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Contribution of Formaldehyde to Respiratory Cancer

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This article reviews the available data on the carcinogenicity of formaldehyde from experimental and epidemiologic studies and makes recommendations for further research. Two definitive chronic inhalation bioassays on rodents have demonstrated that formaldehyde produces nasal cancer in rats and mice at 14 ppm and in rats at 6 ppm, which is within the domain of present permissible human exposure (8-hr time-weighted average of 3 ppm, a 5 ppm ceiling, and a 10 ppm short-term exposure limit). Biochemical and physiologic studies in rats have shown that inhaled formaldehyde can depress respiration, inhibit mucociliary clearance, stimulate cell proliferation, and crosslink DNA and protein in the nasal mucosa. No deaths from nasal cancer have been reported in epidemiologic studies of cohorts exposed to formaldehyde, but three case-control studies suggest the possibility of increased risk. Although excesses of lung cancer deaths have been observed in some studies at industrial plants with formaldehyde exposure, uncertainties in interpretation limit the evaluation of these findings. Excess cancers of the brain and of lymphatic and hematopoietic tissues have been reported in certain studies of industrial groups and in most studies of formaldehyde-exposed professionals, but whether these excesses are related to formaldehyde exposure is not known. Several properties of formaldehyde pose unique problems for future research: the mechanisms responsible for its nonlinear response; its probable mechanism of carcinogenic action as a cross-linking agent; its formation in tissues as a normal metabolite; its possible action as a promoter and/or a cocarcinogen; and the importance of glutathione as a host defense at low exposure.

Formaldehyde is carcinogenic and mutagenic in the laboratory, but the extent of the carcinogenic risk of formaldehyde exposure in humans has not yet been defined. The acute adverse health effects of formaldehyde, including sensory irritation and sensitization, have been reviewed by the National Academy of Sciences (*1*). Two groups of scientists in the United States (*2,3*) and an international group (*4*) have recently considered evidence for delayed health effects, including cancer. This paper summarizes the available information on the carcinogenicity of formaldehyde from experimental and epidemiologic studies, and it incorporates data obtained since the preceding reviews.

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Physical Properties of Formaldehyde

Formaldehyde is a colorless gas. On chilling, it condenses to form a liquid that boils at −19°C and freezes at −118°C. The gas has a pungent odor and is extremely irritating to the mucous membranes of the eyes, nose, and throat. Because it polymerizes readily, it is sold and transported only in solution or in the polymerized state. Formaldehyde is highly water-soluble, and it is marketed chiefly in the form of aqueous solutions containing a stabilizer such as methanol or methyl/ethyl cellulose. The most commonly encountered aqueous solution, often referred to as formalin, contains 37% by weight formaldehyde and 6 to 15% methanol. Other sources of formaldehyde include mixtures of lower or higher molecular weight polyoxymethylene glycols $H(CH_2O)_nOH$, known respectively as paraformaldehyde, or polyoxymethylene, and the cyclic trimer trioxane. These polymeric forms are solids (*5–7*).

Chemical Properties

Formaldehyde is a highly reactive molecule possessing a single carbonyl group flanked by two hydrogen

atoms, $H_2C=O$. Most reactions are of three types, as illustrated by the following reaction sequences (*5,7*).

Oxidation–Reduction

Cannizarro Reaction:

$$2\ HCHO \rightarrow HCOOH + CH_3OH$$

Addition or Condensation

Bisulfite Addition:

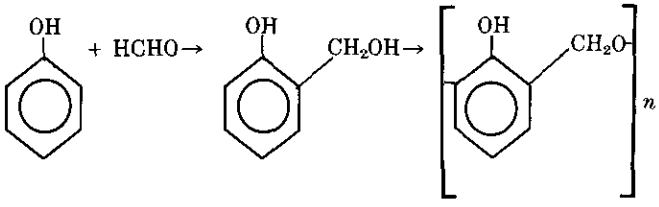
$$HCHO + NaHSO_3 \rightarrow HOCH_2SO_3Na$$

Aldol Condensation:

$$HCO + R'(R'')CHC{=}OR \rightarrow HOCHCR'(R'')C{=}OR$$

Polymerization

Methylol Formation:



Production and Use

Formaldehyde has been manufactured in the United States since 1901. Production has increased virtually every year, with large boosts occurring during the world wars (*5*). In 1984, the annual capacity of the major U.S. producers exceeded 8.5 billion pounds of 37% by weight solution (*8*).

Over 50% of formaldehyde produced is consumed in the manufacture of phenol-formaldehyde, urea-formaldehyde, melamine-formaldehyde, and acetal resins (*7–9*). Formaldehyde resins are used as adhesives in particleboard, plywood, insulating materials, and foundry cores; decorative laminates in table tops, counter tops, and wall paneling; molding compounds in appliances, telephones, and dinnerware; and coatings, such as those given to fabrics to impart permanent press characteristics (*10*). Urea-formaldehyde foam insulation has been widely applied to residences and commercial buildings in northern Europe and North America (*11*). A plethora of other uses of formaldehyde include the manufacture of rubber, photographic film, leather, explosives, dyes, cosmetics, corrosion inhibitors, and embalming fluids. Among various medical and dental applications of formaldehyde is the production of vaccines (*5*).

Occupational and Environmental Exposure

The current federal standard for formaldehyde exposure in the workplace calls for an 8-hr time-weighted-average permissible exposure limit of 3 ppm, a 5 ppm ceiling, and a 10 ppm short-term exposure limit (*12*). In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended that the limit for an 8-hr time-weighted-average exposure to formaldehyde be set at 1 ppm (*13*). In light of data indicating the carcinogenicity of formaldehyde in rats, NIOSH has recommended that this limit be reduced to the lowest feasible level (*14*). Airborne concentrations of formaldehyde have been monitored using a variety of methods of somewhat uncertain validity. There is a paucity of systematic data regarding the severity and duration of formaldehyde exposure among various job categories across industries. Little information is available prior to the early 1970s (*3*).

Substantial exposure of workers to formaldehyde has been noted in several industries, with sample means of 1 ppm or more in the following industries and occupations: formaldehyde production; resin and plastic materials production; apparel manufacture; plywood, particleboard, and wood furniture manufacture; paper and paperboard manufacture; urea-formaldehyde foam insulation dealers and installers; mushroom farms; funeral homes; and pathology and biology laboratories. High concentrations of formaldehyde have also been reported in individual samples from iron foundries and plastic molding facilities. Industries with relatively large numbers of persons exposed full- or part-time include apparel manufacture (897,000), funeral services (52,000 to 70,200), wood furniture manufacture (49,500), and foundries (43,000) (*3*).

