larynx	1.42	0.87	2.43
Professional Cohort				
Harrington, 1975	lung/trachea	0.39	0.22	0.65
Harrington, 1984	lung	0.41	0.21	0.71
Levine, 1984	lung	0.94	0.62	1.38
Stroup, 1986	lung	0.28	0.16	0.45
	1-19 yrs exp	0.40	0.17	0.79
	20-39 yrs exp	0.20	0.07	0.46
	40-69 yrs exp	0.30	0.05	0.94
	psychiatrist refer	0.50	0.23	0.93
Professional PMR				
Walrath, 1983	lung	1.08	0.88	1.31
Walrath, 1984	lung	0.96	0.72	1.24
Professional Case Control				
Jensen, 1982	lung	1.00	0.4	2.4
Industrial Cohort				
Acheson, 1984	lung	0.95	0.85	1.07
	BIP (local)	1.04	0.89	1.21
	(nat'l)	1.24	1.07	1.44
	BIP >2ppm (local)	1.18	1.00	1.38
	(nat'l)	1.41	1.19	1.66
Bertazzi, 1986	lung, all employees	1.86	1.20	2.75
	known exposure	1.36	0.54	2.87
	<4 yrs latency	2.03	0.08	9.65
	>15 yrs latency	1.29	0.22	4.06
	<4 yrs employment	1.13	0.20	3.55
	>15 yrs employment	2.47	0.10	11.53
Blair, 1986	lung	1.11	0.98	1.24
	lung, 20 year latency	1.35	1.17	1.55
Stayner, 1988	lung	1.14	0.86	1.49
Wong, 1983	lung	0.94	0.53	1.56
	pre-1960	0.82	0.43	1.43
	post-1960	2.82	0.49	8.85
	respiratory			
	<5 yrs employment	2.40	1.04	4.74
	15-19 yrs employment	1.57	0.42	4.06
Industrial Case-Control				
Bond, 1986	lung	0.62	0.29	1.34
	15 yr latency	0.31	0.11	0.86

Fayerweather, 1982	lung, 20+ yrs latency	1.00	NG	NG
	adjusted for smoking	1.46	NG	NG
Partanen, 1985	respiratory	1.44	0.69	3.00
	10 yr latency	1.60	NG	NG
	>1 ppm	1.35	0.35	5.26
Industrial PMR				
Liebling, 1984	respiratory	1.29	0.35	3.37
Marsh, 1982	respiratory	0.80	0.35	1.58
	pre-1959	2.37	0.41	7.48
	post-1959	0.61	0.21	1.39
	< 5 yrs exposure	0.41	0.07	1.28
	> 5 yrs exposure	1.53	0.52	3.50
	< 20 yr latency	0.77	0.21	1.99
	> 20 yr latency	0.83	0.22	2.15
Stayner, 1984	lung	0.95	0.53	1.57
Population-Based Case Control				
Coggon, 1984	lung	1.50	1.20	1.80
	high exposure	0.90	0.60	1.40
Professional Cohort				
Harrington, 1984	brain	3.31	1.13	7.62
Levine, 1984	brain	1.15	0.31	2.98
Stroup, 1986	brain	2.70	1.47	4.58
	1-19 yrs exp	2.00	0.68	4.57
	20-39 yrs exp	2.80	0.95	6.40
	40-69 yrs exp	7.00	1.19	21.67
	psychiatrist refer	6.00	3.13	10.47
	gross anatomy	3.90		
	microanatomy	3.20		
Professional PMR				
Walrath, 1983	brain	1.56	0.81	2.71
	embalmers only	2.34		
Walrath, 1984	brain	1.94	1.00	3.34
	<20 years licensed	1.98		
	>20 years licensed	1.89		
Industrial Cohort				
Acheson, 1984	brain	0.40	0.16	0.84
Blair, 1986	brain	0.81	0.52	1.21
Stayner, 1988	brain	0.71	0.28	1.49
Wong, 1983	brain	1.86	0.50	4.81
Industrial Case-Control				
Fayerweather, 1982	brain, 15+ yrs latency	0.50	NG	NG
Industrial PMR				
Stayner, 1984	brain	0.47	0.02	2.21

Professional Cohort				
Harrington, 1975	leukemia	0.63	0.03	2.96
Harrington, 1984	leukemia	0.90	0.04	4.29
Levine, 1984	leukemia	1.60	0.54	3.66
Stroup, 1986	leukemia	1.47	0.80	2.50
	psychiatrist refer'	0.80	0.23	2.15
Professional PMR				
Walrath, 1983	leukemia	1.40	0.81	2.29
Walrath, 1984	leukemia	1.75	1.00	2.82
	<20 years licensed	1.24		
	>20 years licensed	2.21		
Industrial Cohort				
Acheson, 1984	leukemia	0.79	0.41	1.38
Blair, 1986	leukemia	0.80	0.52	1.16
Stayner, 1988	leukemia	1.14	0.60	2.00
Wong, 1983	leukemia	1.18	0.20	3.70
	10 yr latency	1.67	0.29	5.24
	20 yr latency	3.06	0.53	9.67
Industrial PMR				
Stayner, 1984	leukemia	1.68	0.57	3.85

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