Numerous sources of environmental exposure have been reported. These include motor vehicle exhaust; the burning of gas, oil, coal, wood, and rubbish; and photochemical smog (*15–17*). Concentrations reported in ambient air are usually less than 10 to 15 ppb except in cases of heavy motor vehicle traffic or photochemical smog when levels of up to 90 to 150 ppb have been reported (*3*).

The most important source of indoor formaldehyde exposure is formaldehyde resins in wood products such as plywood paneling, particleboard underlays, and fiberboard furniture. Indoor levels may be augmented by the use of gas-fired space heaters and by smoking. In general, concentrations in conventional homes more than 5 years old are below 0.05 ppm; however, levels may frequently exceed 0.1 ppm in new homes, those insulated with urea-formaldehyde foam, and in mobile homes. Mobile homes seem to have the highest levels (*3,18,19*). In contrast to exposure in the workplace, residential exposure may affect different subgroups of the population (e.g., the young and the old) and frequently involves longer daily exposure periods.

Several methods are available for determining the level of formaldehyde gas in air (*20*). Selecting the appropriate sampling and analytical technique is of critical importance and must be consistent with the type of environment to be sampled and the anticipated concentration levels. Most of the available methods have been developed for use in occupational settings, and they may not be suited for the relatively low concentrations of formaldehyde prevalent in nonoccupational environments (*20*). In attempting to improve sensitivity, researchers have modified standard methods (*21,22*). New or modified methods, however, may not have been evaluated sufficiently for sensitivity, precision, accuracy,

and interferences or storage stability, especially under conditions of use by nonprofessionals in residential settings (*23*). The choice of an inappropriate method, improper conduct of sampling or analysis, or the presence of interferences may lead to substantial positive or negative biases in reported exposure concentrations.

Biochemistry, Metabolism, and Pharmacokinetics

Formaldehyde is a molecule that appears to be present in all living cells. It is derived metabolically from numerous sources, including serine, glycine, sarcosine, choline, and methionine, as well as xenobiotic compounds such as methanol, methyl chloride, and compounds containing N-, O-, or S-methyl groups. Formaldehyde is metabolized by oxidation to formate or by incorporation into thymine, serine, purines, histidine, or methionine via its binding to tetrahydrofolate. It combines reversibly with nucleophilic compounds, such as glutathione, and forms stable crosslinks, such as N^5, N^{10}-methylenetetrahydrofolate, which are essential for its oxidation and for its utilization as a one-carbon unit in biosynthetic reactions (*24*).

It is not known whether under normal conditions metabolically produced formaldehyde may be available for covalent binding to DNA and thus contribute to the background occurrence of cancer, to the aging process, or to other deleterious health effects. Likewise, the consequences of exposure to xenobiotics that are metabolized through formaldehyde are not known.

Inhaled formaldehyde mixes with the endogenous formaldehyde pool. Its carbon is metabolically incorporated into DNA, RNA, and proteins (*25*) or is ultimately exhaled as carbon dioxide (*26*). Owing to rapid metabolism following inhalation exposure of rats to 15 ppm of formaldehyde, no detectable increase occurred in the tissue concentrations of formaldehyde, either at the point of entry (the nasal respiratory mucosa) (*27*) or in the blood (*28*). Similarly, no covalent binding of formaldehyde to DNA, RNA, or proteins in the femoral marrow was detected after exposure of rats to concentrations as high as 15 ppm (*25*). Humans exposed to 2 ppm also showed no increase in the blood concentration of formaldehyde as a result of exposure (*28*). The possibility that low levels of formaldehyde might be transported to sites in the body external to the respiratory tract arises from the observation that there may be excesses of brain tumors and leukemia in some formaldehyde-exposed populations. No mechanism for such transport, however, has been proposed.

Formaldehyde is well known to form crosslinks with biological macromolecules. Inhaled formaldehyde has been demonstrated to form DNA-protein crosslinks in the nasal respiratory mucosa of rats at concentrations ≥2 ppm (*25*). Studies of the concentration dependence of DNA-protein crosslinking showed that the yield of crosslinks following exposure to 2 ppm of formaldehyde was significantly less than that expected if the extent of crosslinking were directly proportional to the airborne concentration of formaldehyde. In contrast, the amount of formaldehyde covalently bound to respiratory mucosal proteins was apparently a linear function of the concentration inhaled. The percentage of the total ^{14}C labeling in DNA and proteins that was due to covalent binding (the rest was due to metabolic incorporation) increased nonlinearly over the concentration range 0.3 to 15 ppm. This suggests that within the tested range the covalent binding of formaldehyde in the respiratory mucosa cannot be described by linear pharmacokinetics.

Additional studies of the formation of DNA–protein crosslinks by formaldehyde in the nasal respiratory mucosa have been undertaken using normal rats and rats partially depleted of glutathione. Glutathione, an essential cofactor for formaldehyde metabolism, was reduced to 10% of the control concentration in nasal mucosa by intraperitoneal injection of phorone (*29,30*). In formaldehyde-exposed control animals (treated with corn oil), the yield of DNA-protein crosslinks was a nonlinear function of concentration, as noted previously.

Depletion of glutathione enhanced the yield of DNA-protein crosslinks at each of the concentrations and diminished the amounts of ^{14}C metabolically incorporated into macromolecules. In addition, the concentration-response curve for DNA-protein crosslinking in the respiratory mucosa at concentrations between 2 and 6 ppm was more nearly linear in phorone-treated than in corn oil-treated rats (*29*). These experiments suggest that inhibition of metabolism increases the yield of crosslinks (presumably by increasing the cellular concentration of formaldehyde) and that metabolic defense mechanisms dependent on glutathione are at least partially responsible for the observed nonlinear dependence on inhaled formaldehyde concentration. Glutathione depletion did not affect protein-protein crosslinks, suggesting that such covalent binding was predominantly to extracellular proteins in mucus.

Assays for Genotoxicity

Formaldehyde induces gene mutations in bacteria, fungi, yeast, Drosophila larvae, and cultured rodent and human cells (*3,31,32*). Other genetic endpoints for which responses to formaldehyde have been positive include single-strand breaks in DNA, sister chromatid exchanges, and chromosome aberrations. The carcinogenic potential of the chemical is also reflected in its ability to transform rodent cells in a variety of *in vitro* assays. Although formaldehyde is considered to be a weak mutagen (*3*), consistent effects in a diverse array of test systems suggest that genetic alterations may be fundamental to formaldehyde carcinogenesis.

Although mutagenic activity can be demonstrated reproducibly *in vitro*, efforts to induce *in vivo* genotoxic effects in rodents exposed to formaldehyde have been generally unsuccessful (*3,33–35*). Most of these studies, however, have examined tissues distant from the site of primary exposure. Because formaldehyde is highly

reactive and rapidly metabolized, significant systemic distribution may not occur at ordinary exposure levels.

Studies of genetic alterations in occupationally exposed humans have produced results similar to those obtained with rodents. Three studies have failed to detect cytogenetic alterations in peripheral lymphocytes (*36–38*). In a fourth study, no adverse effects were found on sperm (*39*). It should be recognized, however, that these studies were limited in size and were thus of limited sensitivity. Furthermore, investigators in the Soviet Union have observed an increase in chromosome aberrations among workers exposed to phenol and formaldehyde (*40*). Unfortunately, concomitant exposure to phenol and insufficient description of methodological detail complicate interpretation of these findings.

Mechanisms of Genotoxicity

The genotoxicity of formaldehyde may be related to its ability to produce DNA-protein crosslinks (*41,42*). Stable covalent binding is thought to proceed via a two-step process. Formaldehyde reacts with an amino group on protein or DNA to form an unstable hydroxymethyl intermediate. The intermediate reacts with another amino group, resulting in a stable methylene bridge between protein and DNA. Single-stranded DNA is more susceptible to crosslinking than double-stranded DNA (*31*). Intracellular repair of DNA-protein crosslinks is very rapid (*43,44*) but may not involve excision repair processes (*44*). DNA adenine residues are likely sites for crosslinking to occur (*45,46*), although reactions with cytidine and guanine residues are also possible (*41*).

The molecular mechanism by which DNA-protein crosslinks may produce mutagenic effects is not yet known. Recent studies in bacteria suggest that crosslinks may cause point mutations, such as single-base substitutions (*46*). The sequencing of DNA from formaldehyde-induced Drosophila mutants, on the other hand, has indicated that mutagenesis in this system is largely the result of deletions (*47*).

While it is theoretically possible for formaldehyde to cause DNA-DNA crosslinks, generation of such lesions *in vitro* requires prolonged incubation of naked DNA with high concentrations of the chemical (*48*). Efforts to detect formaldehyde-induced DNA-DNA crosslinks within intact cells have been unsuccessful (*43,49*). Other studies have suggested that formaldehyde mutagenesis might be mediated through reactive by-products resulting from interaction with free amino acids, nucleotide precursors, or hydrogen peroxide (*50–53*). This is because induction of genotoxic events in Drosophila, *E. coli*, and mice may require or be facilitated by concomitant administration of these natural substances. While such studies are of interest, this potential mechanism of genotoxicity has been poorly characterized, and its relationship to formaldehyde mutagenesis at present is speculative.

In addition to the genotoxicity of formaldehyde itself, a number of studies have indicated that exposure to formaldehyde may enhance the effects of other DNA-damaging agents (*31*). Most recently, treatment of cultured human fibroblasts with formaldehyde and methylnitrosourea was observed to produce a mutagenic response greater than that expected from the simple additive effects of the individual agents (*54*). The mechanism of such an enhancement has not been established, although some evidence would suggest that inhibition of DNA repair processes by formaldehyde may be involved (*31,52,55*). Whether formaldehyde might enhance the effects of other DNA-damaging agents during *in vivo* exposures has yet to be determined.

Results of Chronic Formaldehyde Inhalation Bioassays

An inhalation toxicity study of formaldehyde was conducted in male and female Fischer-344 rats and B6C3F1 mice. One hundred twenty animals of each sex and species were exposed to formaldehyde by inhalation at mean concentrations of 0, 2.0, 5.6, and 14.3 ppm for up to 24 months. Some of the animals were followed for an additional 3 to 6 months after completing the 24-month exposure regimen (*56–58*).

Squamous cell carcinomas were observed in the nasal passages of 103 of 232 rats (44%) and 2 of 215 mice (1%) in the 14.3 ppm group and 2 of 235 rats (1%) in the 5.6 ppm group. In addition, two nasal adenocarcinomas, one carcinosarcoma, one undifferentiated carcinoma, and one undifferentiated sarcoma were found in the nasal cavities of rats exposed to 14.3 ppm. Life table adjustments of these data have been published (*58*). Polypoid adenomas of the nasal mucosa were noted in 8 of 236 (3.4%), 6 of 235 (2.6%), and 5 of 232 (2.2%) Fischer-344 rats exposed to 2.0, 5.6, and 14.3 ppm of formaldehyde, respectively, compared to 1 of 232 (0.4%) in the control group (*57,58*). The carcinogenicity of formaldehyde has subsequently been confirmed by other investigators with the induction of squamous cell carcinomas in the nasal passages of Sprague-Dawley rats exposed to 14.2 ppm; papillomas were found in this study (*59*). No significant increases have been observed in neoplasms at other sites. In the opinion of the International Agency for Research on Cancer, there is sufficient evidence to conclude that formaldehyde gas is carcinogenic to rats (*4*).

Dysplastic and metaplastic changes were reported in the respiratory epithelium of the anterior nasal passages of all groups of formaldehyde-exposed Fischer-344 rats. The frequency and severity of these lesions varied with the extent of exposure. Goblet cell hyperplasia and rhinitis were also reported. Epithelial lesions occurred in the proximal trachea, but only at 14.3 ppm. In mice, irritant-induced effects were essentially limited to the nasal cavities of the high-exposure group. Three months after termination of exposure, there was regression of rhinitis, dysplasia, and metaplasia in both species. No evidence of toxicity was detected at sites other than the respiratory tract (*57,58*). Bone marrow hyperplasia present in the rat bioassay was not considered

a primary effect of formaldehyde exposure, but secondary to anoxia due to the presence of obstructive masses in the nasal passages.

Physiologic Responses to Sensory Irritation

In addition to causing a burning sensation and a desire to withdraw from the contaminated atmosphere, stimulation of sensory nerve endings in the nasal mucosa by formaldehyde decreases the frequency of respiration (*60*). In both rats and mice, associated changes in tidal volume do not compensate entirely for the decreased frequency (*61*). As a result, pulmonary ventilation per unit time is reduced during exposure. The magnitude of this response depends on concentration and is greater in mice than in rats. Assuming that all inhaled formaldehyde is deposited in the nasal cavity, one can estimate the rate of deposition onto the mucosal surface by dividing the amount of formaldehyde inhaled per unit time by the mucosal surface area. At 15 ppm, the deposition rate for mice would be about half that for rats (*62–64*) and might account for the greater resistance of mice to the carcinogenic effects of formaldehyde at this concentration. At 6 ppm, both species appear to receive similar doses (*64*). The concentration-dependence of pulmonary ventilation on exposure must also be considered when assessing the risk of a single species to different airborne concentrations of formaldehyde (*65*). For example, rats exposed to 15 ppm for 6 hr inhaled twice, not 2.5 times, the amount of formaldehyde inhaled by rats similarly exposed to 6 ppm (*32*).

Role of the Nasal Mucociliary Apparatus

The mucociliary apparatus presents a continuous layer of mucus, which flows over the surface of the nasal epithelium (*66,67*). Before inhaled formaldehyde can reach the epithelium, it must first traverse the mucus blanket. Studies have recently been conducted to determine the nature and rate of reaction between formaldehyde and rat and human nasal mucus. It was demonstrated that formaldehyde reacts rapidly with mucus and that albumin is probably the major binding constituent (*68*).

At 2, 6, and 15 ppm, formaldehyde inhibited mucociliary function in Fischer-344 rats in regions where squamous cell carcinomas have occurred as the result of exposure (*69–71*). As the concentration of formaldehyde was increased, larger areas of the mucus layer became immobilized. Inhibition of mucociliary function was not observed after exposure to 0.5 ppm for 2 weeks. In human volunteers, nasal mucociliary function was inhibited by exposure to 0.3 ppm for 4–5 hr (*72*). At low formaldehyde concentrations, mucus binding reactions coupled with mucus clearance could reduce exposure of the nasal epithelium; however, quantitative data are lacking.

Cell Proliferation in Response to Cytotoxicity

Formaldehyde is known to react preferentially with single-stranded DNA (*73,74*). As the number of single-stranded sites is much increased during DNA replication, cell proliferation should facilitate formaldehyde-DNA binding. DNA adducts, such as DNA-protein crosslinks, if unrepaired, increase the likelihood that an error in newly formed DNA might occur, causing a mutation. Not only should cell proliferation facilitate binding of formaldehyde to DNA and increase the chance for errors in *de novo* DNA synthesis, but it also will expand the population of initiated cells (*64*).

Restorative cell proliferation and hyperplasia occur in response to formaldehyde cytotoxicity (*64,75*). Slight increases in cell proliferation were demonstrable in rat nasal epithelium after a single 6-hr exposure to 0.5 or 2.0 ppm of formaldehyde. Increased proliferation, however, was not apparent after exposure at these concentrations for 3 or 9 days (*76,77*). At higher concentrations, establishment of a thickened epithelial layer between 3 and 9 days of exposure is associated with a reduction in the overall increase of cell proliferation. Cell turnover continues in the basal layer of the epithelium. During the first few days of exposure, cell proliferation varies with formaldehyde concentration in a nonlinear fashion. A 3-fold concentration increase from 2 to 6 ppm resulted in an 8-fold increase in turnover after 1 day of exposure and almost a 25-fold increase after 3 days of exposure (*65*).

In a 6-month study, rats exposed to 14.3 ppm of formaldehyde 6 hr/day, 5 days/week (450 ppm-hr/week) had similar, but much more severe, inflammatory, hyperplastic, and metaplastic lesions than did animals given approximately the same total dose, but at 3 ppm for 22 hr/day, 7 days/week (462 ppm-hr/week) (*78*). Likewise, in groups of rats exposed to 36 ppm-hr of formaldehyde, but at different concentrations (3, 6, and 12 ppm) and durations of exposure (12, 6, and 3 hr), cell proliferation was affected both by location within the nose and by formaldehyde concentration. In the most anterior portion of the nose, where mucociliary clearance is minimal, cell proliferation increased 5-fold in all exposure groups. By contrast, proliferation was strictly concentration-dependent in the main portion of the respiratory epithelium, where mucociliary clearance is present and squamous cell carcinomas have developed following chronic exposure to formaldehyde (*76*). Collectively, these data suggest that intensity of formaldehyde exposure may be more important than exposure duration for cytotoxicity, restorative cell proliferation, and possibly, for the carcinogenic process.

Dose-Response Relationships and Species Differences Relevant to Data Transfer from Animal to Man

Acute studies of formaldehyde have provided evidence that the dose delivered to the DNA of replicating

cells in the respiratory epithelium of the rat nasal cavity is nonlinearly related to airborne formaldehyde concentration (*25,29*). Specifically, it is reported that significantly less formaldehyde is covalently bound to respiratory mucosal DNA at lower airborne concentrations than would be predicted by downward linear extrapolation from the amounts observed at high concentrations. Other acute studies have demonstrated that exposure of rats to formaldehyde via inhalation depresses respiration (*64*), inhibits mucociliary clearance (*69,70*), and stimulates cell proliferation (*64,75*), all as nonlinear functions of airborne formaldehyde concentration at the concentrations studied. Experiments with glutathione-depleted animals suggest that metabolic degradation of formaldehyde may be more effective below 6 ppm than at higher levels (*29*).

Use of the amount of formaldehyde covalently bound to respiratory mucosal DNA rather than airborne concentration as the measure of exposure leads to lower point and upper bound estimates of risk at low doses, irrespective of the mathematical dose-response model employed (*79*). Whether the data from DNA-protein crosslinking studies should be used in risk assessment is unclear at the present time. Reservations have been expressed and disputed (*80–82*). To the extent that the findings may be substantiated by future studies, use of this information would be appropriate.

Review of Epidemiologic Studies of Cancer in Relation to Formaldehyde Exposure

Rats and mice are obligate nose breathers. Humans, however, may breathe through the mouth or the nose. In humans, therefore, sites at special risk from direct contact with formaldehyde gas may be the nasal passages, buccal cavity and pharynx, larynx, trachea, bronchi, lungs, and esophagus. The human skin may also be at special risk since it is not protected by fur. The incidence of cancers at these sites in human populations varies considerably. Cancers of the nasal passages are extremely rare, while cancers of the lungs and skin are common. Different epidemiologic strategies are required to investigate rare and common tumors. Case-control designs allow the ascertainment of an adequate number of subjects with a rare cancer. Unless cases and controls are drawn from a population where formaldehyde exposure is relatively frequent, however, the proportion of subjects exposed may be inadequate to evaluate moderate levels of relative risk. Cohort studies can evaluate effectively associations between an exposure and multiple diseases, so long as the diseases are not extremely rare. For example, a cohort study of 100,000 persons followed over 20 years would have only a 70% power to detect a 2-fold increase in mortality from nasal cancer. Case-control and cohort studies have both been used to evaluate cancer risks associated with formaldehyde exposure.

A number of epidemiologic studies have been performed of persons occupationally exposed to formaldehyde. Tables 1 and 2 summarize cohort cancer mortality data available from primary literature sources, including theses and government documents, as well as published articles, abstracts, and letters. Listed are deaths due to cancers at sites that may come into contact with formaldehyde gas and those at other locations where significant excesses have been observed previously in a formaldehyde-exposed cohort. For each cause, observed and expected deaths are presented by individual study or plant and in total. The mortality experience of industrial workers is described in Table 1. In Table 2, the experience of professionals—pathologists, anatomists, and morticians—is given along with the combined totals of both tables. National mortality rates were employed to determine the number of expected deaths.

In only one of the studies in Tables 1 and 2 and in one other were attempts made to estimate formaldehyde exposures experienced by the study population (*83–85*). Using data assembled by the Exposure Panel of the Consensus Workshop on Formaldehyde (*3*), measurements of formaldehyde applicable to the study cohorts have been included in Tables 1 and 2, wherever possible. It should be noted that these measurements were not taken from the particular populations reported in Tables 1 and 2 but rather are summarized from the literature on similar or related occupations. At best, they provide rough indications of the relative levels of formaldehyde experienced recently by these occupational groups. A variety of sampling and analytical techniques were used. Sampling duration was reported as 1 to 4 hr in some studies but unreported in others.

Although mean levels in pathology and anatomy laboratories and funeral homes appear higher than in industries producing formaldehyde or formaldehyde resins, the sampling period for measurements in laboratories was often not reported. Employees in anatomy and pathology laboratories and funeral homes are not exposed for 8 hr/day; thus their 8-hr time-weighted average (TWA) may be considerably lower. The peak values reported for such persons, on the other hand, may be more reliable. These suggest that the highest levels experienced by pathologists, anatomists, and morticians may exceed those encountered by industrial workers.

The studies of industrial workers presented in Table 1 reveal increases in mortality from several cancers, none of which were found to be consistently elevated. Two groups of investigators reported significant excesses of lung cancer. Acheson et al. noted an elevated standardized mortality ratio (SMR) for lung cancer at one of six plants (A4 in Table 1: SMR 124) that became statistically nonsignificant (SMR 104) when mortality for the local area, rather than England and Wales, was used as the standard. They pointed out that local mortality would be a more appropriate standard for comparison if the high lung cancer rates found locally were due to risk factors among the local population shared by the chemical workers, such as smoking habits or air

Table 1. Formaldehyde exposure: mortality of chemical and garment workers.

	Observed/expected (O/E) deaths													
	Chemical industry[a]											Garment industry[b]		
Cause of death	A1	A2	A3	A4	A5	A6	Total A (*83*)	B (*98*)	C (*89*)	D (*90*)	E (*87*)	F (*88*)	Total A–F	O/E[c]
All causes	77/93	98/107	49/45	845/983	104/149	446/485	1619/1862	115/—[d]	24/—[d]	146/197		256/—[d]	1765/2059	0.86
All cancers	19/23	32/27	18/11	251/246	21/38	114/123	455/468	20/22	10/6	37/37	42/27	87/73	651/633	1.03
Skin							2/—		0/—	1/0.9		2/1.1	3/2.0	—
Buccal cav. and phar.							5/4.6		2/0.2			3/1.3	10/6.1	1.64
Respiratory								6/7.5	3/2.3	12/12.4		11/12.2	32/34.4	0.93
Nose	0/0.05	0/0.06	0/0.03	0/0.56	0/0.09	0/0.28	0/1.07	0/—	0/—	0/—	0/—	0/—	0/1.1	—
Larynx							4/4.5			1/—		0/—	4/4.5	—
Lung	6/9.3	11/11.5	7/4.7	128/103.4	7/13.3	46/51.6	205/193.8			11/11.7	18/7.6	11/11.6	245/224.7	1.09
Digestive							118/117	8/6.3	4/1.5	5/9.5	14/9.0	22/17.5	171/160.8	1.06
Esophagus									0/—			1/0.9	1/0.9	—
Colon									4/0.6	3/3.0			7/3.6	1.94
Prostate									0/—	4/1.3			4/1.3	—
Kidney							7/8.3		0/—	1/1.0			8/9.3	0.86
Bladder							18/16.9		0/—	1/0.8			19/17.7	1.07
Brain							5/12.5		0/—	3/1.6		1/2.1	8/16.2	0.56
Lymphopoietic							20/26.3	2/2.3	1/0.5	6/4.4	5/2.5	10/6.1	44/42.1	1.05
Leukemia							9/11.4			2/1.7		4/2.4	15/15.5	0.97

[a] Range of mean exposures, 0.17–3 ppm; no. of samples > 142; highest level reported, 5.4 ppm.
[b] Range of mean exposures, 0.7–0.74 ppm; no. of samples, 85; highest level reported, 2.7 ppm.
[c] O/E given only when observed and/or expected deaths ≥ 5.
[d] Proportional mortality study.

Table 2. Formaldehyde exposure: mortality of pathologists, anatomists, and morticians (includes combined totals of observed and expected deaths for Tables 1 and 2).

	Observed/expected (O/E) deaths											
	Pathologist[a]		Anatomist[b]	Mortician[c]							Total Tables 1 and 2	
Cause of death	G1 (*99,100*)	G2 (*99,100*)	H (*92*)	I1 (*101,102*)	I2 (*101,102*)	J (*103*)	K (*104,105*)	L (*106*)	Total G–L	O/E[d]	Total A–L	O/E[d]
All causes	146/244	110/195	737/1129	1132/—[e]	1007/—[e]	319/322	333/—[e]	31/—[e]	1312/1890	0.69	3077/3949	0.78
All cancers	38/62	32/52	120/188	243/219	205/170	58/67	59/60	17/13	772/831	0.93	1423/1464	0.97
Skin			2/3.5	8/3.6*	2/3.4	0/0.9	0/—	1/—	12/11.4	1.05	15/13.4	1.12
Buccal cav. and phar.			1/6.8	8/7.1	8/6.1	1/2.1	3/1.6	0/—	21/23.7	0.89	31/29.8	1.04
Respiratory			13/46.3	74/70.7	43/46.0	20/21.6	13/17.3	4/3.7	167/205.5	0.81	199/239.9	0.83
Nose		0/0.1	0/0.4	0/0.5	0/0.6	0/0.2		0/—	0/1.8	—	0/2.9	—
Larynx			1/2.8	2/3.4	2/2.6	0/1.0		1/—	6/9.8	0.61	10/14.3	0.70
Lung	10/27.4	9/22.0	12/43.0	78/66.8	41/42.8	19/20.2	12/14.0	3/3.4	178/239.6	0.74	423/464.3	0.91
Digestive	12/19.8	8/15.5	38/66.4	68/65.2	69/57.0	17/22.6	16/19.3	5/4.2	233/270.0	0.86	404/430.8	0.94
Esophagus			2/4.6	5/5.3	3/4.1	0/1.7	1/1.3	0/—	11/17.0	0.65	12/17.9	0.67
Colon			20/18.5	29/20.3	30/16.0‡		5/5.4	1/1.4	85/61.6†	1.38	92/65.2†	1.41
Prostate			20/18.7	15/16.4	23/13.1†	3/3.4	5/6.8	3/1.5	69/59.9	1.15	73/61.2	1.19
Kidney			1/4.0	8/5.4	4/4.0	1/1.7	2/1.4	0/—	16/16.5	0.97	24/25.8	0.93
Bladder	1/2.1	2/1.9	5/7.2	7/7.3	8/5.8		6/2.5	0/—	29/26.8	1.08	48/44.5	1.08
Brain		4/1.2*	10/3.7†	9/5.8	9/4.7	3/2.6	1/1.6	0/—	36/19.6‡	1.84	45/35.8	1.26
Lymphopoietic	8/3.8*	2/3.0	18/14.4	25/20.6	19/15.6	8/6.5	10/5.6	1/1.1	91/70.6*	1.29	135/112.7*	1.20
Leukemia	1/1.5	1/1.1	10/6.7	12/8.5	12/6.9	4/2.5	8/2.6†		48/29.8†	1.61	63/45.3*	1.39

[a] Range of mean exposures, 0.16–4.8 ppm; no. of samples, 78; highest level reported, 13.57 ppm.
[b] Range of mean exposures, 0.15–8.3 ppm; no. of samples, 32; highest level reported, 14.8 ppm.
[c] Range of mean exposures, 0.74–2.7 ppm; no. of samples, 200; highest level reported, 5.26 ppm.
[d] O/E given only when observed and/or expected deaths ≥ 5.
[e] Proportional mortality study.
* Significant increase, $p < 0.05$.
† Significant increase, $p < 0.01$.
‡ Significant increase, $p < 0.001$.

pollution, but not if the high rates could be attributed to factors not experienced by the chemical workers, such as carcinogenic exposures in other local industries. The local rates used, however, were for the period 1968–1978, whereas the period of observation of the study cohort also included earlier years. Because mortality due to lung cancer increased wth time, the use of 1968–1978 rates may have exaggerated expected numbers of deaths, thus diminishing standardized mortality ratios (SMRs). Although a trend of increasing mortality with increasing intensity of exposure was observed at this plant (SMRs 58, 79, and 118 for low, moderate, or high levels of exposure, respectively), in men exposed to high levels of formaldehyde (estimated to exceed 2 ppm), SMRs did not increase with increasing duration of employment, cumulative dose of formaldehyde, or time since first hired (*83,84,86*).

No clear explanation is available for the deficit of lung cancer among workers exposed to formaldehyde at low intensity. It could be the result of having included salaried workers in the cohort, but whether or not this was done was not adequately described in the publication. Such persons would be expected both to smoke less and to experience less intense occupational exposures. As direct age adjustment was not employed for the subset comparisons, differences in SMRs might also be related to differences in age distribution rather than mortality rates. In a study in Italy, Bertazzi et al. (*87*) found increased lung cancer mortality regardless of whether expected deaths were derived using national or local rates. When the experience of workers exposed to formaldehyde was compared to that of nonexposed workers from the same plant, on the other hand, lung cancer mortality among the exposed group appeared not to be in excess.

Increased cancer of the buccal cavity and pharynx cancer was observed in two studies of industrial workers exposed to formaldehyde. Stayner et al. (*88*) noted excess buccal cavity and pharynx cancer (3 observed versus 1.3 expected) in a proportional mortality study of garment workers. All three observed deaths were caused by tumors of the parotid glands. The authors questioned whether significant concentrations of formaldehyde could reach the parotid glands (*88*). Liebling et al. (*89*) reported excesses of cancers of the buccal cavity and pharynx (2 observed, 0.2 expected) and colon (4 observed, 0.6 expected). This small study is flawed, however, as the method used for case ascertainment, which included reports of co-workers, may be more likely to detect unusual causes of death.

Several industrial studies detected increases in lymphatic and hematopoietic cancer (*87–90*), a finding that was also noted within most professional groups exposed to formaldehyde. However, Acheson's study of industrial workers in six English chemical plants reported a deficit of these cancers (*83*).

Among pathologists, anatomists, and morticians, except for an elevated proportion of deaths due to skin cancer in New York morticians, excess cancer mortality has not been detected at sites thought *a priori* to be at risk from formaldehyde exposure (Table 2). Several studies have recorded significant increases in the number of deaths from leukemia and cancers at several sites, including colon, brain, prostate, lymphatic, and hematopoietic tissues; moreover, summary totals show significant excesses at all of these sites except the prostate. Excess deaths were observed in 5 of 7 studies due to cancer of the brain and leukemia. Although these excesses, which were not observed consistently in industrial workers, may be ascribed at least in part to the increased mortality from brain cancer and leukemia commonly noted among persons of the upper socioeconomic stratum (*91*), the extent to which social class differences contribute to this gradient is not known. In an attempt to address this issue, Stroup compared mortality from cancer of the brain and leukemia among anatomists with mortality in psychiatrists. Using psychiatrists as the referent, the SMRs for these cancers were larger than those based on the general population standard (*92*).

Two case-control studies of formaldehyde exposures detected no increased risk for lung cancer. Among physicians, the relative risk of lung cancer for those ever employed in pathology, forensic medicine, or anatomy was 1.0 (*93,94*); among workers at formaldehyde-manufacturing plants, the relative risk of formaldehyde exposure for men with lung cancer was also 1.0 (*85*). Odds ratios in the latter study varied little with the number of years elapsed following exposure or with exposure duration, frequency (continuous vs. intermittent), intensity, or cumulative index; furthermore, there was no evidence of an interaction between smoking and formaldehyde exposure.

Three other case-control studies provide indications of a possible association between formaldehyde exposure and nasal cancer. Hardell et al. found that 2 of 44 (4.5%) cases with nasal cancer had worked in particleboard production, as compared to 4 of 541 (0.8%) controls (*95*). Besides formaldehyde, particleboard production also involves exposure to wood dust, an established nasal carcinogen. In a Danish study, after adjusting for wood dust exposure and taking account of age, Olsen et al. (*96*) reported a relative risk of 1.6 for formaldehyde exposure among persons with nasal cancer. This was not significantly different from 1.0. Individuals with exposure to both wood dust and formaldehyde, it was suggested, may have been at greater risk than those exposed only to one agent. A study conducted in The Netherlands noted an association between formaldehyde exposure and squamous cell carcinoma of the nose and nasal sinuses. No quantitative data on the risk of formaldehyde exposure were provided (*97*).

In mortality studies of formaldehyde-exposed cohorts, deaths from nasal cancer have not been reported, although about three had been expected (Table 2). Combined, these studies would have sufficient power (80%) to detect a relative risk of 3 or more (one-tailed $p \leq 0.05$). It should be recognized that this estimate does not consider whether the workers in these studies had

experienced adequate exposures or latency periods for developing nasal cancer.

Overall, there is limited epidemiologic evidence for the human carcinogenicity of formaldehyde. No deaths from nasal cancer have been reported in SMR or proportional mortality ratio (PMR) studies, but three case-control studies of nasal cancer suggest the possibility of increased risk. Excess cancers of the brain and of the lymphatic and hematopoietic tissues have been reported consistently in studies of formaldehyde-exposed professionals, but whether these excesses are related to formaldehyde exposure is not known. Elevated mortality from lymphatic and hematopoietic cancer has also been observed in some industrial groups.

Conclusions and Identifiable Uncertainties

Two definitive chronic inhalation bioassays on rodents demonstrate that formaldehyde can produce nasal cancer in the rat (two studies) and in the mouse (one study); tumors were found only in the respiratory tract. Although there will be a number of instances where additional whole animal studies will be required, these will be related primarily to mechanisms.

The levels at which malignant or benign tumors were found in these studies included those at the extreme limits of human exposure as well as those within the range of past and present exposure. It should be noted that the number of animals used in these studies was small when compared to the number of persons exposed to formaldehyde.

Studies of physiological and biochemical mechanisms related to formaldehyde exposure have moved with surprising rapidity, considering the relatively short time that formaldehyde has been recognized as a carcinogen. In particular, it has been found that the mouse substantially reduces its respiratory minute volume when placed in an atmosphere containing formaldehyde.

Biochemical studies have quantitated the formation of DNA-protein crosslinks in the nasal mucosa, providing a measure of tissue dose. The role of DNA-protein crosslinks in the carcinogenic process is not fully understood.

Endogenous formaldehyde has been identified as a normal part of the carbon metabolic cycle. The relevance of endogenous formaldehyde to spontaneous malignancy has not been clarified.

The rapid entry of administered formaldehyde into the normal endogenous formaldehyde pool clearly favors the production of malignancy at the site of greatest exposure, namely, the upper respiratory tract. Transport at lower levels, not now detectable, or in protective complexes cannot be excluded and could conceivably play a role in reported incidence of cancer at remote sites (e.g., the brain).

The results of epidemiologic studies conducted to date on the carcinogenicity of formaldehyde must be regarded as limited. Positive associations between formaldehyde and nasal cancer have been suggested in three case-control studies (*95–97*). No nasal cancer deaths, however, have been reported in any of a number of cohort studies, each of which individually had little statistical power. Two studies have reported excesses of cancer of the buccal cavity and pharynx (*88,89*). The significance of these observations in regard to the effects of formaldehyde exposure is not clear. A number of investigations, especially of professional groups, are consistent in reporting excess malignancy of the brain and of the lymphatic and hematopoietic systems. Increased mortality from these cancers has been commonly found among persons of the upper socioeconomic stratum, although social class adjustment in one study did not eliminate the excess.

In studies at 2 of 11 industrial plants, lung cancer excesses have been reported (*83,87*). Because aspects of both studies are incompletely described, further elucidation of the data will be necessary.

Epidemiologic investigations are continuing. The role of interaction, as for example with cigarette smoke, is not now answerable, and studies in which wholly reliable estimates of exposure are available are very few.

Scientific Issues Concerning the Carcinogenicity of Formaldehyde: Recommendations for Research

Many of the issues concerning the carcinogenicity of formaldehyde are embedded in the general problems of carcinogen risk assessment, broadly characterized as extrapolation across species and from high to low doses. There are, however, a number of characteristics of formaldehyde, none of which is necessarily unique, but which in the aggregate make formaldehyde an unusual agent: its probable mechanism of carcinogenic action as a crosslinking agent; its formation in tissues as a normal metabolite; its action as a promoter and possibly as a cocarcinogen by interference with DNA repair processes; and the importance of glutathione as a natural chemical barrier.

Dose Considerations

Recommendation 1: There is a need for a better understanding of (a) the regional distribution of inhaled formaldehyde in the human respiratory tract; (b) the effectiveness of mucus as a barrier to the penetration of formaldehyde into the respiratory mucosal cells; (c) particle transport of formaldehyde into the lung; and (d) transport mechanisms from the respiratory tract to other tissues, particularly those with suggestive epidemiological evidence of cancer induction (brain, lymphatic, and hematopoietic tissues).

It is not clear to what extent the mucus blanket constitutes a barrier to the penetration of formaldehyde into respiratory mucosal cells, particularly at low doses. There is need for more experimental evidence and theoretical analysis to clarify this matter. Does squamous

metaplasia protect against the penetration of formaldehyde? Would patches of squamous metaplasia that are not covered by mucus constitute hot spots of attack by formaldehyde? To what depth does formaldehyde penetrate into the human lung with nose breathing and with mouth breathing? Does significant penetration occur at the level of the major bronchi, with an important risk of bronchial cancer, or are the target sites likely to be the nose, mouth, pharynx, and larynx? Is there any substantial transport of formaldehyde into the lung in particulate form? Does formaldehyde vapor adsorb onto airborne particles to any significant extent and thus get transported more deeply into the lung than would the vapor by itself? Is there any mechanism of transport of formaldehyde through the bloodstream for release at tissue sites distant from the respiratory tract?

Molecular Mechanism of Action

Recommendation 2: The molecular mechanisms of the action of formaldehyde need to be clarified in terms of (a) an improved chemical characterization of DNA-protein crosslinks and other potential adducts; (b) the genotoxic consequences of DNA-protein crosslinks and other possible mechanisms of DNA damage; (c) the relative importance of endogenous metabolic sources and exogenous (inhalation) sources of formaldehyde, particularly at low-exposure levels, in the formation of DNA-protein crosslinks.

The current methods for analyzing formaldehyde-induced DNA-protein crosslinks are crude and insensitive. The chemistry of these crosslinks has not yet been defined with improved analytic methodology, nor have the genotoxic mechanisms of formaldehyde been clarified in terms of mutagenesis, chromosomal abnormalities, and effects on DNA repair processes. As there are a substantial number of crosslinking agents of carcinogenic importance, such information would be essential to understanding how this class of carcinogens acts.

The extent to which formaldehyde, as a normally produced metabolite, crosslinks DNA and protein needs clarification. The questions arise as to whether endogenous formaldehyde may contribute significantly to the background occurrence of cancer and if exogenous formaldehyde exposure would act incrementally. Can it be that endogenous formaldehyde is so effectively contained close to the sites of formation that it has no opportunity to damage DNA? This issue is also relevant to the effects of xenobiotics that are metabolized through formaldehyde as, for example, methylene chloride or dimethylhydrazine. Are there levels of metabolic formation of formaldehyde from xenobiotics at which formaldehyde can no longer be contained from attacking DNA?

Carcinogen-Associated Tissue Responses

Recommendation 3: The role of tissue damage in the carcinogenic effects of formaldehyde needs further definition, particularly in relation to the interaction of DNA lesions and cell proliferation as a possible basis for the prediction of low-level carcinogenic effects.

In what way and to what extent do hyperplasia, metaplasia, cell proliferation, and atrophy play roles in formaldehyde carcinogenesis? At highly carcinogenic doses of formaldehyde, there is extensive cell killing. Where do the replacement cells come from? Do they arise from less exposed parts of the nose such as the sinuses or the posterior nasal mucosa? Why does tumor formation seem to favor the edge of the turbinates, when the local doses of formaldehyde are equally high elsewhere? Is there a normal epithelial protective mechanism whereby injured, potentially neoplastic cells are expelled from the mucosa by the process of squamous differentiation? To what extent does cell proliferation affect the carcinogenic process by increasing the availability of DNA for chemical interaction and by converting preneoplastic to neoplastic cells? Can the dose-response pattern for carcinogenesis be estimated from the combined patterns of DNA-protein crosslinks and rates of cell proliferation and thus be used to predict carcinogenic risks at low levels of exposure?

Tumorigenic Mechanisms and Dose Response

Recommendation 4: There needs to be a better definition of (a) the role of formaldehyde as a promoting agent, (b) the nature of its interaction with other carcinogens, (c) the effects of fractionation and duration of exposure, and (d) the effect of age on the tumorigenic action of formaldehyde.

Why are the nasal tumors less malignant as the formaldehyde concentration is reduced? Does nasal carcinogenesis normally progress from benign to malignant lesions even at higher carcinogen doses? Does the preponderance of benign lesions at low doses simply reflect a slowing of this process, or is formaldehyde at low doses acting as a promoting agent? Can formaldehyde, in fact, serve as a promoting agent *in vivo* and, if so, for what kinds of agents? How does formaldehyde interact with other carcinogens? At low formaldehyde doses, for example, which produce mostly benign tumors, will cigarette smoke convert benign lesions to malignancies? Does infection contribute to the carcinogenicity of the chemical? How does age affect carcinogenicity: are infants more susceptible than adults? Is there recovery from the carcinogenic action of formaldehyde: are discontinuous exposures less effective than continuous exposures? How is the carcinogenicity of chronic exposure affected by administering the same dose of formaldehyde over a shorter duration?

Epidemiologic Studies

Recommendation 5: Previously conducted epidemiologic studies of persons exposed to formaldehyde contain gaps in the reported data. A national committee should be established to identify data gaps and encourage authors of the studies to conduct further analyses

of their data in order to close these gaps. The mortality experience of important cohorts should be periodically updated.

Recommendation 6: Epidemiologic studies should be conducted in populations with well-characterized exposures to formaldehyde. Methods for assessing exposure require refinement.

Recommendation 7: There is an urgent need to incorporate into epidemiologic studies of persons exposed to formaldehyde techniques derived from molecular biology. Numerous epidemiologic studies of persons exposed to formaldehyde have been initiated. While many are now complete, a few important studies remain underway. Interpretation of findings has been undermined by several factors. The preponderance of investigators failed to consider intensity of exposure, duration of exposure, latency, and smoking habits. Use of the general population for comparison may introduce biases because of differences between the general population and the exposed group in social class, smoking habits, or other health-related factors. As is evident from Tables 1 and 2, many of the studies did not report findings for cancers at sites now believed to be of special interest, perhaps because these sites were not considered important at the time the studies were conducted. Were it possible to rectify these deficiencies, the carcinogenic effects of exposure to formaldehyde in humans at concentrations of a few parts per million or less might still be difficult to detect using traditional epidemiologic methods. The development of ultrasensitive techniques for measuring DNA-protein crosslinks or other DNA adducts in human tissues would provide epidemiologists with new, powerful, potentially more sensitive tools for assessing human risk.

Risk Assessment

Recommendation 8: A sounder biological basis for the mathematical extrapolation of respiratory tract risks from formaldehyde to low levels of exposure must be developed. The utility of pharmacokinetic and DNA adduct data in the mathematical modeling of cancer risk must also be explored.

Summary

It seems reasonable to view formaldehyde as though it were a carcinogen for humans. The central question is how much of a carcinogenic risk does low-level exposure to formaldehyde pose under realistic environmental conditions?

A formidable number of questions in regard to the carcinogenicity of formaldehyde require clarification. Some of these have been indicated above. The issues are worthy of investigation not only to strengthen the risk assessment of a chemical of great economic importance but also to contribute to improved understanding of carcinogenic processes in general.

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